List of appendices

Appendix 5

Electrophysiology and pharmacology of the septo-hippocampal system

A5.1 Introduction

The previous appendix showed that ‘the hippocampus is a relatively simple part of the cortex with respect to its internal anatomy. At the same time it is a highly complicated and enigmatic structure of the brain, if one considers the complexity of its inputs and its possible functional roles’ (Seifert 1983, p. ix). In this appendix we will take the most important step towards uncovering those functional roles.

Relative to the neocortex the layering of the hippocampus is very simple. It consists of a number of discrete modules, most with only one principal cell layer. The connections between these modules (and from external sources) arrive in specific parts of the dendritic trees. For much of the trisynaptic circuit, the flow of information can be viewed as travelling within one lamella (so that each module of the hippocampus is repeated many times in parallel, like the circuit boards in a computer; although the number of functional lamellae may vary and, in the rat, on occasion be as low as three or four, see below). Finally, the external inputs to and outputs from the hippocampus appear to be topographically organized by origin in relation to both the septo-temporal axis (i.e. orthogonal to the lamellae) and with respect to its modules (dentate gyrus, CA1, etc.). All of these features suggest a device which carries out a more or less standard series of transformations on any one of a wide variety of separated parallel inputs.

Against this superficially discrete, massively parallel, organization can be put three essentially orthogonal features. First is the fact that there are extensive longitudinal connections within the septo-temporal axis of each hippocampus. Second is the spread of connections in the commissural system between the two hippocampi. Third is the apparent mixing by the hippocampal formation of the dorsal (‘what’) and ventral (‘where’) trends of information that are processed in parallel in sensory and frontal areas (see Appendix 3 for a detailed discussion of trend organization). This mixing is particularly obvious in the inputs from and outputs to the entorhinal cortex.

These orthogonal connections do not necessarily negate the view of the hippocampus as, in essence, a set of parallel processors. In some cases (e.g. the longitudinal association fibres) the net effect of the connections may be to increase rather than decrease the discreteness of lamellar processing through lateral inhibition (Bernard and Wheal 1994; Sik *et al*. 1994; Sloviter and Brisman 1995).[1] It also appears that such retrograde flow as there is normally from CA1–CA3–CA4 is inhibitory (Sik *et al*. 1994); so is the feedback from CA3 to dentate (Kneisler and Dingledine 1995), although blockade of inhibition can unmask strong excitatory links from CA3 to the dentate (Scharfman 1994*b*). Likewise, the commissural input seems to function to suppress rather than potentiate excitation (see below). The mixing of dorsal and ventral trend information also does not necessarily imply a mixing of modalities or classes of information as such, since the topographical organization inherent to each trend appears to be maintained even after mixing of the trends.

Similarly, while there is considerable local recursion (e.g. the feedback from CA3 to the hilus and the dentate), even where this is excitatory (e.g. Scharfman 1994*b*) the flow of information within the hippocampal formation as a whole will maintain its essential unidirectionality. In this respect the hippocampal formation contrasts with the neocortex and with the subcortical structures from which it receives its input (with the exception of the amygdala). Its function, then, is unlikely to be just a variant of a type of information processing which can also occur in most other parts of the brain.

Anatomy can go this far. But it cannot tell us what type of information processing the hippocampal formation performs. We are too deep in the brain to draw direct clues from the specific known operations of the structures to which the hippocampus is connected (except to note that its main outflow is to structures directly concerned with the generation of actions: the hypothalamus, amygdala, cingulate cortex, and prefrontal cortex). To understand its function, therefore, we must look at the specific neural activity of the hippocampus. This is the business of the next three appendices. In the present appendix we will discuss basic electrophysiological properties of hippocampal neurons. In Appendix 6 we will discuss the relationships of the firing of individual cells and groups of cells in different parts of the hippocampal formation to behaviour; and in Appendix 7 we will discuss the effects of electrical stimulation of inputs to the hippocampus on behaviour.

A5.2 The electrophysiology of the hippocampal formation

The orderliness of the hippocampal formation has made it a favourite target for electrophysiologists, pharmacologists, and molecular biologists who have used it ‘as a model for studying brain structure and function’ (the subtitle of the volume edited by Storm-Mathisen *et al.* 1990). In consequence, a huge amount is known about specific details of its functioning.

We will not attempt to review this mass of data, as most is both too molecular and insufficiently integrated to have great impact on the behavioural level which it is our ultimate goal to explain. Rather, we will concentrate on just a few molar phenomena which are emergent properties of the more molecular aspects of hippocampal neurons. These molar phenomena, we believe, must be incorporated into any modern theory of hippocampal function. Among them, pride of place is occupied by two: theta activity (the synchronous burst firing of neurons which can give rise to the rhythmical slow electrical activity, RSA, or ‘theta rhythm’ described by Green and Arduini 1954), which is a marked feature of hippocampal operation in most animals; and plasticity, particularly long-term potentiation (LTP) and long-term depression (LTD). LTP and LTD are remarkable long-term changes in synaptic response.

The phenomena of LTP and LTD, in that they indicate that plasticity can occur at the level of individual synapses, are vitally important for the arguments we put forward about memory systems (Chapter 8). Luckily, how they occur at the molecular level is not important as for ‘almost any assertion about LTP . . . the literature will supply evidence to support the opposite assertion’ (Collingridge and Bliss 1995; see for a brief and witty review; see also Eichenbaum 1995, 1996). Nor is it yet clear that LTP and LTD are directly involved in learning as such (e.g. Cain 1997), but instead they ‘may serve as a neural equivalent to an arousal or attention device in the brain’ (Shors and Matzel 1997, but see accompanying commentaries for alternative views; see also Appendix 6). (This less specific role would, nonetheless, be important for at least some types of learning to occur.) LTP and LTD also need not be the basis for memory itself, but could represent the initial steps of a cascade of ‘markers’ which provide the synaptic specificity for modifications which depend on genomic transcription (Sossin 1996). Such transcription would otherwise not be synapse-specific. On the other hand, ‘despite the fundamental place that synapse specificity occupies in our theoretical ideas about the way the brain works, there is still

little direct experimental evidence that long-term changes in neuronal connections are synapse specific' (Sossin 1996, p. 215).

LTP and LTD were first described in the hippocampal formation and are easiest to observe there. But, as we will see, they are not specific to the hippocampus at all. We will devote a final section of this appendix to a discussion of the possible relationships of theta with LTP.

A5.3 Basic electrophysiology

The electrophysiology of the hippocampal formation and related limbic areas has recently been reviewed by Lopes da Silva *et al*. (1990). The wide variety of putative neurotransmitters and cofactors in the hippocampal formation, details of channels and currents, and the properties of action potentials can all be found in their review.

Here, we will described only a few basic features of the electrophysiology (for further details and references see Lopes da Silva *et al*. 1990). There are five main points to note (Lopes da Silva *et al*. 1990, p. 474):

1 The unidirectional connections starting at the entorhinal cortex and terminating in output from the subiculum are, as might be expected, excitatory—predominantly glutamatergic. The receptors involved at any individual synapse can be of more than one type and we will consider the functional significance of this fact, and of the *N*-methyl-d-aspartate (NMDA)-type of glutamate receptor in particular, below.

2 There is substantial, predominantly GABAergic, inhibition (see review by Thompson 1994). This involves local recurrent inhibition, feedforward inhibition by glutamatergic afferents, direct inhibition from septal afferents and from afferents from the contralateral dentate. As noted above, the longitudinal connections are likely to have a net inhibitory effect. However, as also noted above, GABA can, in addition, be depolarizing in the hippocampus (see also Scharfman 1994*a*).

3 Acetylcholine (ACh), predominantly from the medial septal–diagonal band complex, can act both as a fast excitatory transmitter and, in essence, as a slower modulator of hippocampal excitability (e.g. Madison *et al.* 1987). Different effects are obtained in different types of cell, and the slow depolarization will prove important when we consider the literature on the control of theta activity.

4 Monoamines modulate hippocampal function, producing an increase in signal-to-noise ratio (Appendix 10).

5 Neuropeptides of various sorts are clearly important modulators of hippocampal function. This is also true for pituitary–adrenal hormones (not mentioned by Lopes da Silva *et al*. 1990). However, their actions are sufficiently complex and ill understood that we omit discussion of neuropeptides entirely from this book and deal with pituitary–adrenal hormones only in the context of acute interactions with anxiolytic drugs (Appendix 1).

Overall, then, the hippocampus passes information from one field to the other (both step by step and skipping one or more levels). All levels of the hippocampal formation receive excitatory input from both the entorhinal cortex and the septum; and all receive essentially inhibitory input from the septum (GABA). They all receive input from basal forebrain (ACh), locus coeruleus (noradrenaline, NA), raphe (5-hydroxytryptamine, 5-HT), and from dopaminergic and histaminergic nuclei. These act to inhibit weak inputs and, effectively, increase strong ones. The input from the entorhinal cortex also appears to have an inhibitory component (e.g. Levy *et al.* 1995).[2] There are recursive connections and orthogonal connections which seem to be capable of

both net excitatory and net inhibitory effects.

A5.4 Hippocampal plasticity

The most influential class of electrophysiological phenomena in shaping recent theories of septo-hippocampal function is plasticity. We will concentrate here on the long-term (hours/months) plastic changes that reflect interactions between primarily excitatory inputs to the hippocampus. We have dealt elsewhere with short-term interactions of excitatory inputs with the primarily inhibitory inputs ascending from subcortical nuclei (Appendix 10). We will provide only modest mention of the multitude of similar short-term (seconds/minutes) changes associated with activation of any input. These are at present not well characterized and are, in any case, difficult to relate to the specific details of any of the current theories of hippocampal function. It has also become clear that the capacity for LTP and LTD can itself be altered for substantial periods, a phenomenon for which Abraham and Bear (1996) have coined the term ‘metaplasticity’, i.e. plasticity of plasticity. We will ignore metaplasticity below since its functional significance is not yet clear, although this may be to maintain the plastic capacities of the hippocampus in an unsaturated state.

Plasticity, in this context, is any change which occurs in the response to a single stimulus as a result of preceding activity. The hippocampus shows changes which are both short term (‘frequency potentiation’; ‘habituation’; ‘post-tetanic potentiation’; ‘paired pulse potentiation’) and long term (LTP; LTD) and which, as the names suggest, include both increases and decreases of response. It is the long-term changes which are currently receiving the most attention in the literature, with new phenomena being discovered at a great rate and old phenomena demonstrating ever more complex mechanisms.

The links in the trisynaptic chain, perforant path to dentate, mossy fibres to CA3, and Schaffer collaterals to CA1, are all, as we have noted, excitatory, the transmitters probably being the amino acids glutamate or aspartate (Storm-Mathisen 1978). If trains of moderate frequency (5–20 Hz) electrical stimulation are applied to any of the links in this chain, frequency potentiation can be observed—that is the response to successive pulses of the train increases (Alger and Teyler 1976; Andersen 1978). This is also true of excitatory septal input to the dentate gyrus (McNaughton and Miller 1984) and to CA1 (e.g. Stanley *et al.* 1979). So far, habituation (i.e. ‘frequency depression’) has been reported only in the granule cells of the dentate gyrus (Alger and Teyler 1976; Teyler and Alger 1976; Harris *et al*. 1978; White *et al*. 1979). Habituation appears to occur preferentially at relatively low frequencies of stimulation and potentiation at relatively high ones (White *et al*. 1979).

The use of the term ‘habituation’ rather than ‘frequency depression’ begs a number of important questions. In particular, we need to know whether the response decrement seen is the same phenomenon as the behavioural habituation described, for example, by Sokolov’s (1960) group in Moscow. Teyler and Alger (1976) go some way to meeting this point by showing that it shares a number of the parametric properties of behavioural habituation.

Winson and Abzug (1978) also report findings which suggest that gating of the entorhinal input to the hippocampal formation at the level of the dentate granule cells may play a role in normal behaviour. They stimulated the perforant path in free-moving rats and recorded the response one, two, or three synapses around the hippocampal circuit during different stages of alertness or sleep. They found transmission to be best during slow-wave sleep, intermediate during rapid eye movement sleep and awake moving (both of which are accompanied by theta), and poorest during still alertness. These differences in transmission were almost entirely due to changes at the perforant path–dentate synapse.

These observations suggest that there is an important gating of neural transmission at the dentate entry point to the 'linear' hippocampal processing units. Segal (1978) showed similar results to those of Winson and Abzug, but measuring the commissural response resulting from stimulation of the contralateral hippocampus. However, in addition to a short latency (10–15 ms) response which was smaller during awake theta than during non-theta states, he reported a late (30–40 ms) response which was greater during theta than non-theta. As we shall see in Appendix 6, Segal (1977*a*,*b*,*c*) has demonstrated that this late potential is specifically enhanced by procedures, such as classical conditioning, which cause the animal to pay particularly close attention to its environment at the time the commissural response is tested. Thus, theta may facilitate transmission of only those stimuli which are important for the animal. We discuss in detail the idea of a generalized suppression of most responses, coupled with privileged transmission of important ones, when we consider the role of the ascending cholinergic and monoaminergic inputs to the hippocampus in Appendix 10.

Medial septal stimulation can produce single spike activation and population spikes from presumed granule cells. These population spikes undergo paired pulse potentiation which (like perforant path paired pulse potentiation) maximizes in the middle of the recurrent inhibitory pause; also, a preceding septal response can produce paired pulse potentiation of perforant path potentials (McNaughton and Miller 1984). A similar paired pulse potentiation of perforant path responses is produced when the septal and hippocampal electrode placements are arranged so as not to produce a septal population spike and where the effect appears to result from GABAergic inhibition of interneurons (Bilkey and Goddard 1985).

A5.5 Long-term potentiation and long-term depression

From the point of view of the psychologist, long-term potentiation is probably the most exciting purely electrophysiological phenomenon ever discovered. Originally described by Bliss and Lømo (1973) as a long-term change in synaptic plasticity induced by a high-frequency train in the anaesthetized rabbit, LTP has been shown to last for weeks or months, to occur when a single afferent volley arrives at depolarized neurons (Abraham *et al.* 1986), and to have the critical 'Hebbian' properties of 'persistence, input specificity, cooperativity and associativity' (Abraham 1988; but see Shors and Matzel 1997 for a contrary review). It should be noted 'that inhibitory synaptic transmission [also] possesses an enormous, and perhaps underappreciated, capacity for plasticity' (Thompson 1994, p. 603).

The persistence of LTP is, compared to other electrophysiological phenomena, truly amazing—although probably not sufficient to account by itself for long-term memory. Input specificity consists in the property that only the active input onto a particular depolarized cell is strengthened. This, coupled with the requirement that the postsynaptic cell must be depolarized, generates the properties of cooperativity and associativity. Cooperativity is the property of two weak inputs, which will not separately produce potentiation, to potentiate each other when activated concurrently (because each provides additional depolarization of the postsynaptic cell). It should be noted that such cooperativity has been observed with the amygdala input to the hippocampus even under conditions where no amygdaloid evoked potential was observable (Ikegaya *et al.* 1995). Associativity is the special case of cooperativity of two quite distinct inputs where one is weak and the other strong. Note that, in this case, the strong input alone will fire certain cells when the weak will not (they are made 'strong' and 'weak' by adjusting the stimulation strength) but, after pairing the weak with the strong input, the weak input will thereafter produce a similar response to that originally elicited only by the strong input. This is what is required of the simplest form of Pavlovian conditioning.

