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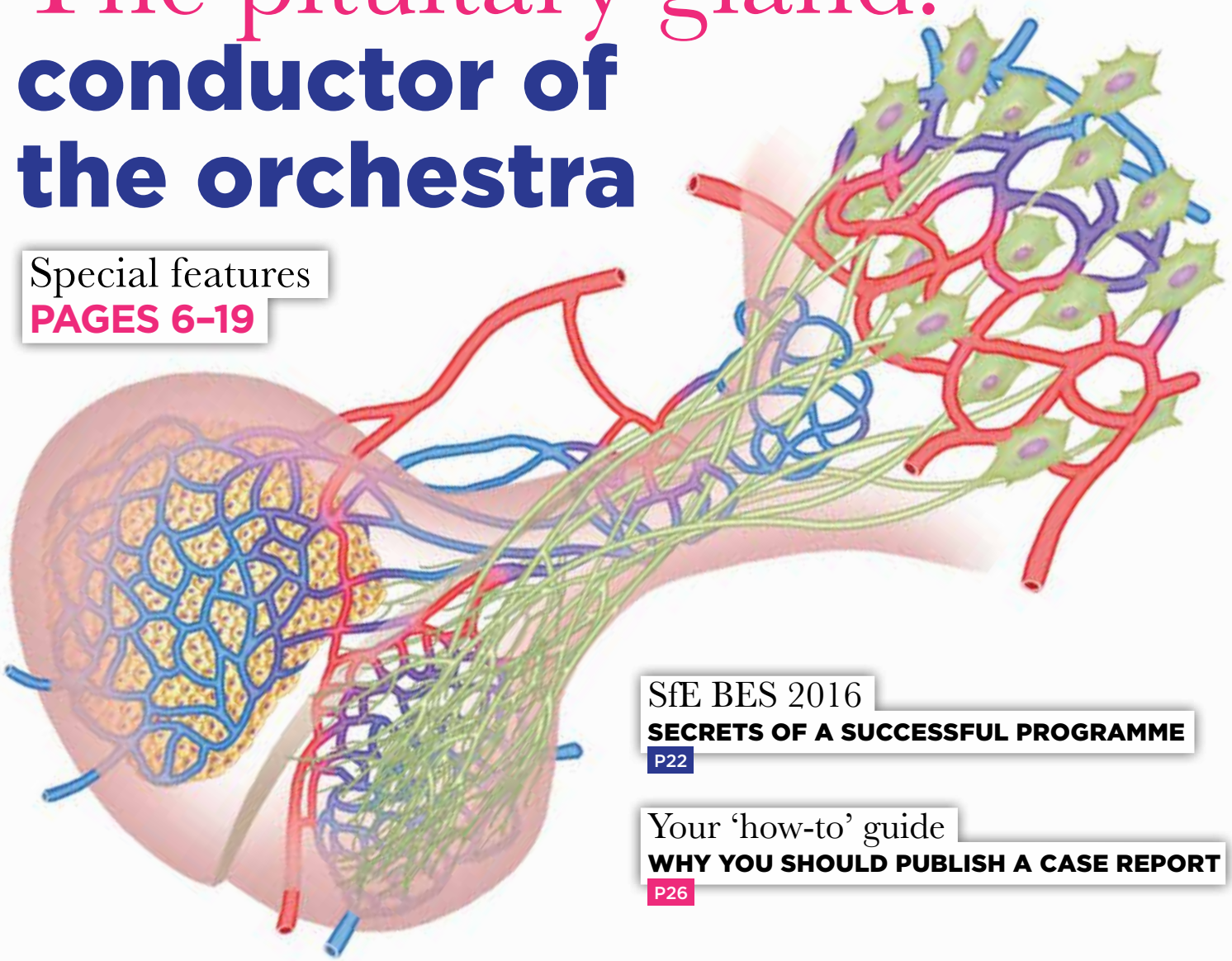
The pituitary gland: conductor of the orchestra



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PROLACTIN: THE 'SWISS ARMY KNIFE' OF THE PITUITARY GLAND

WRITTEN BY DAVID R GRATTAN

In the minds of most endocrinologists, prolactin has been 'pigeon-holed' as the hormone that promotes milk production during lactation. Furthermore, hyperprolactinaemia can sometimes be labelled as a straightforward condition that usually responds well to dopaminergic drugs. There seems to be little consequence of not having enough prolactin, and it does not require replacement after pituitary removal.

However, for many years, researchers have been striving to highlight that prolactin has many more functions than just lactation. From an evolutionary perspective, it is an old hormone, present in all vertebrates, most of which do not lactate. In a variety of species, prolactin is involved in functions as diverse as fluid balance, immune regulation, metabolism and behaviour. Prolactin receptors are present in many different tissues, including the liver, gut, pancreas, bone, fat, reproductive tissues and brain. The question is, are any of these other actions of prolactin still important in humans?

In a recent review of the field for *Journal of Endocrinology*'s issue marking '60 years of neuroendocrinology', I highlighted prolactin as a multi-purpose hormone.[1] It is a bit like the iconic 'Swiss army knife': it is pretty clear what its main function is – but then there are many other gadgets whose role is more obscure, until you work out what they do and realise they could be just what you need in certain situations!

Lactation is clearly the main function of prolactin in mammals. But the other functions can play critical roles under specific circumstances. Some complement the main function, while others remain enigmatic. For example, why do males have prolactin?

WHY SO MANY FUNCTIONS?

