Neuro-endocrinology

16 BRIEFINGS

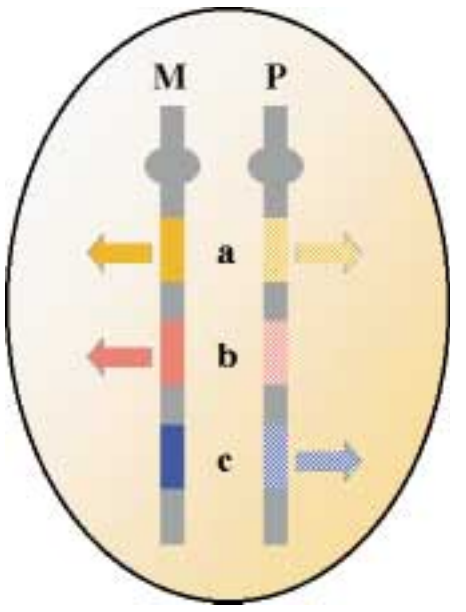
GENOMIC IMPRINTING, HORMONES AND BEHAVIOUR

SUMMARY

Imprinted genes are a recently discovered category of mammalian genes some of which appear to target the neuroendocrine system. Whilst the detailed data are still emerging, it is likely that these genes will provide new insights into the genetics of neuroendocrine control. Understanding the links between imprinted genes and neuroendocrine functioning has implications for both normal and abnormal physiology and may provide further evidence for the notion that, at the molecular level, the sexes are engaged in a form of evolutionary competition.

Imprinted genes: breaking the law

As our understanding of genetics and molecular biology grows, the more complex it appears. Mendel's work on peas may have laid the foundation of genetics, but time and time again, we find his laws of inheritance broken. One such violation of Mendel's laws is genomic imprinting. Genomic imprinting refers to the differential expression of a gene depending on whether it is inherited from the male or female parent. Normally both the paternal and maternal versions of a gene are expressed. However, in imprinted genes, only one copy is expressed due to a form of molecular silencing involving DNA methylation; for some imprinted genes, it is always the copy inherited from dad, for others it is always the copy inherited from mum. Currently there are approximately 40 known imprinted genes, although the estimates of total number are 100-200. Despite making up such a tiny fraction of the genome, this subset of genes appears to be very important physiologically, influencing key aspects of development and growth.



A stylised diagram demonstrating the difference between normal (a) and imprinted (b,c) genes. Both the maternally (M) inherited version (solid) and paternally (P) inherited version (hashed) of gene **a** *are expressed. However, only the maternally inherited version of imprinted gene* **b** *is expressed. Imprinting can occur in both ways and, conversely, only the paternally inherited version of gene* **c** *is expressed.*

Imprinting and neuroendocrine systems

Imprinted genes also appear to impact significantly on brain and behaviour, with one of the main foci of action being within neuroendocrine systems. For example, both the classical imprinted gene syndromes, Beckwith-Wiedemann (BWS) and Prader-Willi (PWS), include neuroendocrine problems, with PWS showing multiple severe abnormalities due to hypothalamic insufficiency; including feeding deficits, rapid weight gain, infantile lethargy and a host of behavioural problems. Although both BWS and PWS occur as the result of abnormalities in known regions of the human genome (chromosomes 11 and 15, respectively), these abnormalities affect several genes. Consequently, it is currently difficult to ascribe particular neuroendocrine defects to specific imprinted loci.

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Mouse models: chromosome 2 effects.

More systematic evidence for a role for genomic imprinting in neuroendocrine functioning comes from work with mice. One region of the mouse genome that is of especial interest lies on chromosome 2. Early work investigating mice that were disomic (having two copies) for maternally or paternally inherited copies of chromosome 2 found a 'reciprocal' phenotype. Those mice that inherited their two copies of chromosome 2 from their father were *hyperkinetic*; those that inherited their two copies from their mother were *hypokinetic* and failed to suckle. Both died within a few days of birth.

'. . . their offspring gained less weight than offspring of normal mothers'

More recently, the nature of the individual imprinted genes on chromosome 2 has begun to be dissected using knockout (KO) and molecular technology. Two genes have been identified that are expressed in brain. The function of the first, *Nesp* (*ne*uroendocrine *s*ecretory *p*rotein) is not clear. The second, *Gnas*, encodes the alpha-subunit of the G-protein G_S which functions to couple many transmitter, neuropeptide and hormone receptors to intracellular responses. The human version of this gene is also imprinted and mutations in this gene give rise to Albright hereditary osteodystrophy.

'. . . the idea is that paternally expressed genes try to maximise resource allocation to their offspring'

Pegged out mothers?

Screening methods based on subtractive hybridisation of uniparental embryos have revealed novel imprinted genes. *P*aternally *e*xpressed *g*enes (*Peg*) 1 and 3 are both expressed throughout the brain, but at particularly high levels in the hypothalamus. KO studies revealed that both play an important role in mothering behaviours. Female heterozygous mice that inherited the knocked-out *Peg1* gene from their father failed to respond to and retrieve pups. These females were also impaired in their nest building skills and placentophagia (eating the placenta), a normal mammalian parturitional behaviour.

The *Peg3* KO also had similar effects on pup retrieval and care, but in addition these females had impaired lactational abilities. Not only did *Peg3* KO mothers take longer to assume the required crouching position, but their offspring gained less weight than offspring of normal mothers, despite equal time spent suckling. Histological examination of heterozygous females who had inherited the knocked-out *Peg3* gene from their fathers revealed normal mammary glands, but a reduced number of oxytocin producing neurones in the hypothalalmus. A decrease in the amount of this hormone would result in lowered milk let down, despite normal mammary gland function.

Battle of the sexes

One dominant, though not exclusive, theory to explain the existence of imprinted genes is that they have arisen as a result of genetic conflict between maternal and paternal interests within the offspring. Basically, the idea is that paternally expressed genes try to maximise resource allocation to their offspring, whereas maternally expressed genes try to reduce those demands, and distribute them evenly across the litter and between litters. It may be that, within this broad evolutionary framework, the neuroendocrine system, with its repertoire of behaviours and physiology able to impinge directly on resource allocation, plays a pivotal role in this molecular 'battle of the sexes'.

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