For those who wish to construct memory machines, it is convenient to be able to adjust synaptic

strength both up and down—and it turns out that this is possible in the nervous system too. Long-term depression has been obtained in the mammalian central nervous system (CNS) and follows very similar rules to those of LTP (for reviews, see Linden 1994; Bear and Abraham 1996). The difference between LTP and LTD can be encapsulated in two now well-worn phrases. For LTP, 'cells that fire together wire together', while for LTD 'cells out of synch lose their link'.[3] Plasticity of inhibitory synapses may also be important (Kano 1995).

Both LTP and LTD have a variety of parameter dependencies and molecular properties which have been extensively, although not completely, worked out, and by now it would be easy to write an entire book covering this subject alone (e.g. Haas and Buzsáki 1988). Given that LTP is probably not entirely specific to the depolarized cells, but can occur in adjacent cells (Schuman and Madison 1994), it may also be necessary to make some additions to the classical Hebbian rules when considering the operations of the real brain (Montague and Sejnowski 1994). However, for much of our analysis the mere fact of the occurrence of LTP and LTD is much more important than the parametric, molecular, or network modelling details. For the most part, therefore, we will pass these by (see Shors and Matzel 1997).

One very important point for experiments we will consider later, however, is that LTP and LTD at many (but not all) synapses depend on activation by glutamate of the specific NMDA subtype of glutamate receptor. This receptor is linked to a calcium channel which is not only transmitter-gated (as is the case for the conventional excitatory sodium channel and inhibitory chloride and potassium channels), but also has a voltage sensitivity roughly similar to that of the sodium channels which support the action potential. It is the transmitter sensitivity of the NMDA receptor which provides the input specificity of LTP and LTD, and it is its voltage sensitivity which provides the cooperativity, and hence associativity. An influx of calcium through the channel is thought to be the initial step in the complex molecular cascades that produce both pre- and postsynaptic changes. For our purposes the critical point is that selective NMDA antagonists can often be used to block both LTP and LTD without altering the responses to a single pulse stimulus at the synapses of interest.[4]

The specific properties of LTP and LTD have made them obvious candidates for the mechanism through which the nervous system forms memories (for a recent review in support of the link between LTP and learning and memory, see Martinez and Derrick 1996). The fact that they were discovered, and are most easily demonstrated, in the hippocampus has seemed only right and proper to those who view temporal lobe 'amnesia' as a loss of memories. This is in fact a *non sequitur* and so a word of caution is in order. First, we should note that, as discussed in Chapter 8, there is little evidence that the hippocampus is the repository of any kind of memory (including 'intermediate' memory). Second, learning-related plasticity occurs in other areas. As noted elsewhere (Chapter 6, Appendix 2), fear conditioning in the amygdala appears to depend on LTP; and so does conditioning in the spinal cord (Wolpaw 1994); while spatial learning is accompanied by LTP-like changes in the lateral septum (Garcia *et al.* 1993). Third, LTP and LTD have been observed, so far, in 'visual cortex, dorsal [and ventral] horn of the spinal cord (LTP), and cerebellum (LTD)' (Pockett and Figurov 1993, p. 97) as well as 'sensory and motor areas of the cortex and prefrontal cortex' (Doyère *et al*. 1993) and olfactory cortex (e.g. Collins 1994). At least in the motor cortex, LTP can be obtained in the connections between one layer and another within the same segment of cortex (Kimura *et al*. 1994). LTP has also been observed at peripheral synapses of both mammals and amphibia (see Dolphin 1985). Long-term plasticity, based on LTP and LTD, may then be a general property of all synaptic junctions. It has even been suggested, by the late Graham Goddard (personal communication), jocularly playing devil's advocate, that LTP is easiest to see in the hippocampus because that is the one place in the brain where it does not normally occur! That is, other areas do not show experimental LTP so readily because they have synapses which are close to saturation, since LTP is a common

occurrence in them.

Despite Goddard's attractively paradoxical argument, there are many data which suggest that intact LTP in the hippocampus is, in fact, necessary for proper hippocampal function, but not for learning in general. For example, blockade of the NMDA receptor (which blocks LTP but not normal synaptic transmission) can block spatial learning in the water maze, but not visual discrimination (Morris *et al*. 1986). However, that LTP is the basis, in the hippocampus, for the storage of particular memories has been more difficult to prove, and is probably not true. Blockade of LTP (using NMDA antagonists or gene knockout mice) can leave spatial learning intact (Bannerman *et al*. 1995; Saucier and Cain 1995; Nosten-Bertrand *et al*. 1996); and the effects of NMDA receptor antagonists on spatial learning appear to be the result of sensorimotor impairments (Cain *et al*. 1996).

It should be noted here that, even if LTP and LTD are integral to proper hippocampal function, they need not constitute 'memory' in the sense usually used by psychologists. Computer-brain analogies are always suspect, but it should be noted that the 'program' in a computer is resident in a form of 'non-data memory'. Modifying the instructions of the program, then, requires identical operations to those required to store and retrieve data, but in a different area of the computer. Within the hippocampus, then, LTP/LTD may reflect modification of the operations performed by the hippocampus on information stored elsewhere, rather than reflecting modification of information about the world. This view, if correct, would still leave open the possibility that, in other cortical and subcortical areas, LTP/LTD might indeed reflect information storage. The suggestion by Shors and Matzel (1997) that LTP is akin to an alteration of local attention is a special case of this more general view; and relates to the fact that stress appears to alter the capacity for LTP and hence behaviour (e.g. Diamond *et al*. 1996, 1997).

A final point is that the effect of LTP on the function of the hippocampus could well be different than is assumed by simple memory models. On the simplest scenario, LTP should strengthen connections and hence increase the likelihood of cell firing. However, LTP of the perforant path renders *inactive* cells in the hippocampal formation which, prior to LTP, responded to discrete external stimuli (Vinogradova, personal communication). Thus, LTP in the hippocampus could represent an 'ignore' signal rather than a 'store' signal—a kind of negative memory. Likewise, while LTP in the hippocampus approximates Hebbian rules, it also has a number of non-Hebbian properties which suggest that it may be particularly appropriate for storing temporal (and possibly other) sequences of information, and with much higher densities than a simple Hebbian system (Granger *et al*. 1994). We consider all of these issues in the context of the theory of Chapter 8. Similarly, in the cerebellum and, more clearly, in the electric fish, learning may depend on 'anti-Hebbian', LTD-like processes rather than LTP (Bell *et al*. 1993).

A5.6 Theta activity

The other important global phenomenon of hippocampal electrophysiology is theta activity. This is the regular burst firing of hippocampal cells which can give rise to the theta rhythm, one of the most regular rhythms of the brain.

Theta rhythm (Fig. 10.1) is almost sinusoidal and can be recorded at amplitudes as great as 1000 μV through gross electrodes placed almost anywhere in and around the hippocampal formation and entorhinal cortex. Its apparent simplicity and ease of recording have resulted in a voluminous literature. Unfortunately, the simplicity of theta is only superficial and, more than most areas of physiological psychology, the study of theta rhythm (and the more fundamental theta activity) is bedevilled by a number of false assumptions and terminological problems.

The name 'theta rhythm' itself is an example of such a problem. It was used originally because,

in earlier experiments with animals anaesthetized with urethane, or with unmoving rabbits, or with cats and dogs, the frequency of the rhythm was in the range of the human EEG theta band (4–7 Hz). However, it is now clear that, depending on behavioural conditions and species, its frequency can range from 4 to 12 Hz, or even on occasion 14 Hz (Vanderwolf *et al.* 1975). For this reason Vanderwolf has suggested that the term 'rhythmic slow activity' or RSA for short, should be preferred. While agreeing with Vanderwolf that the term 'theta' is potentially confusing, we will continue to use it here since it is still the commonest term in the literature for temporal lobe slow waves. Furthermore, RSA is normally equated with theta rhythm and we wish to distinguish this from 'theta activity': the underlying rhythmic activity of the cells which can, on occasion, give rise to a recordable 'theta rhythm'. However, we should note that 'theta rhythm' recorded from, for example, the frontal pole in human beings cannot be automatically linked with 'hippocampal theta rhythm' on the basis of frequency or its apparent relation to memory (e.g. Burgess and Gruzelier 1997), despite some superficial validity in this parallel (Klimesch *et al.* 1994, 1997; Gevins *et al*. 1997). First, the frequency and relations to behaviour of hippocampal 'theta' in human beings must be determined and, ideally, specifically linked to the occurrence of frontal pole theta. This is not an easy task (but see Klimesch 1996 for an extensive justification). There is some indication of a link between frontal midline and hippocampal theta in cats (Demiralp *et al*. 1994), but this study used an average evoked potential rather than conventional EEG recording methodology. There also appears to be a link between hippocampal and occipital theta in rats (Bringmann 1997).

A second major terminological problem arises from the distinction often made between what are called Type 1 and Type 2 theta activity. As we will see, there are two distinct signals (cholinergic and serotonergic) which permit theta to occur (we will refer to this as 'gating'). However, as we will also see, these two 'Types' of theta do not depend on two fundamentally separate control systems. Rather they permit a common source of predetermined rhythmic input from the medial septum–diagonal band complex (MS/DBB) to take control of target structures such as the hippocampus. Thus, contrary to popular impression, the two types are not mutually incompatible (both gates can be open at the same time); and they cannot be distinguished on the basis of frequency. There are also quite separate definitional problems with the relation of the types of theta to types of behaviour—we will deal with this mostly in the next appendix.

Theta *rhythm* is easily recorded in rats, rabbits, cats, dogs, and other small mammals. There has been controversy about its existence in primates. This is likely to be partly because of a failure to create the appropriate eliciting conditions (Appendix 6); partly because of a failure to correctly locate recording electrodes (see Robinson 1980); and possibly because, in primates, theta activity may occur in only a restricted part of the hippocampal formation at any one time (perhaps because of the existence of a larger number of functional lamellae) and may, in any case, not result in a recordable rhythm. This last follows from the highly topographic organization of the subcortical input to the hippocampal formation and from the fact that, even in rodents, it can be demonstrated that there are systems which actively suppress theta. These latter may be present because theta is not uniformly beneficial; thus, evolution of more and more selective suppression of theta is not unlikely. In this context we can note that, across species, as the occurrence of theta becomes less widespread, it appears to become restricted to those behaviours which are most sensitive to hippocampal lesions (Appendix 6). It should also be noted that some reports of theta in humans provide only spectral analysis (as opposed to raw EEG), and that of a type which makes it impossible to determine whether theta was theta or not (e.g. Meador *et al*. 1991).

The occurrence and frequency of theta depend markedly on behaviour and species, as we will see in Appendix 6, in which we will argue that appropriate conditions for eliciting theta in humans and other primates have seldom been used, and may sometimes be unethical. Nonetheless, there is good evidence for the presence of all the neural machinery required to produce theta even in

primates. For example, theta can be elicited in the human hippocampus by hypothalamic stimulation (Sano *et al*. 1970) in precisely the same way as in other species (see Bland 1986). Power spectrum analysis of the human hippocampal EEG also shows a peak in the 4–7 Hz band (Brazier 1968), the frequency of which increases with the intensity of specific behaviours (Arnolds *et al*. 1980). Most recently, clear theta activity, with a pharmacological resemblance to rodent theta, has been demonstrated in urethane-anaesthetized monkeys (Stewart and Fox 1991). Theta rhythm has also been observed in monkeys as a result of an unprogrammed failure of delivery of reward, when criterion performance is reached on no-go trials of a go/no-go problem (Crowne *et al*. 1972), and it may be that 'in the monkey . . . the theta rhythm [is] virtually impossible to see, excepting under conditions likely to produce extreme emotional reactions' (Green 1960, cited by Crowne *et al*. 1972). Given that the production of theta is clearest in rats when they are moving or are stationary close to a predator, it is perhaps not surprising that monkeys restrained in a chair and required to perform boring tasks in a relatively unchanging environment show minimal theta. However, humans (like cats) do not appear to show a strong relation between theta and movement (Arnolds *et al*. 1980) and, even in rats, passive bodily rotation, in the absence of voluntary movement, can produce high-frequency theta, suggesting that movement per se is not crucial for theta (Gavrilov *et al.* 1996; see also Gavrilov *et al.* 1995).

A final, and particularly important, point to note in this context is that (as we will see below in relation to area CA3) failure to record theta rhythm with gross electrodes does not mean that theta activity is not occurring at the single-cell level. In particular, the topographic organization of the septo-hippocampal system makes it possible that in primates and humans (with hippocampi which are very large in absolute terms) theta activity can occur selectively in specific parts of the hippocampal formation. We should also note that analysis of primate EEG under anaesthetic has not involved the same stimulation protocols (e.g. stimulation of dorsomedial posterior hypothalamus, reticularis pontis oralis, etc.) which make it easy to detect in rodents.

A5.7 Origins of theta rhythm

Detecting theta activity in individual cells is much more difficult than recording the gross extracellular theta rhythm which is the result of synchronous theta activity in great numbers of cells. The bulk of the work on theta activity has therefore used the rhythm as the main measure of cellular activity. While it is easy to see that rhythmic activity in cells could produce a gross extracellular rhythm, it is less easy to see precisely how this occurs; and the details are important if we are to understand not only the nature of theta but also some of the controversies in the literature.

Theta rhythm can be recorded in most parts of the hippocampal formation. It is most often recorded from the easily accessible septal (i.e. dorsal) hippocampus, but can also be recorded from the temporal (i.e. ventral) hippocampus (McGowan-Sass 1973; Rawlins *et al.* 1979), entorhinal cortex (see Bland and Colom 1993), and posterior cingulate cortex (Feenstra and Holsheimer 1979; Borst *et al.* 1987; but see Bland and Colom 1993, pp. 167–70). Its localization within the various subfields of the hippocampus has been determined by mapping its distribution, observing where its amplitude is maximal and minimal, and where it is in-phase or reversed with respect to a fixed reference electrode. The ideal method of determining the source of the recorded rhythm is current source density analysis. Early mapping studies revealed a maximum near the pyramidal cells of CA1 and a larger, phase-reversed maximum in the dentate (Fig. A5.1; Winson 1974, 1976*a*,*b*; Bland *et al.* 1975; Bland and Wishaw 1976). A variety of evidence has shown that these two maxima reflect activity in two distinct generators, one in area CA1 and one in the dentate gyrus. There are also quite distinct generators in the entorhinal cortex (see Bland and Colom 1993, p. 170).

Fig. A5.1 [plate for this figure to be recovered from Figure 4.2 of the first edition]

Fig. A5.1 Changes of theta amplitude and phase at different depths in the hippocampus of different preparations: (a) rabbit and curarized rat; (b) freely moving rat. In each panel the left graph shows relative amplitude on the abscissa and the right shows a single theta wave at each level and the phase relations amongst them. (From O'Keefe and Nadel 1978, after Winson 1976b.)

There is doubt as to whether theta *rhythm* can be recorded in area CA3 (O'Keefe and Nadel 1978, p. 146; Green and Rawlins 1979). This is, superficially, surprising since area CA3 receives input from the dentate (which does show theta) and CA3 cells fire in the same rhythmic patterns as cells in CA1 and the dentate (see below). CA3 cells also show an *intracellular* theta similar to that seen in CA1 cells (Fox *et al.* 1983). One possibility is that the organization of inputs and outputs of CA3 is such as to produce local cancellation of those fields which would have to be summed if theta rhythm was to be recorded by gross electrodes. The difficulty of recording extracellular theta rhythm in CA3 of rodents is worth remembering in relation to the difficulties which have been experienced in recording it from any part of primate hippocampus, given the rather different conformation and location in the brain of the latter.