Prolactin secretion from the pituitary is actively inhibited by dopamine released from the hypothalamus, largely keeping serum prolactin low most of the time. During pregnancy, however, prolactin comes into its own, and the multiple functions become prominent. Mammals have evolved elaborate mechanisms to enable hyperprolactinaemia during pregnancy and lactation. These include production of lactogens by the placenta and/or decidual tissue to activate the prolactin receptor, thereby bypassing the negative feedback regulation of pituitary prolactin secretion.

The hypothalamic feedback itself is remarkably plastic, with dramatic changes occurring in late pregnancy and into lactation, such that the dopamine neurones show greatly reduced dopamine release, allowing increased pituitary prolactin secretion. Finally, once lactation starts, the act of suckling by the offspring provides the most powerful stimulus to prolactin secretion known. It does this both by maintaining the state of low dopamine output from the hypothalamus, and potentially by adding a stimulatory signal – although if there is a hypothalamic prolactin-releasing factor, we still don't know what it is.

The prolonged elevation in prolactin that is generated by these adaptations is clearly important for milk production, but there are many other actions of prolactin that support this primary role. Lactation requires more than just milk production, demanding behavioural change in the parents, as well as profound metabolic and physiological adaptation in the mother. Almost all of her systems have to function differently to support this new situation, with prolactin co-ordinating an integrated response. It stimulates appetite, suppresses fertility and reduces the stress response and anxiety. It augments insulin secretion and mobilises calcium from bone. It may even alter hair growth to help with temperature regulation. Might abnormalities in prolactin signalling, therefore, underlie various pregnancy complications?

'Prolactin is an old hormone, present in all vertebrates, most of which do not lactate.'

A NOVEL PROLACTIN RECEPTOR MUTATION IN HUMANS

In 2013, an intriguing report in *New England Journal of Medicine*[2] described a family carrying a novel mutation causing a non-functional prolactin receptor. The three sisters who were heterozygous for the mutation exhibited a range of symptoms, some of which were consistent with our understanding of prolactin function, while others raised new questions. The most obvious phenotype was hyperprolactinaemia, probably due to the loss of the regulatory feedback discussed above. But this explanation was not without controversy, because it was claimed that such feedback has not been proven in humans.[3] Ironically, those expressing this doubt seemed to overlook the fact that this study might have provided the very evidence that had previously been lacking!

The second phenotype revealed in this family was a deficiency in fertility. Now, this is where things really got interesting. The women were hyperprolactinaemic, and it is well known that this causes infertility. But if they have non-functional prolactin receptors, how might prolactin be acting to affect fertility? The best explanation would seem to be that prolactin exerts a previously unrecognised positive influence on reproduction in humans,[3] as it does in some animals, and that, when this effect was impaired, there were problems with reproduction. So we have more to discover.

APPROPRIATE VERSUS INAPPROPRIATE HYPERPROLACTINAEMIA

The mechanisms by which prolactin inhibits reproduction remain an active area of research. Few of the gonadotrophin-releasing hormone (GnRH) neurones that control reproduction express prolactin receptors, but recent work has highlighted how prolactin might be working indirectly in the brain, through altering activity of kisspeptin or GABA (γ-aminobutyric acid) afferent neurones.

It seems likely that hyperprolactinaemia at an inappropriate time

recapitulates the adaptive responses normally seen during pregnancy or lactation. Infertility is a normal, appropriate response during lactation, but when prolactin is inappropriately elevated, infertility occurs. Potentially, other consequences might also occur during hyperprolactinaemia. For example, patients on anti-psychotic medication (anti-dopaminergic drugs that interfere with the normal regulation of prolactin) suffer not only from loss of libido and infertility from hyperprolactinaemia, but are also at increased risk of metabolic disturbances more characteristic of changes seen in pregnant women.

LOOKING AHEAD

As the hormone responsible for lactation, prolactin has clearly played a critical role in the evolution of mammals. Within this context, it is possible that distinct roles for the hormone have developed in different species, including humans, but it is likely that many common functions remain.

Factors that influence hormone secretion during pregnancy could potentially have consequences for the outcome of the pregnancy on the mother, the offspring or both. Small changes, caused by diet, stress or illness at an inappropriate time, might have effects that do not become apparent until some time later. For example, in mice, suppression of prolactin during early pregnancy causes a decrease in neurogenesis in the maternal brain, and results in postpartum anxiety and impaired maternal behaviour some weeks later. Other diseases of pregnancy and postpartum, such as gestational diabetes or postpartum depression, might similarly have their origins in impaired neuroendocrine responses.

Looking forward, it is an exciting time to be involved in prolactin research. There is a wealth of new research tools available, from genetic approaches conferring the ability to regulate prolactin action in specific cells and tissues, to novel antagonists and antibodies that block prolactin action in clinical trials as potential therapies for a range of disorders and cancers.

Perhaps we will be able to harness the power and utility of nature's 'Swiss army knife' to help us understand the causes of pregnancy complications and to intervene appropriately.

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1. Grattan DR 2015 *Journal of Endocrinology* **226** T101–T122.
2. Newey PJ *et al.* 2013 *New England Journal of Medicine* **369** 2012–2020.
3. Correspondence 2014 *New England Journal of Medicine* **370** 976–978.

FURTHER READING

All the reviews in the special *Journal of Endocrinology* issue celebrating 60 years of neuroendocrinology are open access and can be read at **http://bit.ly/JOEthemedissue**