There may be similar problems in the cingulate cortex where theta can regularly be recorded, but a phase reversal (which would rule out volume conduction from the hippocampus) often cannot be seen (Feenstra and Holsheimer 1979). Despite this, phase-locking of unit activity is observed in the cingulate (Leung and Borst 1987) and theta is actually increased in cingulate cortex when hippocampal theta is disrupted by medial septal lesions (Borst *et al.* 1987). Thus, it may be that a phase reversal of theta rhythm can only be found in some parts of cingulate, or under some specific conditions, despite underlying cellular theta activity. Likewise, it should be noted that, if theta rhythm behaved like monosynaptic-evoked potentials in area CA1 and the dentate, there should be two or three reversal points, rather than one (with separate true electrotonic reversals centred on each of the cell body layers and an apparent, non-electrotonic reversal in the region of the hippocampal fissure).

The evidence, then, shows that there is clear theta rhythm generated by both entorhinal cortex and hippocampus proper. In the hippocampus proper there are separate CA1 and dentate generators of theta, and it appears that the bulk of the recorded extracellular activity is due to fields generated by the principal cells (pyramidal and granule, respectively). However, interpretation of the fields themselves is not simple, since in each of the generators there are many physically and pharmacologically distinct sources and sinks (Buzsáki *et al*. 1986). Likewise, in the free-moving rat, the maximal amplitude of theta is obtained in the region of the hippocampal fissure (i.e. at the *interface* between two sets of principal cells); and the size of this maximum is reduced, and the presence of two other maxima in stratum oriens and stratum granulosum is eliminated, by either urethane anaesthesia or lesion of entorhinal cortex (Ylinen *et al*. 1995*a*).

This makes current source density analysis almost mandatory since, for example, 'a substantial portion of [CA1 theta rhythm] may result from ventrally located . . . dipoles' (Heynen and Bilkey 1994; see also the literature cited by them). Heynen and Bilkey found that procaine blockade of the perforant path produced a substantial reduction in theta amplitude recorded in CA1. However, their current source density analysis showed not only a major reduction in dentate sources and sinks (potentially contributing to volume conduction to CA1) but also phase shifts of up to 180° in sources and sinks located in CA1. This latter result is like the finding that CA1 lesions can eliminate dentate theta (Monmaur and Thomson 1985) in suggesting that theta is not just the result of rhythmic external inputs but also depends on recurrent interactions within and

between the hippocampi. Thus the phasic input from the septum can be thought of as harmonically driving a pre-tuned system which has the additional capacity, under appropriate conditions, to reinforce its own oscillations through internal feedback loops. As we noted earlier, there are a substantial number of excitatory recurrent circuits within the septo-hippocampal system which can support activity of this kind. However, the fact that a massive reduction in the number of granule cells in the dentate does not produce an equivalent massive reduction in dentate theta (Whishaw *et al.* 1978) makes it clear that much more needs to be known about the relationship between cell firing and extracellularly recorded theta fields. The current version of our theory treats theta activity as resulting simply from phasic drive from the medial septum, and does not attempt to deal with the complex interactions in its hippocampal control which undoubtedly also exist.

The intrinsic and extrinsic factors which give rise to theta have been reviewed by Bland and Colom (1993; see also Vertes and Koscis 1997). Where no reference is given for a fact in the following paragraphs, it will be found in their paper. The few points at which we disagree with their conclusions will be noted as they occur.

The *capacity* to produce theta-like waves is intrinsic to hippocampal cells and their circuitry. Bland and Colom (1993) suggest, indeed, that individual hippocampal cells show membrane potential oscillations (MPOs) which 'are entirely due to their intrinsic membrane properties. Synaptic inputs to these cells achieve three purposes: (1) they synchronize the MPOs of these cells and *it is this synchronization that is manifested as extracellular theta*. . . . (2) [they] serve to drive the MPOs at different frequencies by providing varying levels of tonic depolarization. . . . (3) [they] serve to reset the ongoing MPO frequencies . . . This is primarily achieved by inputs from MS/vDBB [the medial septal area/ventral diagonal band of Broca complex]' (Bland and Colom (1993, p. 201, our emphasis).

Consistent with this hypothesis, if slices of hippocampus are superfused with carbachol, they will show strong rhythmical activity. This occurs not only in area CA1 and the dentate, but also in CA3 and in slices of entorhinal cortex (Konopacki *et al.* 1988, 1992*a*). This observation could be due to intrinsic membrane properties of the hippocampal cells. But, it could also be due to the recurrent inhibition which is found throughout the septo-hippocampal system. In favour of membrane properties is the fact that reduction of GABAergic inhibition potentiates the effects of carbachol (Konopacki and Golebiewski 1993); and the timing of recurrent inhibition would be expected to produce oscillations of a higher frequency than is in fact observed (Leung 1980). However, it seems most likely that the intrinsic tuning of individual cells depends on their membrane properties, but that the phase-locking of the population depends on one-to-many recurrent inhibition by GABAergic interneurons (Cobb *et al*. 1995).

An interesting question is whether, in the intact undrugged rat, the hippocampus ever produces theta as a result purely of either intrinsic MPOs or simple tonic cholinergic activation interacting with intrinsic circuitry. We believe that there is no evidence, at present, that the hippocampus shows theta in the absence of external phasic synchronizing input under normal physiological conditions. There is also evidence that deficits in spatial performance in the water maze induced by transection of the fornix–fimbria (eliminating the synchronizing input from the medial septum) can be reversed by rhythmic electrical theta-frequency stimulation (Turnbull *et al.* 1994). However, the fact that septal lesions abolish theta is not strong evidence against the intrinsic oscillation hypothesis, since such lesions also eliminate the tonic cholinergic input to the hippocampus as well as any phasic influences. Against this, it should be noted that, unlike hippocampus, isolated septal slices show rhythmic bursting activity, and septal cells retain some rhythmicity under a wide variety of manipulations. Similarly, undercutting of the septum makes this region insensitive to brain stem input, but leaves intact a very low frequency (less than 4.5

Hz) theta rhythm (see Vinogradova 1995, pp. 562–3, 566).

Paradoxically, the capacity of hippocampal slices to show an apparent theta rhythm in response to tonic carbachol application is evidence against the likelihood that this normally occurs. If the hippocampus were capable of synchronizing itself in a functionally appropriate fashion in response to a tonic input under normal conditions, there would be no need for the evolution of the complex circuitry which we now know underlies the synchronized input arising in the supramammillary area and other nuclei. Similarly, if that circuitry is important, any tendency for the hippocampus to oscillate independently would surely produce anomalous results such as beats, which are not in fact observed. There is also evidence to suggest that 'carbachol-induced oscillations are fundamentally distinct from theta rhythm in vivo' (Williams and Kauer 1997, p. 2631).

Whether or not carbachol-induced oscillations are distinct from theta is not critical for the present theory and, whatever the role of intrinsic mechanisms, Bland and Colom accept that extrinsic inputs can and usually do reset and synchronize the firing of temporal lobe cells, and hence control the frequency of theta. However, if we accept the view that cholinergic input is not normally responsible for the phasic aspects of theta, this will help in the interpretation of a number of otherwise confusing data: on the two 'types' of theta; and on the otherwise anomalous effects of phasic high-frequency stimulation of the medial forebrain bundle. We will discuss these issues at the relevant points below.

A5.8 Pacemaker input to the hippocampal formation

The main source of the resetting of MPOs, and by implication the source of the high degree of concurrent synchrony across the entire septo-hippocampal system (including the entorhinal and posterior cingulate cortex), is the 'pacemaker' in the MS/DBB complex. The term 'pacemaker' is one of which the ambiguity can lead to confusion. Its simplest meaning (and the one we will use here) is that the pacemaker controls phasic activity in the hippocampus. However, it could also be taken to mean that it is the site at which the phasic frequency itself is determined. As we will see this latter is not in the septum, and may be in a set of distributed sites.

There are cells in the MS/DBB which fire in bursts that are locked to a specific phase (for any individual cell) of the waves of the theta rhythm simultaneously recorded in the hippocampus (Petsche *et al*. 1962; Stumpf 1965; Apostol and Creutzfeldt 1974). GABAergic interneurons within the septum appear to keep the whole septum synchronized (Brazhnik and Fox 1997). Disruption of the firing of the septal cells disrupts the theta rhythm. This occurs both with temporary disruption by local injection of the local anaesthetic procaine or the GABA agonist muscimol, and with permanent disruption by destruction of the MS/DBB (Green and Arduini 1954; Petsche and Stumpf 1960; Stumpf 1965; Gray 1971; Rawlins *et al*. 1979; Bland *et al*. 1996). Medial septal procaine also eliminates both theta rhythm and theta activity in the entorhinal cortex (Dickson *et al*. 1995; Jeffery *et al.* 1995). By contrast, disruption of input from the hippocampus to the septum *increases* the regularity and persistence of theta activity in the septum (see Vinogradova 1995, p. 562); disruption of hippocampal theta by medial septal lesions increases cingulate theta (Borst *et al.* 1987); and partial section of the descending columns of the fornix increases the frequency of theta, an effect which can be reversed with the noradrenergic agonist clonidine (Amassari-Teule *et al.* 1991). These observations make sense if the septal production of hippocampal rhythmicity is under negative feedback control (and if the MS/DBB pacemaker has a similar topographic organization to the MS/DBB cholinergic system—with output to the cingulate cortex being from more ventral locations).

A particularly important point is that theta is replaced by small irregular activity if the MS/DBB

is stimulated continuously at high frequencies, above about 70 Hz (Fig. A5.2). As seen in the figure this blockade of theta can, in the best cases, last as long as the stimulation, with theta returning immediately the stimulation is terminated (Stumpf 1965; Ball and Gray 1971). This observation can be attributed to blockade of the normal phasic pattern of MS/DBB firing. It would be difficult to understand if theta was the result only of tonic cholinergic afferent drive onto intrinsically oscillatory hippocampal neurons, or if the MS/DBB complex were the site of frequency determination. But it can be explained by there being both excitatory and inhibitory inputs from the MS/DBB to the hippocampal formation (Bland and Colom 1993, p. 159), and by the driving of the septum by phasic input from elsewhere.

Fig. A5.2 [plate for this figure to be recovered from Figure 4.3 of the first edition]

Fig. A5.2 Blocking of hippocampal theta rhythm by high-frequency stimulation of the medial septum in the free-moving rat. The recording site was in the dorsomedial subiculum. Septal stimulation (77 Hz, 0.5 ms pulse width, about 100 μA) was applied during upward deflection of the top marker pen; bottom marker pen, time in seconds. (From Ball and Gray 1971.)

Also consistent with the idea of a septal pacemaker (in the limited sense defined above), stimulation of the medial septum with trains of single pulses at frequencies within the theta range can 'drive' theta rhythm: each pulse eliciting a wave locked in phase to it (Fig. 9.1A, B; Stumpf 1965; Gray and Ball 1970; James *et al*. 1977; Wetzel *et al*. 1977). This is in strong contrast to most other areas of the brain, which require *continuous high-frequency* stimulation to elicit theta, the frequency of theta then generally increasing with the strength of stimulation (Sailer and Stumpf 1957; Stumpf 1965; McNaughton and Sedgwick 1978; see Vinogradova 1995).

A5.9 Tonic activity/phasic frequency transduction

Until recently, the generally accepted view was that the general level of tonic activity in the midbrain was converted to phasic theta activity in the MS/DBB. As we have seen, Bland and Colom (1993) suggest that the septal input effectively resets MPOs so as to produce theta. An effect of this kind can obviously occur through inhibitory as well as excitatory input. Recently, we have shown that the septum itself receives phasic input which effectively resets the activity of septal cells and controls their bursting activity. This observation explains some of the previous anomalies associated with the 'septal frequency transducer' hypothesis.

It has been known, but unexplained, for some time that injections of procaine and other drugs into the medial septum could reduce the amplitude of theta, and even totally eliminate it, but without any signs of a reduction in theta frequency (e.g. Bland *et al*. 1996). It is also interesting to note that sites at which tonic activation (typically 100 Hz) produces theta were reported in many parts of the brain, including the lateral hypothalamus and the midbrain reticular formation (e.g. Stumpf 1965; Anchel and Lindsely 1972; Whishaw *et al*. 1972; Robinson and Vanderwolf 1978); but all of these sites were well caudal to the MS/DBB and did not include sites in the medial forebrain bundle carrying the afferents to the MS/vDBB.[5] Where, then, is the phasic intensity/tonic frequency transducer for theta activity?

Vertes (1980, 1981; see 1982) has mapped the midbrain to determine the sites from which theta can be elicited by uninterrupted high-frequency stimulation. He reported that the nucleus reticularis pontis oralis (RPO) was one of the optimum sites for eliciting theta, but that the MS/DBB receives virtually no afferents from there. Rather the septum receives input from, and the RPO sends input to, the medial supramammillary nucleus (SUMM) of the hypothalamus (there are some indications that RPO output may also be relayed to the SUMM, but this is not

critical for our current analysis). We have shown that SUMM neurons fire rhythmically in phase with theta, and that this rhythmicity is undisturbed by blockade of the medial septum which eliminates theta (Kirk and McNaughton 1991), a result which has been replicated by others (Kocsis *et al.* 1993; Bland *et al*. 1995; Kirk *et al*. 1996). It appears that all SUMM cells show this rhythmicity, and that this is not shown by posterior hypothalamic nucleus cells. There are rhythmic cells in the mammillary bodies but, rather than supply rhythmic input to the septum or hippocampus, rhythmic mammillary 'cells may . . . act to relay the theta-rhythmic signal from the septum or hippocampus to other parts of the limbic system' (Bland *et al*. 1995, p. 322; but see Vinogradova 1995 on the mammillary bodies). In agreement with this hypothesis, intra-septal procaine eliminates theta activity in cells of the mammillary bodies (Kirk *et al*. 1996). Both the SUMM and the mammillary bodies have subpopulations of cells which fire selectively at different phases of theta (Kocsis and Vertes 1997). As in the case of the septum, the SUMM appears to be under negative feedback control, since septal procaine greatly increases SUMM cell discharge rates and slightly increases their phasic burst rate (Kirk *et al*. 1996). Theta rhythmicity has also been seen in the dorsal raphe (Kocsis and Vertes 1992), median raphe (Kocsis and Vertes 1996), and the inferior colliculus (Pedemonte *et al.* 1996), but in none of these cases do we know if this, like the theta in the mammillary bodies, is simply the result of output from the hippocampus, although this does seem to be the most likely possibility (Kocsis and Vertes 1996; Kinney *et al.* 1994, 1995; see also below).

We have also shown that, in urethane-anaesthetized rats, injections of procaine between the RPO and the MS/DBB reduce theta frequency if they are made between the RPO and the SUMM. They reduce theta amplitude when between the SUMM and the MS/vDBB, and they reduce both the frequency and amplitude of theta only at the SUMM (Kirk and McNaughton 1993). Under urethane anaesthesia, SUMM procaine can occasionally eliminate theta altogether (Kirk, personal communication). Injections of chlordiazepoxide (an indirect GABA agonist) into the SUMM reduce frequency in freely-moving animals (McNaughton *et al*. 1995), while injections of the benzodiazepine antagonist Ro15-1788 into the SUMM appears to partially reverse the frequency, reducing the effects of peripherally injected chlordiazepoxide (McNaughton, Logan, and Panickar, unpublished preliminary data). We conclude that the SUMM relays input from the RPO to the MS/DBB (but probably not directly to the hippocampus; Donnett and O'Keefe 1995), and is a key site at which *frequency* as opposed to other aspects of theta is coded.

These data seem, at first glance, inconsistent with Bland's view that the dorsomedial posterior hypothalamus (DMPH) is an important relay in the ascending systems controlling theta, since the supramammillary area (SUMM) is posterior to DMPH. Unlike Bland and Colom (1993), we do not view the SUMM as part of a DMPH/SUMM complex. Rather, we see the DMPH as a separate afferent to the SUMM, fulfilling a similar function to that of the RPO. Our reason is that Kirk has shown that injections of procaine into the SUMM in urethane-anaesthetized rats interfere with theta elicited from the DMPH in the same way that they interfere with theta elicited from the RPO (Kirk 1993). Thus, the DMPH sends output caudally to be relayed in the SUMM; and the SUMM converts this output to phasic pulses which it relays rostrally to the MS/DBB. Whether the DMPH relays information from the RPO to the SUMM or represents an independent input remains to be seen. Bland *et al*. (1994) report data which suggest that the DMPH acts as a relay between the RPO and the SUMM. However, they used an injection volume of 4 μl, which could have resulted in spread to the medial forebrain bundle or the SUMM, and they provided no mapping data (see also Bland *et al*. 1995). The DMPH may also be able to affect the medial septum through routes other than the SUMM in freely moving animals (see below). In particular, it is likely that the DMPH is more a critical component of the ascending cholinergic gating system (see below) than of the frequency control system, since intra-DMPH administration of the cholinergic antagonist, atropine, blocks theta (Bland *et al*. 1994).

Vertes identified two additional synchronizing pathways ascending from the pons in urethane-anaesthetized animals. Their exact relation to the RPO, the DMPH, and the SUMM has not yet been determined. One of these arises in the pedunculo-pontine tegmental nucleus (PPT), and also perhaps the latero-dorsal tegmental nucleus (LDT). Unlike the RPO–SUMM pathway, it shows a very modest intensity–frequency relationship, and its main rostral output appears to course well above the SUMM. Injections of procaine into the SUMM have no effect on PPT-elicited theta rhythm; and we have shown (McNaughton *et al*. 1997) that this pathway has a permissive/gating effect on theta (like that of the cholinergic system described below, for which indeed it may be the neural substrate), but has no influence on theta frequency. Bringmann (1997) has also shown that systemic administration of nicotine can reverse the theta loss in the occipital cortex produced by lesions of the PPT.

A surprising feature of the cholinergic gating of theta is that this appears to be controlled by a cooperative reticulum of reciprocal interconnections rather than a simple ascending pathway. Thus, small (0.2 μl) injections of procaine into any of the ascending branches of the PPT system (including the projections to the superior colliculus, substantia nigra, midbrain reticular formation, thalamus, and amygdala) block the elicitation of theta by PPT stimulation (McNaughton *et al*. 1997). Similarly, mapping with injections of scopolamine shows that each of the superior colliculus, substantia nigra, and midbrain reticular formation contains cholinergic synapses which are activated by PPT stimulation and which contribute to theta elicitation. Taken together, these data suggest that PPT stimulation activates much of the widespread ascending cholinergic system in the diencephalon, and that the different nuclei activated by this stimulation cooperate via reciprocal interconnections, so acting as a reticulum.

Positive feedback would be expected to contribute strongly to the active state in a system of the kind sketched in the preceding paragraph. Such feedback can account for the fact that only a modest amount of suppression of any part of the system was sufficient to depress the whole system below the threshold for eliciting theta. It is perhaps relevant that all of the areas concerned in the system, except the amygdala, have, at one time or another, been implicated in different aspects of ‘attention’. In this regard, while the amygdala may be part of a tonic cholinergic theta control network, very few cells there show theta modulation (Paré and Gaudreau 1996); and this modulation can be accounted for by input to the amygdala from the hippocampal formation rather than because of any direct control of the amygdala by the medial septal pacemaker.

The basic picture we have built up so far, then, is that tonic activity in areas such as the RPO and DMPH (where there are non-phasic cells which increase their firing rate during theta, i.e. ‘tonic theta-on cells’ in Bland’s classification) is fed to the SUMM (and some other interconnected nucleus or nuclei), where it is integrated and the summed input converted to the frequency of phasic output. This output is relayed to the MS/DBB and thence to the hippocampal formation (including the entorhinal cortex and posterior cingulate) and from there to the mammillary bodies. In parallel with this route is a complex, probably cholinergic, system which possibly arises in the PPT, but which is more likely to behave as a cooperative reticulum with multiple entry points involving at least the PPT, superior colliculus, substantia nigra pars compacta, reticular nuclei at the level of the superior colliculus and substantia nigra, the amygdala (Dringenberg and Vanderwolf 1996), and probably the DMPH as well.

There are a number of reasons for thinking that the subcortical control of frequency involves more than a simple RPO–SUMM–MS system.

First, while we have shown that procaine and chlordiazepoxide injections into the SUMM in both urethanized and free-moving animals reduce reticular-elicited theta frequency and, in the case of procaine, amplitude, Thinschmidt (1993) has reported that lesions of the SUMM, which

in at least one case appear to have destroyed all of it, did not eliminate behaviourally-elicited theta, nor indeed affect either frequency or amplitude of theta to a large extent. Thinschmidt suggests a variety of explanations (including functional reorganization) for the discrepancy between the effects of procaine (which he replicated) and electrolytic lesion, respectively. Perhaps the most interesting is that the 'septo-hippocampal system may have received enough input through alternative pathways to appear unaffected following SUM lesions' (Thinschmidt 1993, p. 51).

We have data which suggest a modification of this hypothesis. We injected procaine into Thinschmidt (1993) SUMM in freely moving animals and found that, unlike effects under urethane, only a modest reduction in frequency could be obtained. Moreover, in a few animals given repeated procaine injections, the injections produced a lesion which, on histology, proved to eliminate all of the SUMM. These lesions both eliminated the procaine effect and reduced pre-procaine theta frequency to values similar to those obtained with procaine before lesion (McNaughton *et al*. 1995). This pattern of results suggests that there are at least two quite distinct pathways controlling theta frequency: one synapsing in the SUMM and relatively insensitive to urethane, and one synapsing elsewhere and blocked by urethane. The urethane-sensitive system may also have frequency-determining nuclei in the hypothalamus, since movement associated theta activity has been recorded from a range of hypothalamic sites (Slawinska and Kasicki 1995).

We also found that injections into the SUMM, which reduced frequency when this was elicited by RPO stimulation, had no effect on theta frequency when the same rats were tested during exploration of an open field (Pan and McNaughton 1996). Movement per se (present in the open field but absent with RPO stimulation) is not the sole determinant here, because injections into the SUMM reduced frequency (as well as impairing learning) when rats were tested in the water maze (Pan and McNaughton 1997). This observation suggests that the parallel (but reciprocally connected) pathways may be to some extent behaviourally separable. Thinschmidt's (1993; see above) tests of behaviour (which were of an open-field type) may therefore have been of a type that produces minimal involvement of the SUMM and maximal involvement of the other frequency controlling nuclei.

Similar results were found by Faris and Sainsbury (1990) with lesions of the RPO: these did not affect either movement-related or immobility-related theta. These authors suggested, therefore, that the RPO 'is one of a number of diffuse inputs to the hippocampus which when stimulated is sufficient to drive the [theta] system but is not a necessary component to the integrity of the system' (Faris and Sainsbury 1990, p. 1198). However, like Thinschmidt's, their recordings were made in an open field-like situation. It seems likely, therefore, that the RPO is important for theta activity, but only under specific behavioural circumstances (most likely when the animal is required to inhibit movement, see Appendix 6).

As yet we have very little idea as to the number or nature of additional nuclei involved in tonic intensity/phasic frequency transduction. There are parts of the hypothalamus from which both theta rhythm can be recorded and movement elicited by electrical stimulation (Slawinska and Kasicki 1995). Interestingly, stimulation of the related posterior hypothalamus also elicits theta and movement; and, in this case, the movement as well as the theta can be blocked by septal injections of procaine (Oddie *et al*. 1996). These hypothalamic areas could, then, be part of the second(/third) frequency control system which our results suggest must exist in addition to that provided by the SUMM. The dorsal raphe is another possibility (Kocsis and Vertes 1992). If so, the theta activity of dorsal raphe cells should be insensitive to septal procaine; unfortunately, this has not yet been tested (Vertes, personal communication). However, theta activity of median raphe cells is more coherent than that of dorsal raphe cells (Kocsis and Vertes 1996) and yet is

blocked by septal procaine (unpublished data cited by Partlo and Sainsbury 1996). Because of this, and for reasons given below, we will assume that the theta activity of all raphe cells is (like that of mammillary body cells) the result of feedback from the septo-hippocampal system or input from the SUMM (Vertes 1992), and that their output does not control the phasic firing of hippocampal cells. Rather, we will argue, the dorsal raphe provides a gating input of the same type as septal cholinergic input. The fact that the theta-controlling nuclei additional to the SUMM appear to be suppressed by urethane means that it will be a long time before we have a clear idea of their number or organization.

On the data so far, then, we can conclude that the frequency of theta activity is determined, in at least some cases, caudal to the medial septum. This process involves a tonic intensity–phasic frequency transduction in the medial supramammillary nucleus and in at least one other nucleus. The nuclei encoding frequency must be interconnected in at least two ways: (1) via strong one–many inhibitory connections, since independent oscillators would produce beats, and these are not observed; (2) via excitatory connections, since our data show that elimination of the SUMMreduces frequency, implying a synergistic interaction with the undamaged elements of the system. The various nuclei must, therefore, be phase-locked as a whole and act as an integrator of ascending input as a whole.

Given the idea of a number of separate (but interconnected) nuclei coding for theta frequency, and the topographic organization of the cholinergic and other projections from the MS/DBB, it would not be too surprising if there were also some form of topographic (not necessarily matching) relation of the inputs to the MS/DBB pacemaker from the frequency coding nuclei. Something of this sort is likely to underlie the finding that different MS/DBB lesions can doubly dissociate theta during waking from theta during paradoxical sleep (Monmaur *et al.* 1979).

A5.10 The determination of theta frequency

Considerable effort has gone into the pharmacological analysis of septal and hippocampal synapses. Unfortunately, as we have just seen, as far as the control of frequency is concerned, the supramammillary and related nuclei would be better targets, but very little is known about them.

The key question is how tonic afferent input from areas like the DMPH and RPO can be converted to phasic, theta activity. One possibility is some intrinsic membrane property of the cells. Test of this possibility requires intracellular recordings from the SUMM *in vivo*. Given the difficulty of obtaining even extracellular isolation of the small cells of the SUMM, it may be necessary to wait a long time for this.

The simplest synaptic possibility is that of recurrent inhibition. Collaterals of excitatory projection cells in the SUMM would fire recurrent inhibitory interneurons. These would then inhibit the projection cells at a fixed latency, and so produce a fixed-length burst of action potentials. This should, in turn, provide a fixed amount of inhibition decaying at a fixed rate over time. The duration of functional inhibition of the projection cells would then be inversely related to the intensity of afferent drive from the reticular formation: greater afferent excitation overcoming the decaying inhibition at an earlier point than would weaker excitation. A system of this kind could give rise to the linear relationship between the strength of reticular stimulation and the frequency of theta activity.

The most likely neurotransmitter for the production of this effect would be GABA. We have tested both $GABA_A$ and $GABA_B$ agonists with reticular elicitation of theta. Systemic injections of muscimol (a $GABA_A$ agonist) had two surprising effects. First, its initial action was to produce an increase in frequency of theta, as opposed to the decrease in frequency or blockade of theta which would be predicted. Second, it had a U-shaped dose–response curve (over a very

wide range of doses), so that at the highest doses it had no effect (Coop *et al.* 1991). $GABA_A$ receptors come in a variety of flavours, in particular a high- and a low-affinity version. A possibility, to which we will return, is that the increase in frequency is obtained by the action of muscimol on a high-affinity $GABA_A$ site, while the reversal of this effect (an effective decrease in frequency) is obtained at a low-affinity $GABA_A$ site. Baclofen (a $GABA_B$ agonist) produced a decrease in frequency at high, essentially sedative, doses (Coop *et al.* 1991), which interestingly are also the doses required to produce impairments in spatial learning (McNamara and Skelton 1996).

The fact that GABA agonists produce frequency decreases (absolute or relative) only at high doses raises the question of whether they are changing frequency simply by producing behavioural sedation. However, their action appears more specific than that. As can be seen from Fig. 9.2, the *frequency* of theta elicited by reticular stimulation is unaffected by blockade of dopaminergic, noradrenergic, serotonergic, or cholinergic systems. Yet a number of the drugs used produced considerable behavioural sedation. (As we will consider in more depth later, cholinergic antagonists block the occurrence of theta in an intermittent fashion, but they produce behavioural activation at the doses used.)

By contrast, many classical and novel anxiolytic drugs (the latter producing minimal sedation) reduce the frequency of reticular-elicited theta (Chapter 1). A single possible exception to this rule is ondansetron, which fails to change reticular-elicited theta (McNaughton, unpublished observations) and in fact appears to increase the frequency of spontaneous theta (Stäubli and Xu 1995). We argued earlier, however, that there is as yet no convincing evidence that ondansetron is anxiolytic. As we noted in Chapter 4, novel and classical anxiolytics share very few side-effects. Their similarity in this test is therefore very suggestive that a change in theta frequency may contribute to their anxiolytic action. The fact that this test shows similar effects for imipramine as well as for all the other drugs conventionally used as *clinical* anxiolytics is particularly important for the theory of this book, as there are a wide variety of anxiolytic screening tests which do not detect imipramine. It is particularly interesting, in this context, that novel and classical anxiolytics change theta through quite distinct mechanisms. The effects of benzodiazepines are blocked by the benzodiazepine receptor blocker Ro15-1788, but not by the $5\text{-}HT_{1A}$ receptor blocker pindolol, while the reverse is true of buspirone (Coop *et al.* 1992). (We have also shown that the effects of buspirone are not mediated by dopamine D_2, $5\text{-}HT_2$, or $5\text{-}HT_3$ receptors; Coop and McNaughton 1991.) *Pindolol* also blocks the effects of imipramine, while depletion of 5-HT with *p*-chlorophenylalanine blocks the effects of imipramine but not buspirone (Zhu and McNaughton 1994*c*; see also Hirose *et al*. 1990; Kasamo *et al*. 1994). Both imipramine and buspirone, therefore, must be acting presynaptically or postsynaptically through $5\text{-}HT_{1A}$ receptors on neurons which do not themselves use 5-HT (i.e. the relevant $5\text{-}HT_{1A}$ receptors are not autoreceptors); and this presynaptic or postsynaptic action must be on $5\text{-}HT_{1A}$ receptors which are not tonically active in normal freely moving animals. These effects are obtained both when the animal is immobile and theta is elicited by *reticular stimulation* (Zhu and McNaughton 1994*c*) and when theta accompanies movement (Kasamo *et al*. 1994).

We can conclude that, in the system which determines theta frequency in rats, imipramine increases 5-HT at $5\text{-}HT_{1A}$ receptors and buspirone acts as an agonist at these receptors, while benzodiazepines act quite separately at the benzodiazepine receptor. These separate actions have effects which ultimately converge on a final common path to reduce frequency. The benzodiazepines probably amplify the effects of GABA and so increase recurrent inhibition in the supramammillary (and related) nuclei since, as noted above, Ro15-1788 injected into this nucleus appears to reduce the effects of peripherally administered chlordiazepoxide, while chlordiazepoxide injected into the SUMM reduces frequency. Where buspirone and imipramine act is not yet known, but it does not appear to be in the SUMM (McNaughton and Samarasinha,

in preparation).

There are no reports of benzodiazepine receptors being linked to $GABA_B$ receptors. Given the results with muscimol and baclofen, then, it would seem likely that the benzodiazepines act to increase the sensitivity to GABA at the low-affinity $GABA_A$ site (since $GABA_A$ agonism at the high-affinity site produces an increase in frequency). Luckily for this inference 'benzodiazepines influence GABA binding only to the low affinity sites' (Johnston 1990).

As we noted above, muscarinic cholinergic blockers, depletion of noradrenaline, depletion of serotonin, and blockade of dopamine do not reduce frequency and neither does blockade of monoamine oxidase (Zhu and McNaughton 1995*a*). The lack of involvement of cholinergic and serotonergic systems (other than 5-HT_{1A}) in frequency control is particularly important for our consideration of 'types of theta' later.

A5.11 Anxiolytics and the reticular elicitation of theta rhythm

We noted above that a reduction in the frequency of theta is produced not only by benzodiazepines (via an increase in the effects of endogenously released GABA) but also by drugs such as buspirone and imipramine. These latter drugs have no known action in common with benzodiazepines in the clinic other than anxiolysis. In particular, they are not anticonvulsant, hypnotic, muscle relaxant, or addictive. The commonality of action of all these anxiolytic drugs on theta frequency is quite surprising given the general failure of most animal models to achieve this. There are a number of features of the pharmacology of their effects on reticular-elicited theta which are important for interpreting correlations with clinical action.

First, long-term administration produces little change in the effects on theta frequency of benzodiazepines, buspirone, or imipramine (Zhu and McNaughton 1991*a*,*b*), whereas all these drugs require at least a week's administration to achieve their full clinical effect. This is consistent with the argument put forward in Appendix 1 that the anxiolytic drugs impair the acquisition of anxiety rather than necessarily impairing well-learned anxiety itself directly.

Second, the acute effects of the monoamine oxidase inhibitor and antidepressant, phenelzine, and the effects of antipsychotic drugs are totally unlike those of anxiolytics (McNaughton *et al.* 1986; Zhu and McNaughton 1994*b*). The effects of the anxiolytics on theta frequency are more likely, then, to be related to generalized anxiety than to schizophrenia, endogenous depression, or atypical depression.

Third, the action of buspirone appears slightly different from that of classical anxiolytics in that it does not change the slope of the function relating stimulation intensity to frequency. For reasons which we will discuss below in relation to septal stimulation, we would attribute this to a release by buspirone of corticosterone. Certainly, when chlordiazepoxide is administered together with corticosterone, similar effects to those of buspirone are produced (McNaughton and Coop 1991). It is probably this release of corticosterone which gives buspirone its U-shaped dose–response curve in many animal tests, and probably also in the clinic. This release of corticosterone can be presumed to have an anxiolytic-blocking or anxiogenic effect (Johnstone and File 1988). Tolerance to the antagonistic effects of corticosterone is also a possible explanation for the slow onset of *buspirone's* effects; see Zhu and McNaughton 1995*c*; McNaughton *et al.* 1996).

Fourth, a reduction in frequency when that frequency is low would have the effect of eliminating theta under such conditions. This has been observed by Caudarella *et al*. (1987), who found a

virtual elimination of theta by a benzodiazepine in a forced running situation when the moving belt was stationary. Of particular interest was a second observation. ‘Under diazepam, the mice . . . engaged far more often in a pattern of behaviour that they engaged in only occasionally without the drug: a pattern of walking quickly . . . followed by riding back immobile on the moving belt. . . . The EEG was irregular during periods of walking or running . . . [and] only if the animal had just stopped moving . . . very low frequency [theta] predominate[d]’ (Caudarella *et al*. 1987, pp. 208–9). This suggests that the reduction in the higher frequency of theta normally observed when the animal is running had disrupted the normal pattern of running and replaced it with a type of running closer to that of a fixed action pattern (see Appendix 6). All of the above data suggest that apparently modest changes in theta frequency may be functionally very important. (Note also that increases in frequency may be as dysfunctional as decreases; Ammassari-Teule *et al.* 1991).

In contrast to their effects on theta frequency, 5-HT_{1A} agonists appear to increase theta amplitude (Marrosu *et al*. 1996) and to elicit theta if they are injected into the median raphe (Kinney *et al.* 1996). This may be an additional reason for a less extreme behavioural effect with these drugs than with benzodiazepines.

A5.12 The septal pacemaker

Although we have shown that the supramammillary nucleus determines the frequency of theta, we also concluded that its phasic output is likely to be relayed by the medial septum. Our new data do not, then, controvert the well-established view that cells in the medial septal area are the pacemakers (in the simple sense we defined earlier) for hippocampal theta (Brûcke *et al*. 1959; Stumpf 1965). This section will look at the pathways and mechanisms which underlie the septal pacemaking of theta.

As noted in Appendix 4, there is a topographic relation between the septum and the hippocampus, with more ventrolateral aspects of the septum projecting to more temporal aspects of the hippocampus. This organization is also evident within the fornix–fimbria in relation to theta. Theta in the dorsal hippocampus depends on fibres travelling in the fornix superior, while theta in the ventral hippocampus depends on fibres travelling in the fimbria (Myhrer 1975; Rawlins *et al*. 1979). Andersen *et al*. (1979) report that the septal fibres controlling theta in the dentate generator take a medial route to the dorsal hippocampus, but travel more ventrally than those interrupted by the dorsal fornix lesions used by Rawlins *et al*. (1979); this suggests a dorsal–ventral organization of septal fibres controlling CA1 and dentate theta respectively.

It is of particular interest to note that unilateral fornix–fimbria lesions abolish theta ipsilaterally and that, in this preparation, relatively normal activity can be restored by grafts of foetal septal tissue (and to some extent by foetal hippocampal tissue) if these are placed between the septum and hippocampus, but not if septal suspensions are placed into the hippocampus itself (Buzsáki *et al*. 1987*a*). This is very strong evidence that it is the integrity of the septo-hippocampal pathway that is critical for theta activity. Interestingly, the hippocampal tissue grafts themselves acquired functional connections from perforant path and showed theta activity, and occasionally even theta rhythm (Buzsáki *et al*. 1987*b*), phase locked to the theta in the contralateral intact hippocampus. In this case, then, it appears that connections from the intact septum to the graft reinstated theta activity in the graft but not in the deafferented hippocampus. We can conclude that neonatal septal cells are largely programmed to create a pacemaker nucleus (this being a second copy in the case of the septal graft) which connects to the hippocampus, while hippocampal cells are programmed to receive input from this pacemaker and from the entorhinal cortex and to integrate them.

The observations on the topographic organization of the theta pathway are consistent with the known anatomy of the cholinergic projection from the medial septal area to the hippocampus (Appendix 10); and the disappearance of theta in different regions of the hippocampus correlates well with the disappearance of acetylcholinesterase after different lesions (Rawlins *et al*. 1979).

In addition to the direct GABAergic projection from the septum, inhibitory actions of GABA (Stefanis 1964; Curtis *et al.* 1970) are likely to arise from recurrent and feedforward inhibition (which in some cases will be mediated by the same interneuron; Buhl *et al*. 1996). There is evidence (O'Keefe and Nadel 1978, pp. 117–18, 146–7) that each basket cell is capable of inhibiting hundreds of projection cells (whether in CA1, CA3, or the dentate gyrus). Thus, as Lynch *et al*. (1978) point out, 'By innervating the interneuron population the numerically inferior septal inputs to the hippocampus could exert an influence that would be far greater than could be achieved by their direct termination on hippocampal pyramidal or granule cell dendrites'. Whether inhibition arises directly or indirectly from septal input, Andersen (1978, p. 312) concluded from observations of intracellular membrane potential oscillation in dentate granule cells, occurring in phase with extracellularly recorded theta rhythm, that 'the rhythm is caused by regularly occurring inhibition, cutting into the ongoing steady background activity.' One consequence of this would be that the theta rhythm would maintain 'large areas of the hippocampus . . . in the same, or related, phases of excitability' (O'Keefe and Nadel 1978, p. 148). As we have noted, the SUMM, MS/DBB, dorsal raphe, and particularly the entorhinal cortex and posterior cingulate will also share this relation.

An important point about the circuitry we have just invoked to explain theta activity in SUMMcells, the action of benzodiazepines on SUM, and the relations between reticular input and theta frequency, is that the same one–many recurrent inhibitory circuitry is also present in the medial septum and in all the targets of medial septal afferents within the hippocampal formation.

Remembrance of this fact can help us to avoid a number of false conclusions. For example, it leads to the prediction that tonic activation of either the septum or the hippocampus would produce something almost indistinguishable from theta activity. The occurrence of carbachol-induced 'theta' from the septum or in slices of hippocampus, therefore, is evidence for the presence of intrinsic tuning, but provides no evidence that this tuning normally contributes to the control of theta *frequency*. Indeed, 'direct cholinergic activation of hippocampal formation theta activity appeared to functionally deafferentate [sic] the dorso-medial-posterior hypothalamus—medial septum/diagonal band—hippocampal formation pathway' (Christie 1989, p. iii; see also Vinogradova *et al*. 1993*a*). Likewise, the bursting of septal cells, after separation from their medial forebrain bundle input, argues simply that septal cells, like hippocampal cells, can auto-oscillate given an appropriate tonic level of depolarization (Vinogradova *et al*. 1980). This auto-oscillation of hippocampal cells is at a frequency below the normal theta range, even when it is blocking the effects of higher frequency septal input (Vinogradova *et al*. 1993*a*). Most importantly, manipulation of the cholinergic system changes the number of cells and the stability of the cells showing theta activity, but without any change in the frequency of theta modulation (Brazhnik *et al*. 1993; McNaughton and Sedgwick 1978).

This is not to say that recurrent inhibition in the septum and hippocampus is not important for theta activity. The cells of the SUMM (in contrast to those of the lateral nucleus) are very small, and the entire SUM–medial septum–hippocampus pathway appears to be unmyelinated. Conduction times will therefore be long and variability in conduction time high. The recurrent inhibition at each relay station in the pathway, therefore, will be essential to keep the outputs in phase. However, this recurrent inhibition will not contribute to the interval between bursts under physiological conditions.

So far we have presented the primary drive for the production of theta activity as largely excitatory. Certainly the input from the reticular system to the SUMM is likely to be excitatory. However, at least under urethane, the phasic input seems to be largely inhibitory in CA1 and CA3 (Leung and Yim 1986; Fox 1989). This is likely to involve both direct GABAergic inhibition from the septum and also disinhibition, since there is good evidence that GABAergic cells from the septum synapse on GABAergic cells in the hippocampus (Freund and Antal 1988). Certainly, there does seem to be phasic inhibition of tonically active inhibitory hippocampal interneurons (Konopacki *et al*. 1992*b*; see also Lopes da Silva *et al*. 1990, p. 483). This could be coupled with the phasic inhibition of principal cells suggested by Andersen. Ylinen *et al*. (1995*b*) have made intracellular recordings from principal and basket cells which show that, in anaesthetized rats, both types of cell show intracellular theta oscillations which reverse at the chloride potential. This dependence on chloride suggests that both principal cells and interneurons receive a phasic inhibitory drive. There is no reason why the same should not be true of the phasic inputs from the SUMMto the septum. But this would mean that, in addition to the phasic input, we would need some intrinsic or extrinsic source of depolarization before hippocampal (and possibly septal) cells would show any phasic firing (although see Vinogradova 1995). Why should we postulate such a complicated parallel excitatory/inhibitory system when a simple excitatory one would do? The answer is simply that there is good evidence that the system is built in this more complicated way—with interesting functional consequences (see the section on gating below).

There is some disagreement in the literature as to the nature of the afferent drive which gives rise to intracellular theta in that, in the dentate and in CA1–CA3, there are some reports that it is almost totally excitatory (Muñoz *et al*. 1990; Núñez *et al*. 1987), whereas the other reports we cited above suggest that in CA1 and CA3 it is almost totally inhibitory. While Núñez *et al*. argue that the drugs used in the different preparations are unlikely to be the source of the discrepancy, they failed to note that their preparation differed from those finding inhibition in using curare as well as urethane (Vertes and Koscis 1997). The excitatory components, themselves, do not appear to reflect incoming phasic EPSPs 'but rather involve Na^+ dependent, intrinsic membrane potential oscillations evoked by [tonic] depolarization of the pyramidal cell membrane' (Vertes and Koscis 1997). Whatever the resolution of these issues, we are probably best to conclude that both excitatory and inhibitory drive can contribute to theta in varying amounts under varying conditions. This is particularly true given the evidence from current source density analysis for there being a very large number of independent sources and sinks concurrently contributing to theta rhythm.

At present all that is clear is that septal pacemaking input is not simply phasic excitation. Indeed, phasic excitation of principal cells is the one possibility for which there is almost no evidence. Rather, as reviewed by Stewart and Fox (1990), there are a number of concurrent influences originating in the septum. There is tonic cholinergic excitation of principal cells, which may arrive phasically or tonically (Vertes and Koscis 1997) but has a net tonic effect (see the section on gating below); there is phasic cholinergic excitation of inhibitory interneurons (producing a net phasic inhibition); there is direct phasic GABAergic inhibition; and there is phasic GABAergic inhibition of GABAergic inhibitory interneurons (producing a net phasic disinhibition). To this must be added a net tonic excitatory serotonergic influence (see section on gating), frequency-specific, noradrenergically-gated intrahemispheric phasic excitation (see section on septal driving below), and some phasic excitation arriving via the perforant path. These influences, and their relation to hippocampal circuitry, are represented diagrammatically in Fig. 10.2.

In this context, it is worth noting that any phasic cholinergic excitation of the hippocampus is likely to have been phase locked by recurrent inhibition in the septum. We have already argued

that recurrent GABAergic inhibitory circuitry keeps the GABAergic projection to the hippocampus tightly phase locked as a result of a one–many connectivity, and that this will combat the conduction-induced phase dispersion between the SUMM and the MS/DBB. The same arguments would require phase locking of any phasic cholinergic excitation. Even when deafferented from the medial forebrain bundle, the septum contains circuitry which maintains rhythmicity via inhibitory interneurons (Vinogradova *et al*. 1980); and injections of the GABA agonist muscimol into the septum not only eliminate theta but also significantly decrease acetylcholine utilization in the hippocampus. These data suggest that at least some cholinergic projection cells are subject to the global phase-locking GABAergic inhibition in the medial septum. Other cells (tonic theta-on cells in Bland's terminology) are likely to have similar afferents but to lack the GABAergic input, and perhaps project to somewhat different hippocampal cells.

In the freely moving animal it has been reported that fewer septal cells are obviously rhythmic than under anaesthesia; that many cells which fire phase-locked to hippocampal theta fire only occasionally rather than in a regular rhythmic pattern; and that some cells 'displayed rhythmic activity only when the rat ran in a specific direction'(King *et al.* 1998, p. 464). These observations suggest that there may not only be multiple types of cell within the septal pacemaker, but also that different populations of septal cells may be involved in controlling hippocampal rhythmicity under different behavioural conditions.

A5.13 The pharmacology of septal driving of theta rhythm

(See Fig. 9.1 in the printed text for details of theta driving, its pharmacology, and citations to relevant papers for the material covered in the figure.)

Once theta frequency has been determined, the information is transmitted to the septum. Unfortunately, there has been little analysis of this specific input. Studies (in free-moving animals) of the effects of phasic stimulation of the SUMM(or perhaps the medial forebrain bundle) on medial septal cell activity would be very useful.

Phasic stimulation of the medial forebrain bundle entrains septal theta activity (with cell firing locked either to the bursts or the inhibitory pauses). This effect is not blocked by systemic anticholinergics. Furthermore, systemic physostigmine (an acetylcholinesterase inhibitor) induced regular theta-like activity, but also rendered the cells insensitive to medial forebrain bundle stimulation (Brazhnik and Vinogradova 1988). These results suggest that the 'theta activity' which can be produced by application of cholinergic drugs to the septum or hippocampus (see above) represents a functional deafferentation of the normal ascending theta control system, rather than its activation (see also Monmaur and Breton 1991); and the resultant oscillations may be closer to a paroxysmal discharge than to theta activity.

Phasic stimulation, which can drive hippocampal theta rhythm from the septum, and its pharmacology have been studied extensively in freely moving animals. The threshold for elicitation of theta has been of particular interest. To study this, one stimulates the septum at theta frequencies to elicit theta (Fig. 9.1A, B) and adjusts the stimulating current to determine the minimal (threshold) stimulation required just to elicit theta for any particular frequency. In the free-moving male rat, this produces a characteristic U-shaped function where frequencies at the extreme of the normally observed range are most difficult to drive and intermediate frequencies are easiest, with a minimum being obtained at a frequency of 7.7 Hz (an interpulse interval of 130 ms). This function is not produced with evoked responses to equivalent stimulation (Fig. 9.1A, B).

The U-shaped function is reliably observed in individual male rats of several strains (Gray and

Ball 1970; James *et al*. 1977) and is dependent on circulating testosterone. Females or castrated males show a flat function, but the U-shaped function can be produced in both by injections of testosterone (Drewett *et al*. 1977). In male rats, the U-shape appears abruptly between 15 and 16 days of age (Lanfumey *et al.* 1982).

We have carried out an extensive pharmacological analysis of this function. The function is flattened by depletion of noradrenaline and by increased GABAergic action (at $GABA_A$ or $GABA_B$ receptors) (Gray *et al*. 1975). The minimum in the curve is shifted to a lower frequency (6.9 Hz, 145 ms) by depletion of serotonin, by manipulation of the pituitary–adrenal axis, and by administration of footshock (Valero and Gray, unpublished). The results shown in the figure are only a selection from a range of manipulations, all of which are consistent with the results shown.

Since septal serotonergic terminals were unaffected in the experiment illustrated (the injection of the serotonin-specific neurotoxin 5,7-dihydroxytryptamine was made into the fornix–fimbria and cingulum bundle), these changes, and probably also those produced by dorsal noradrenergic bundle lesions, are produced within the hippocampus itself (McNaughton *et al*. 1980). Since, in the case of the loss of noradrenaline, the effect on septal driving is *contralateral* to the loss of noradrenaline (Gray *et al*. 1975), it is likely that this effect, and possibly also that of changing serotonin input, is the result of changing the capacity of one hippocampus to interact with the other. This effect could be achieved via feedback from the hippocampus to the septum, since section of the fimbria has the same effect (Rawlins *et al*. 1979), or it could be mediated commissurally, or via the entorhinal cortex (Deadwyler *et al.* 1975).

McLennan and Miller (1974, 1976) reported electrophysiological observations suggesting that feedback via the fimbria from the hippocampus activates a frequency gating mechanism in the lateral septal nucleus. The 7.7 Hz minimum in the driving curve may be related to the capacity of a medial septal pulse to potentiate the population spike response to a subsequent commissural pulse, since this shows a maximal effect (in mice) in the region of 130 ms (Jeantet and Jaffard 1982). Functionally, this interaction of the septal and commissural inputs may relate to the impressive capacity for interhemispheric integration of information acquired under temporary unilateral hippocampal blockade (Fenton *et al.* 1995). That is, the role of theta in consolidation (see Appendix 7) may include a role in the control of interhemispheric transfer.

Thus, the noradrenergic input to the septo-hippocampal system from the locus coeruleus lowers thresholds in the middle of the frequency range (possibly by inhibiting inhibitory interneurons, given the effects of GABA agonists), while serotonergic input eliminates a minimum threshold which would otherwise be observed at 6.9 Hz. The possibility that these two effects are independent of each other is discussed in relation to the effects of buspirone, considered below. Noradrenaline may also have inhibitory effects, reducing the amplitude of theta (Heynen and Sainsbury 1991), although this latter effect may depend on the presence of urethane anaesthesia.

The effects of GABA agonists, noted above, immediately suggest the possibility that classical anxiolytic drugs will affect septal driving since, as we noted in Appendix 1, they are all indirect GABA agonists. However, we will consider them here together with buspirone and imipramine since, while the latter are, as we have noted already, pharmacologically quite different from the classical anxiolytics, one might predict from the drug–lesion comparison of Chapter 1 that these drugs would have effects similar to those of the classical anxiolytics. As was discussed in Chapter 1, this is indeed the case.

As with the effects of the anxiolytic drugs on reticular-elicited frequency, this common effect is quite surprising. It should also be noted that it is completely independent of the reticular effect, since the latter is (a) determined before the septum, (b) not frequency dependent, and (c)

unaffected by depletion of noradrenaline (McNaughton and Sedgwick 1978).

Like the reticular test for stimulation of theta (but in contrast to Schaffer collateral stimulation; Xu *et al*. 1997), the septal test shows only minimal variations with repeated injections over many days of chlordiazepoxide, buspirone, or imipramine (Zhu and McNaughton 1994; 1995*b*); it shows effects of the antidepressant phenelzine opposite to those of anxiolytics (including the anxiolytic antidepressant imipramine; Zhu and McNaughton 1994); and the minor differences between the effects of buspirone and chlordiazepoxide are removed if injection of chlordiazepoxide is combined with injection of corticosterone (McNaughton and Coop 1991).

The latter result is of particular interest in relation to the possible independence of changes in the 7.7 Hz minimum and changes in the 6.9 Hz minimum. There are complicated interactions between serotonin depletion and manipulations of the pituitary–adrenal axis. Adrenalectomy and injections of corticosterone have the *same* effect as each other—producing a 6.9 Hz minimum—which is surprising given their opposite effects on the pituitary–adrenal axis. The combination of adrenalectomy and corticosterone returns the curve to normal (Azmitia *et al*. 1984). As we noted, depletion of serotonin also produces a 6.9 Hz minimum; and, which is difficult to explain, combination of serotonin depletion with either adrenalectomy or corticosterone returns the curve to normal (Azmitia *et al*. 1984). Most puzzling of all, given this last result, adrenalectomy plus corticosterone plus serotonergic depletion produces a 6.9 Hz minimum (Azmitia *et al*. 1984). While a complete explanation of these various effects is not available, a key point to note in all of these experiments is that the depth of the 6.9 Hz minimum produced and its variations with treatment remain at or below the depth of the 7.7 Hz minimum when this appears. By contrast, when corticosterone is combined with chlordiazepoxide (or when buspirone is given) there is a modest 6.9 Hz minimum in a curve which is, throughout, well above the value for the 7.7 Hz minimum in the control condition. It seems probable, therefore, that the two minima are under entirely separate neural control, with the deepest 6.9 Hz minimum resulting from the superposition of a modest 6.9 Hz minimum on a curve already lowered throughout its range and maximally lowered at 7.7 Hz. This would be reasonable if each minimum (or rather the depression of thresholds throughout the frequency range which accompany the minimum) results from the activation of a separate neural loop tuned to the appropriate frequency.

A5.14 Gating of theta activity

The phasic inhibitory or disinhibitory inputs which we discussed above (see also Stewart and Fox 1990) may seem unduly complicated, compared to a phasic excitatory input, if we view the purpose of this input as the *production* of theta activity. Instead, suppose that the phasic input is there to *synchronize* activity if and only if this is produced by other inputs. Under these conditions, inhibition or disinhibition is the best method. An advantage of this purely synchronizing view of the phasic input is that it allows us to resolve a number of controversies and complexities in the pharmacological and anatomical literature on theta activity.

The nub of the arguments we will put here is that, whenever there is theta activity in structures receiving input from the MS/DBB (and also perhaps for MS/DBB cells themselves), the specific time at which the cells fire is determined by a largely inhibitory or disinhibitory input. It follows, therefore, that simply activating this phasic input will not, of itself, produce theta activity. Other, net excitatory inputs will be required in addition. In at least one case, we will see, this input is effectively tonic rather than phasic and so we can view it as ‘gating’ theta activity. We have then a phasic input which is, in principle, invisible (except at the intracellular level) and excitatory inputs (which need not be phasic) which cause certain cells to fire, with the timing of their firing determined by the phasic inhibitory/disinhibitory input.

To put this concept to work we must review (albeit in a rather compact fashion) the mass of literature on the pharmacology of hippocampal recording which has accumulated on the 'two types of theta'. This literature has to be reconciled with the evidence that there is a single, septal pacemaker for both 'types', which would then be distinguished simply by 'different levels of rostral brain stem activation' (Vinogradova *et al*. 1980, p. 365). In this context it is worth noting that at least some MS/DBB cells show a continuous intracellular theta rhythm, suggesting a continuous 'clock'-like function against a background of only occasional hippocampal theta rhythm (Barrenechea *et al*. 1995; see also Vinogradova 1995).

The literature on the two types of theta stems from work carried out originally by Vanderwolf (e.g. 1969; see Appendix 6; Vanderwolf and Leung 1983). He set out to relate the occurrence and frequency of theta to specific behaviours and classes of behaviour as such without any appeal to unseen psychological processes. He succeeded admirably in attempts to link specific behaviours to theta, but it has proved difficult to determine any underlying factor which allows distinction between theta-related and theta-non-related behaviours. As a result, these are best termed, at present, Type 1 and Type 2 behaviours (e.g. Vanderwolf 1988).

Type 2 behaviours (i.e. theta non-related) can normally be clearly distinguished from Type 1. However, in the original classification, Type 2 'behaviours' included immobility. It has now become clear that theta can occur during immobility. This could destroy the very basis of the Type 1/Type 2 distinction. However, immobility itself could clearly result from activation of more than one type of behavioural system and becomes a special case where we cannot easily determine the type of behaviour.

We will discuss the details of the Type 1/Type 2 classification of behaviour in much more detail in Appendix 6, but have mentioned it here because it provides the historical context for certain views of the 'two types of theta'—and a source of potential confusion in the terminology.

Vanderwolf's work had shown that there were distinct theta- and non-theta-related active behaviours and, by implication, quite distinct neural systems underlying them. It was only in the case of immobility that there appeared to be a problem; and even here this could be viewed as a methodological problem only. It was then discovered that, pharmacologically speaking, there were two types of theta. The theta accompanying Type 1 behaviour was insensitive to muscarinic antagonists, whereas immobility-theta was blocked by them (see Vanderwolf 1988). The combination of serotonin depletion and muscarinic antagonists resulted in total abolition of theta (Vanderwolf and Baker 1986; Vanderwolf 1987; but note that nicotinic synapses may also be involved in the control of theta, Bringmann 1997).

It is easy, given these data, to talk about Type 1 theta. It is the theta which occurs during Type 1 (i.e. active theta-related) behaviours. However, the term 'Type 2 theta' (e.g. Sainsbury *et al.* 1987*a*) is open to misinterpretation. It cannot be the theta which occurs during Type 2 behaviours since these are defined *purely* in terms of the lack of any theta accompanying them. Rather, it might be defined (Sainsbury *et al.* 1987*a*, p. 489) as that which 'occurs during alert immobility *in response to the presence of sensory stimuli*' (our emphasis).

Note that the prior, largely successful, categorical distinction between Type 1 and Type 2 *behaviour* could lead to the assumption that there is a similar categorical distinction between Type 1 and Type 2 theta. However, this assumption is faced with two anomalous facts. First, serotonin depletion alone does not appear to affect 'Type 1 theta' (Vanderwolf and Baker 1986). This observation shows that so-called 'non-cholinergic' Type 1 theta has an underlying cholinergic component. Second, averaging techniques have demonstrated the presence of a weak atropine-resistant theta under urethane anaesthesia. This observation shows, conversely, that 'anaesthetic-resistant' Type 2 theta has an underlying *non*-cholinergic component. It is becoming

generally accepted, therefore, that ‘Type 1’ and ‘Type 2’ theta can occur concurrently under some conditions (see, for example, Leung 1985). But it does not seem to have been noticed that this idea runs totally counter to the original ‘Type 1/Type 2’ categorical behavioural distinction.

The situation appears to become worse if we attempt to find totally distinct pathways controlling the ‘two types’ of theta. Entorhinal cortex lesions (which would interrupt supracallosal serotonergic fibres), coupled with systemic atropine, appear to abolish theta completely (Vanderwolf *et al.* 1985), implying that ‘Type 2’ theta is eliminated by these lesions. However, medial septal lesions (which of course leave the entorhinal area intact) have long been known to abolish all theta; and, moreover, both types of theta remain intact in decorticated rats provided the operation is performed neonatally (Whishaw *et al.* 1991). To complicate the issue further, Montoya and Sainsbury (1985) found both Type 1 and Type 2 behavioural relations with theta after entorhinal lesions.

All of these results can be reconciled if we replace the (perhaps subliminal) notion of categorically distinct types of theta with the idea of two (or more) gating or enabling inputs. Let us take as our starting point the fact that the depolarizing effect of acetylcholine on principal cells of the hippocampus is far too slow to support theta frequencies (see, for example, Madison *et al.* 1987). Let us also note that septal input to the hippocampus is about equally divided between cholinergic and GABAergic synapses. It is a small step, then, to suggest that, *in some cases*, theta results when an effectively tonic cholinergic activation is accompanied by phasic GABA inhibition. Similarly, theta could result from a tonic serotonergic input coupled with phasic GABA input. Given that the aminergic inputs act to enable theta rather than control its frequency, there is a third scenario in which both could operate together (possibly synergistically). Indeed, Vanderwolf (1988, p. 262) has suggested that

> during the occurrence of Type 1 behaviour, [theta] is produced by the joint action of cholinergic and serotonergic inputs to the hippocampus. [So that], if either of these inputs is experimentally inactivated, the other input, acting alone, will produce [theta] during Type 1 behaviour. Both the cholinergic and serotonergic inputs [would] normally be inactive during Type 2 behaviour (allowing large amplitude irregular activity to occur), but under some circumstances (depending on the environmental situation and the animal species) the cholinergic input may be active alone producing [theta] during Type 2 behaviour.

According to Sainsbury (e.g. 1985; Sainsbury *et al.* 1987*b*) these circumstances are the combination of a source of arousal with the occurrence of sensory stimuli and, in the cat, cholinergic theta accounts for theta during Type 1 as well as Type 2 behaviour (but note that serotonergic activation may contribute to theta amplitude even in the cat; Marrosu *et al*. 1996). A contribution from noradrenergic input under some conditions also seems likely given the similarities between the aminergic systems discussed in Appendix 10 (see also Ammasari-Teule *et al.* 1991). The notion that serotonergic input would occur during active behaviours is consistent with the idea that the serotonergic system primes and activates gross motor activity (Jacobs 1994; see Appendix 10).

It follows that the occurrence of theta may be enabled by separate cholinergic or serotonergic inputs, by both types of input occurring concurrently, or conceivably by other inputs not yet demonstrated because the appropriate eliciting conditions have not been used. The critical factor for the occurrence of theta might be a certain threshold sum of all these inputs. This would account for the fact that entorhinal lesions in adults eliminate some aspects of theta, but decortication neonatally, which would allow sprouting and compensation of gating inputs, does not. Likewise it accounts for the crucial role of the medial septum, which is the source of the phasic, at least partially GABAergic, input (and also contains some cholinergic ‘enabling’ cells). Selective immunotoxin lesion of all the medial septal cholinergic cells, leaving GABA cells and their connections to hippocampus intact, substantially decreased the amplitude of theta but left its frequency and occurrence intact (Lee *et al*. 1994). Similar results are obtained with immunotoxin

lesion of basal forebrain cholinergic neurons (Bassant *et al*. 1995). Likewise, systemic cholinergic manipulations 'control the number of hippocampal neurons with theta modulation and stability, but not the frequency of theta modulation' (Brazhnik *et al*. 1993), and septal grafts which reinstate cholinesterase staining in the hippocampus do not reinstate theta (Buzsáki *et al*. 1992), presumably because they reinstate only the cholinergic gating input but not the inhibitory pacemaker input.

Theta activity (phasic theta-on and phasic theta-off firing in Bland's terminology) should occur extensively in the SUMM (and on preliminary data may be a property of all SUMM cells; Bland *et al*. 1995); it is likely to occur less extensively in the MS/DBB (where some cells will be gated by cholinergic and other inputs; see Stewart and Fox 1990); and it is likely to occur less extensively again in the hippocampal formation (where the influence of such septal cells as are active will again be gated by, for example, cholinergic inputs). Gating almost certainly occurs in both the MS/DBB and the hippocampus. A septal cholinergic gate is suggested by the fact that septal atropine can block theta. A hippocampal cholinergic gate is suggested by the fact that septal driving stimulation (which by-passes afferents to the MS/DBB) is blocked by anticholinergics in a movement-dependent fashion (Kramis and Vanderwolf 1980) similar to the blocking of free-moving theta activity.

The idea that cholinergic and serotonergic systems provide gating inputs also accommodates the otherwise difficult facts that neither cholinergic nor serotonergic blockade alters the frequency of theta (McNaughton and Sedgwick 1978); that the effects of anticholinergics on septal driving are not frequency dependent (McNaughton *et al*. 1977); and that the effects of 5-HT_{1A} agonists on frequency are achieved through pre- or postsynaptic actions on 5-HT_{1A} receptors on non-serotonergic neurons (Zhu and McNaughton 1994*c*).

It follows from all the above that the idea of two types of theta should (as suggested by Vinogradova) be abandoned. Rather, there are at least two types of gate which may be separately or concurrently open; and the serotonergic gate is apparently open only during Type 1 movement, and the cholinergic gate open during both Type 1 movement and theta-related immobility.

These pharmacologically distinct gates may be further subdivisible, with at least the cholinergic system involving a number of separate pathways originating in separate nuclei.

An increase in the level of stimulation of the (presumed cholinergic) PPT has a very modest effect on the frequency of theta, while producing a clear, large-amplitude response (Kirk 1993). As noted above, we found that injections of procaine into this pathway do not alter frequency of theta at all (unlike injections of procaine into the pathway ascending from the RPO). Rather, there is a simple on/off effect of the injections (McNaughton *et al*. 1997). This suggests that stimulation of the PPT activates two separate pathways: a presumed cholinergic one which has a permissive effect on the production of theta; and a non-cholinergic one which travels by some different route and which produces a modest activation of a frequency-control system, gated by the cholinergic system.

Likewise, electrical stimulation within the median raphe (Graeff *et al*. 1980; Peck and Vanderwolf 1991) elicits both immobility and a theta rhythm which shows only a moderate increase with stimulus intensity. This elicitation is unaffected by the administration of serotonergic drugs, and is blocked by anticholinergic drugs. It is therefore likely to involve the cholinergic (Lewis and Shute 1967) rather than the serotonergic (Dahlström and Fuxe 1965) cells of the median raphe.

Thus, the median raphe and the PPT may provide quite separate sources of cholinergic gating

input to the theta control system, both of which are likely to contribute to immobility-related theta as well as movement-related theta, since median raphe lesions actually release, rather than block immobility-theta (Maru *et al*. 1979). Given the effects we have obtained with procaine blockade, it appears that both the PPT and the median raphe may also have a small input to the frequency–intensity transducer.

The elicitation of theta from these two sites might be non-physiological and akin to the carbachol 'theta' in slices. However, an alternative which cannot be ruled out on present data is that there are occasions when the SUMM phasic control system is not operating and tonic input directly from the cholinergic systems to the hippocampus can produce theta, or that such input can engage the septum as both frequency controller and pacemaker (Monmaur and Breton 1991).

A further important point is that additional, tonically active, serotonergic inputs, also arising in the median raphe, actively *block* the occurrence of theta and replace it with fast activity. Thus, stimulation of this system produces desynchrony (Macadar *et al*. 1974; Vertes 1981; Peck and Vanderwolf 1991). Conversely, lesions of the system produces an increase in the amount of immobility-related, atropine-sensitive theta activity (Maru *et al*. 1979; see also Vinogradova 1995, p. 564). Similarly, injections of muscimol (Kinney *et al.* 1995) or `of procaine or the 5-HT1A agonists, ... 8-OHDPAT ... and buspirone (which inhibit the activity of 5-HT neurons by their action at the 5HT1A autoreceptor), into the median raphe generated theta at short latencies and for long durations' (Vertes and Kocsis 1997, p 913). In cats, where serotonergically gated theta is not commonly observed, systemic administration of 5-HT_{1A} agonists releases theta through an action on autoreceptors, presumably in the median raphe (Marrosu *et al*. 1996).

Thus, within the median raphe there may be cholinergic, theta-permitting cells and serotonergic, theta-restricting cells. Also, the dorsal and median raphe serotonergic systems may be permissive and restrictive, respectively, of theta (assuming that the serotonergic 'Type 1' gating input arises in the dorsal raphe). It should be noted that the 5-HT_{1A} receptors on which buspirone acts to alter the frequency of theta cannot be on the targets of any of these classes of cell since serotonergic depletion does not affect theta frequency. However, they could be on the targets of an as yet unidentified, normally silent class of dorsal or median raphe cell. The elicitation of theta through autoreceptors, seen with median raphe injections of buspirone, must normally be masked by suppression of theta through non-autoreceptors. As we imply in Appendix 10, the dorsal raphe system may be specifically involved in the generation of movement. Gating of theta would then be a minor corollary activity. This seems more likely than the alternative that the dorsal raphe is involved purely in theta control and receives as input corollary discharge from the movement control system (Robertson *et al.* 1991).

The fact that there are systems which can actively block theta when this would otherwise occur is important for attempts to account for species differences in the ease of recording theta and in its behavioural correlates. Not only can variation in the activity of such systems account for variations in the occurrence of theta activity, but the fact that such systems exist implies that there are circumstances under which theta is not adaptive.

A5.15 Frequency versus type of theta

A final point should be noted here, because it runs counter to ideas current in the literature. There is an often-expressed view that the two types of theta (which we have already concluded can co-occur) are associated with different frequencies: 'cholinergic' theta being presumed to have a low frequency and 'serotonergic' to have a higher frequency. There are even cases in which frequency, in the absence of pharmacology, has been used to deduce the 'type' of theta present.

However, the 'types of theta' are, on the model discussed above, quite independent of the

frequency control system (and can occur concurrently in any case). It follows that, whatever the frequencies normally *correlated* with one type or another, there is no necessary relationship between frequency and type. Certainly, the entire range of frequencies of theta can be obtained in the presence of anticholinergic drugs (McNaughton and Sedgwick 1978). In this experiment, the frequency of theta was unchanged by the drug, but at *all* frequencies the occurrence or not of theta appeared to depend on whether, at the time of stimulation, the animal was moving, however slightly (McNaughton, unpublished observations). Likewise, the entire range of frequencies of theta can be obtained after blockade of serotonergic transmission (McNaughton and Sedgwick 1978; Zhu and McNaughton 1994*c*); and the frequency obtained in response to any particular level of stimulation is unaffected by this blockade. Furthermore, immobility theta (which appears always to be purely cholinergic) can, where arousal is very high, reach frequencies as high as 12 Hz (Sainsbury, personal communication; see Sainsbury and Montoya 1984, Fig. 1). Similarly, in a figure reporting the effects of atropine on theta in freely moving animals (Vanderwolf 1975, Fig. 5), such theta as occurs after atropine is essentially identical to that which occurs before it (fitting the idea that gating is independent of frequency control). The non-movement theta that is lost as a result of atropine is also essentially the same frequency as that which is resistant. We will have more to say of this in Appendix 6.

A5.16 Theta rhythm and LTP

The extracellular theta rhythm, or theta activity of individual cells, is the result of phasic changes in the membrane potential. LTP occurs when an input coincides with sufficient depolarization of the postsynaptic cell. It follows that naturally occurring LTP will be most likely at the intracellular peak of theta and least likely at the trough. Consistent with this inference, brief trains of pulses to the perforant path can produce LTP at the peak at intensities which fail to produce LTP or LTD at the trough of the dentate theta rhythm (Pavlides *et al*. 1988; see also Rudell *et al.* 1980), but which can produce *de*potentiation at the trough (Holscher *et al.* 1997). Similarly, 0.1 Hz stimulation delivered at the troughs can produce LTD (Huerta and Lisman 1996*a*), and very powerful results of this type can be produced during carbachol-induced theta-like oscillations in slices (Huerta and Lisman 1996*b*).

There may be an even closer relationship between LTP and theta. If a single pulse precedes a brief high-frequency burst of pulses, it will enable the latter to produce LTP, whereas a train of the same number of pulses, or a burst followed by a single pulse, will not (Rose and Dunwiddie 1986). Since the single pulse appears to prime the system to allow LTP to the burst, the phenomenon has been referred to as ‘prime-burst potentiation’, in contrast to ‘classic’ LTP produced with a single train. The interval between prime and burst is typically set in the region of 200 ms. The coincidence between the implied frequency of 5 Hz and that of theta rhythm has been regularly noted and forms the basis for the titles of some papers (e.g. Larson *et al.* 1986; Greenstein *et al.* 1988).

A peculiarity of this literature, however, is the general use of 5 Hz as the ‘theta’ frequency. Under normal circumstances clear and regular theta rhythm in the rat appears only in the range 6–12 Hz. When a prime-burst interval of 100 ms is used (corresponding to the perfectly respectable theta frequency of 10 Hz), much less (sometimes no) potentiation is found (e.g. Larson *et al*. 1986; Greenstein *et al.* 1988). The patterning of stimuli which produces LTP may contain another anomaly. At least with an average train frequency of 2 Hz (it is not clear why the authors chose a value below the theta range), when the number of pulses and the intervals between pulses in a train are held constant and the ordering of intervals is varied, a regular alternation of brief and long intervals (which is closest to the burst and pause of theta activity) produces no potentiation, while less regular patterns (which have occasional larger bursts interspersed with much lower frequency intervals) do produce potentiation (Tsukada *et al*. 1994).

This observation is consistent with the fact that hippocampal-evoked potentials are larger during large irregular activity than during theta (Leung 1980; Vinogradova *et al*. 1993*b*,*c*).

Taken together, these findings raise the possibility that the temporal patterns which are most conducive to LTP are not specifically related to theta activity. However, they do show that more natural patterns of activation are more effective than the original 'unphysiological' continuous high-frequency trains. Indeed, it has been suggested that:

> the irregularly occurring large amplitude hippocampal sharp waves (SPWs) [which] are correlated with synchronous population bursts of CA1–CA3 and subicular pyramidal cells, dentate granule cells and interneurons in all hippocampal fields . . . [provide] the best candidate for a physiological basis of long-term potentiation. They can occur [at 0.01 to 2 Hz] isolated or in groups of several successive waves (40–150 msec in duration). . . . Concurrent with the SPWs a large number of pyramidal cells in all hippocampal fields fire in bursts of 2 to 7 action potentials. (Buzsáki and Haas 1988, p. 90.)

Furthermore, when similar population cell bursts are induced with bicuculline, they produce LTP (Buzsáki *et al.* 1987*c*). Thus the 200 ms interval which appears optimal for prime-burst potentiation 'is similar to intervals between the SPWs during a SPW burst' (Buzsáki *et al.* 1987*c*). (There are also 200 Hz 'ripples' linked to the sharp waves which produce phase-locked activity across large portions of the hippocampal formation, and could provide the bases for consolidation; Chrobak and Buzsáki 1996).

A further important point is that activation of medial septal input to the hippocampus can suppress LTP (e.g. Bilkey and Goddard 1984; Pang *et al.* 1993), as do cholinergic manipulations which induce theta rhythm (Olpe *et al*. 1988), and stressful manipulations which might be presumed to induce theta (Foy *et al*. 1987; Diamond *et al*. 1990, 1994). Suppression of LTP in this way may be related to the fact that theta rhythm appears to be inhibitory of seizures (perhaps the most extreme manifestation of hippocampal hyperpolarization) and also of sharp waves (Bland *et al*. 1996). However, with septal stimulation which produces an excitatory response in the dentate, LTP is enhanced (Robinson 1986), and increases in theta frequency produced by ondansetron are accompanied by increased LTP as well as improved memory performance (Stäubli and Xu 1995).

Disentangling the processes involved here will be complicated because, in addition to the GABAergic inhibition of inhibition which underlies part of the phasic generation of theta, the presumably tonic cholinergic component could have a bidirectional effect, reducing LTP at low concentrations of extracellular acetylcholine, while increasing it at higher concentrations (Maeda *et al.* 1993). Conversely, APV (a favoured NMDA receptor blocker) not only blocks LTP but also impairs theta (Leung and Desborough 1988), introducing a confound into any experiments which wish to separate the two. Likewise, while benzodiazepines (which interfere with the control of theta) also impair LTP (Yasui *et al*. 1993; del Cerro *et al.* 1992), these latter experiments were carried out in slices. The effect of the drugs on LTP was obtained, therefore, in preparations which had no theta input or intrinsic theta activity. In this context, it should also be noted that benzodiazepines are anticonvulsant, in addition to their effects on theta (buspirone has not been tested on LTP).

It is clear that the relationships between theta activity and LTP (and the extent to which observed experimental effects reflect normal physiological processes) require extensive investigation. For example, how far one pulse preceding a burst by 200 ms produces effects equivalent to a train at, say, 130 ms is completely unclear. There may also be much more complicated effects waiting to be discovered. For example, delivery of a low-frequency (5 Hz) train (10 pulses) eight times to the lateral perforant path has no effect on responses to subsequent single-pulse stimuli but potentiates subsequent associative (but not non-associative) LTD in barbiturate-anaesthetized rats (Christie and Abraham 1992). This 'priming' effect on LTD was, if anything, more effective

with a 2-h prime-LTD interval than with a 10-min one. Likewise, 80 priming pulses 10 min prior to tetanization in pentobarbital-anaesthetized rats facilitated LTP with a priming frequency of 5 Hz but not 1 or 15 Hz (Christie *et al.* 1995). This type of result cries out for a host of parametric experiments—and probably considerable modelling—if we are to be able to guess at the capacities of the normal system with natural inputs.

A5.17 Conclusions

Information is fed into all levels of the hippocampal formation in parallel from the entorhinal cortex and from the septum. It then passes through the hippocampal formation in a largely unidirectional fashion via the excitatory links, which can be viewed as starting in the entorhinal cortex and medial septum and finishing (before exit from the hippocampal formation altogether) in area CA3, area CA1, the subiculum, or the posterior cingulate. There are local recurrent excitatory and inhibitory connections (the combination of these prove important for the theory developed in Chapter 10), but these do not destroy the net linear flow of information. This is a feature which distinguishes the hippocampal formation as a whole from neocortex as a whole, but which it shares with the amygdala. All of the excitatory inputs and connections appear capable of LTP, and probably LTD. Activity in the structure as a whole will often be modulated by synchronous, essentially inhibitory, phasic input which can, in some areas, give rise to an extracellular theta rhythm.

It appears that LTP is most likely to occur, at a macroscopic level, during the sharp waves which involve highly synchronous firing of hippocampal cells and, by implication, highly synchronous input to them. This appears likely to occur at times when the hippocampus is receiving only modest external input. The function, if any, of such macroscopic potentiation is unclear. If it represents a wholesale resetting of the basic circuitry to a high level, this would imply that input-specific LTD rather than LTP would be the substrate for specific information coding by synapses.

LTP should also occur at the microscopic level at any synapses which are active when the target cell is highly depolarized. In this case, in principle, single synapses could be potentiated in isolation. In practice, population coding is more likely; and, indeed, LTP of the input to one neuron has been shown to spread to close, but not distant, neighbours receiving the same terminal input but not concurrently depolarized to the same extent (Schuman and Madison 1994). This latter fact will prove important when we try to unravel the specific functions of the hippocampal cells in the next two appendices.

Theta rhythm is a surprisingly sinusoidal activity reflecting synchronous activation of large numbers of the neurons in areas CA1 and the dentate, the entorhinal cortex, and occasionally the posterior cingulate cortex. Such synchronous firing also occurs, but usually without recordable extracellular theta rhythm, in area CA3, in the subcortical structures that supply the phasic input which controls its frequency, and in structures (such as the mammillary bodies, nucleus reticularis pontis oralis, and the median and dorsal raphe) which receive feedback from the hippocampal formation.

The superficial simplicity of theta activity is belied by the complex ascending circuitry which maintains the phasic locking of activity at every relay from the intensity–frequency transducer up to and including the hippocampus. Likewise, the apparently simple relation between intensity of reticular activation and frequency of theta depends on complex parallel circuits which are summed by a network rather than a single nucleus; and the occurrence of theta is gated by separate serotonergic and cholinergic systems. The latter gating process is, itself, complex and appears to involve mutual cooperation in a reticulum of nuclei. Figure 10.2 provides a diagram

of the more important components of the theta control system.

The phasic input arises in the SUMM, and other as yet unidentified *reciprocally connected* nuclei, which, between them, sum afferent input from what appears to be a complex web of nuclei both more caudally within the reticular formation and more rostrally within the hypothalamus. This summed input is converted into the frequency of the phasic output. The phasic output is relayed to the hippocampus by the medial septum. An efference (collateral) copy of this output (e.g. from the SUMM) is likely to be the basis for the synchronous firing seen in some subcortical nuclei, such as the raphe nuclei.

The systems controlling CA1–dentate, septal–temporal, and waking–paradoxical sleep (see next appendix) theta may each (and severally) involve different topographies of the ascending synchronizing control system, which has been shown anatomically to have a high degree of topographic organization.

Benzodiazepines appear to act directly, and buspirone may act indirectly, on the SUMM to reduce the frequency of theta. This frequency is not normally dependent on the presence of noradrenaline, dopamine, serotonin, or acetylcholine. The neurotransmitters afferent to the SUMM intensity–frequency transducer are not known, nor are those which link the SUMM to the MS/DBB. One speculative possibility is that the SUMM provides, directly or via interneurons, GABAergic phasic inhibitory or disinhibitory input to the septum, while the ascending cholinergic systems arising in the PPT and median raphe provide tonic or phasic cholinergic excitatory input, and the dorsal raphe provides serotonergic (net) excitatory input.

The medial septum relays phasic inhibitory GABAergic information to the hippocampus. It also relays (and for some cells is gated by) cholinergic information. Acetylcholine probably produces both presynaptic inhibition and effectively tonic postsynaptic increases in cell excitability, which can gate (or enable) the phasic information to entrain theta, depending on the precise balance between GABA and acetylcholine (Smythe *et al.* 1992). This arrangement suggests that ‘the main function of the septohippocampal cholinergic input consists of filtering out the signals appearing at the background of theta-rhythm triggered by a previous signal, thus preventing their interference with [the] processing and registration [of that signal]’ (Vinogradova *et al*. 1993*c*, p. 981). Serotonergic input from the dorsal raphe provides a second such gate, with a critical component of its input taking the supracallosal route to the hippocampus. Both gates can be open concurrently and it is likely that they can act synergistically. Other gating inputs could also exist. Natural, reticularly elicited and septally driven theta all appear to have the same type of gating, indicating a direct hippocampal action of acetylcholine and serotonin. However, a similar gating mechanism appears to operate in the septum as well (at least in the cholinergic case). In addition to these permissive gates, median raphe serotonin acts to block theta and replace it with desynchrony.

The ease with which septal phasic information can entrain theta depends on frequency, and the form of the frequency tuning function depends on noradrenergic, serotonergic, and GABAergic influences. This frequency dependence is most likely to reflect activity in two separate recurrent circuits. One of these is tuned to 7.7 Hz (130 ms round trip) and conveys information between the two hippocampi, possibly via the lateral septum. This is normally active under resting conditions in male but not female rats, and depends on tonic contralateral noradrenergic input. The other recurrent circuit is tuned to 6.9 Hz (145 ms round trip) and is not normally active under resting conditions in either male or female rats, due to tonic inhibition by serotonergic input. Benzodiazepines, buspirone, and imipramine produce effects similar to blockade of noradrenergic transmission and to increases in GABAergic transmission; these effects appear to result in an impairment of entrainment of one hippocampus by the other at intermediate frequencies.

The lack of effect of noradrenergic and serotonergic depletion on reticular-elicited theta contrasts with the effects obtained with septal driving, as does the fact that there are no non-linearities in either the control data or the drug effects with respect to frequency. The frequency control demonstrated by the reticular test must, therefore, be viewed as neurophysiologically and pharmacologically distinct from the threshold control demonstrated by the septal test. We probably need to assume, in addition, that reticular stimulation of the type used in these tests (as opposed to more physiological activation) produces septal activation which is well above threshold as determined in the septal test.

There is one point at which the two tests match. When anticholinergic drugs are given, theta is sometimes observed and sometimes not in an apparently random fashion. This randomness affects all frequencies equally in the septal case (McNaughton *et al*. 1977; Kramis and Vanderwolf 1980). In the reticular case, it does not change the observed frequency (McNaughton and Sedgwick 1978). What we are seeing here is the consequence of activating, from the reticular formation or the septum, an intact frequency-generating mechanism, for which the final input to the hippocampus is phasic GABAergic pulses, but which can result in theta only when an additional, non-cholinergic tonic input enables it. The distinction between separate cholinergic and serotonergic enabling mechanisms is clearly important, and will become more so when we consider the relationship of behaviour to hippocampal electrical activity (Appendix 6).

A final point to note is that changes in the shape of the threshold-frequency septal driving curve (which we attributed to interhippocampal, and possibly hippocampo-septal, interactions) reflect changes in the ease of synchronizing theta, rather than changes in its amplitude. There is evidence that the amplitude of theta depends on a number of other factors, including positive feedback via the hippocampal output to the lateral septum (Leung *et al.* 1994). Even at the level of the hippocampus there are types of cell which can increase or decrease their activity during theta rhythm, respectively. For both types there are some which do not themselves show phasic firing (in Bland's terminology they are tonic theta-on and tonic theta-off cells).

The presence of theta rhythm appears to be inhibitory of hippocampal electrically evoked potentials, as well as spiking (Leung 1980), and perhaps of cortical sensory evoked potentials (Pond and Schwartzbaum 1972; but see also Parmeggiani and Rapisarda 1969), as well as strongly inhibiting the spread of seizures (Miller *et al.* 1994). By contrast to sharp waves, then, the hippocampal theta rhythm would be expected to inhibit LTP overall, while nonetheless facilitating LTP at the peak of the theta wave relative to the trough. Theta is likely to occur at a time when there is extensive afferent input to the hippocampus. The net effect, then, would be to leave the overall tendency to LTP intact (by counterbalancing the increased probability of LTP due to increased afferent drive), and to restrict its occurrence in time. This would result in a major increase in the *temporal* signal-to-noise ratio. An increase in this kind can be seen as matching the increase in the *spatial* signal-to-noise ratio that, we propose in Appendix 10, occurs with the noradrenergic and serotonergic inputs to the hippocampus. As we shall see, these produce a general baseline inhibition, while facilitating the response to major extrinsic inputs (but see Moser *et al*. 1994, for some potentially contradictory data). Systems which suppress theta could, then, be required at times when the input to the hippocampus is so weak that inhibition would eliminate the signal as well as the noise.

While theta activity could be present simply to modulate the occurrence of LTP, its very frequent occurrence in rabbits and rats makes it much more likely that it is a critical component of *non-plastic* aspects of hippocampal processing. Indeed, all the aminergic inputs have transient as well as longer-term effects on hippocampal activity, and in all cases it appears that they produce a general sharpening, in time or space, of hippocampal processing. In the case of theta activity, it seems likely that synchrony of information processing is its major function (why this might be

necessary we will discuss later).

Despite the essential linearity of information transmission through the hippocampal formation, there is good evidence for both recurrent inhibitory and, perhaps more importantly, recurrent excitatory feedback. We have evidence for both inter-hippocampal (commissural) and hippocampo-septal excitatory loops, and indications that the extent to which these loops are operative is subject to modulation by aminergic input to the hippocampal formation.

We will discuss in later appendices theories that link the frequency of theta rhythm to the tuning of extrahippocampal recursive circuits and theories that see phasic input as necessary for the synchronizing of specific information-processing operations. As we will see, these have two drawbacks: they do not usually account for the specific microstructure of frequency-behaviour relations; and they incorrectly predict that alterations in theta frequency, or obliteration of theta, should produce total dysfunction of the hippocampus. They usually fail to explain why other areas of the brain do not require the equivalent of theta.

The presence of recurrent excitation in the hippocampus leads to an alternative possibility. The net effect of such circuitry is to provide the hippocampus with chaotic dynamics which (as in epilepsy) have the capacity for sudden, explosive changes in state. A chaotic system is, of course, particularly good at using sudden changes in state to produce categorical output. However, one can have too much of a good thing in that the system can escape into, for example, seizure activity. It is possible to maintain a chaotic system within a limited portion of its dynamic range by the occasional application of carefully timed inputs, and such control has been demonstrated in hippocampal slices (Schiff *et al*. 1994). However, a process of this kind requires quite complex computation; and a similar level of control can be obtained by a regular periodic input to the system (Schiff *et al*. 1994). It seems possible, therefore, that theta rhythm (and its frequency relationships) have evolved to maintain the chaotic dynamics of the hippocampus for functional purposes, while preventing the system from escaping into dysfunctional modes of operation (e.g. epileptic discharge). The same may be true of the gamma rhythm (see, for example, Jefferys *et al.* 1996), which we have ignored because there are few data which indicate its role in hippocampal function.

Both this view and the more general view that theta synchrony could provide an increase in temporal signal-to-noise ratio require a fundamental change in the theory of the first edition of this book. There, theta was viewed as essential to hippocampal function. Here, it is seen, instead, as important under some circumstances (particularly where the hippocampus must function optimally), but not essential. Thus, at least approximate computations will be possible in the absence of phasic input or if the frequency of the phasic input is altered. However, when a higher level of accuracy is required, loss of phasic input, and so of temporal resolution, will have major consequences.

There is one, final, particularly important conclusion to be drawn from the data reviewed in this appendix. It is important because it is fundamental to the theory of this book; and because the data on which it is based are studiously ignored by other theories of the hippocampus (e.g. Cohen and Eichenbaum 1993) or reviews of theta rhythm (e.g. Bland 1986), including theories in which theta is fundamental (e.g. Miller 1991). It is clear from the data we have reviewed that the control of hippocampal theta rhythm, both subcortically and within the hippocampus, is affected in a similar fashion by clinically anxiolytic drugs of all currently known chemical types. More importantly, no drug which has these specific effects on the control of theta has been shown not to have clinical anxiolytic action. This strongly suggests that an action on theta activity is fundamental to their clinical effects since, other than having a common anxiolytic effect, each of the drugs has a quite different clinical profile (see Chapters 1 and 4) and quite different side-effects.

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Notes

1. This lateral inhibition may be facilitated by the capacity of GABAergic cells to directly excite each other via $GABA_A$-mediated depolarization (Michelson and Wong 1994).

2. There has been some controversy recently as to how far entorhinal input to CA1 is excitatory and how far inhibitory (see *Hippocampus* (1995) **5**, 101 et seq.; Jones 1993; Empson and Heinemann 1995). Predominantly inhibitory responses have been seen in slices, in isolated whole brain preparations, and in compartmental models. However, in each case there has been some excitatory component. On the other hand, with natural stimulation there seems to be equivalent simultaneous excitation of both CA1 and dentate. It seems that the precise balance of excitation and inhibition may vary depending on species, preparation, frequency of stimulation, and other factors. Our own experience (N. McNaughton, unpublished observations) is that, at least in urethane-anaesthetized rats, individual CA1 cells are as readily fired by perforant path stimulation which has been optimized to produce dentate population spikes as are dentate granule cells themselves, but that the evoked potentials associated with this firing are very much smaller, even when comparison is made in the planar portions of the dentate (as opposed to the curved portions which give much larger responses in the region of the cell layer, but negligible dentate dendritic responses).

3. We are not sure who originated the first of these phrases, but suspect that the second can be attributed to Mark Bear.

4. As we will see later, however, NMDA antagonists can eliminate theta activity (a multi-pulse phenomenon), which limits their usefulness if specific conclusions are to be drawn about LTP.

5. There are a few apparent exceptions to this rule (e.g. Destrade 1982; Destrade and Ott 1982) with high-frequency stimulation of the medial forebrain bundle. However, these authors used trains with phasic gaps. This type of stimulation of the septum is known to be capable of driving theta in the same way as phasic single pulses (James *et al*. 1977), and inspection of their data (e.g. Fig. 1A and especially 1B in Destrade and Ott 1982) suggests that their stimulation was driving theta at various harmonics of the gap frequency. The authors reported that the frequency of theta increased with increasing strength of stimulation, as would be expected with more posterior stimulation sites. However, inspection of the figures suggests that this was the result of increasing phase locking of activity with the gaps in the phasic delivery of the high-frequency pulses. Unlike conventional ‘theta driving’, the phasic frequency was below the theta range. However, septal input (or sensory stimuli; Givens 1996) can reset ongoing theta as well as drive it. Since the hippocampus has a tendency to intrinsic oscillation in the theta frequency range, Destrade’s results appear to be due to driving of various harmonics of the imposed phasic frequency, with the resultant theta frequency determined by the natural period of oscillation of the septo-hippocampal system. Thus, the driving in Fig. 1B of Destrade and Ott (1982) is at the third harmonic of the stimulation gap frequency.

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