REVIEW ARTICLE

Prader–Willi syndrome and the hypothalamus

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Dysfunction of various hypothalamic systems may be the basis of a number of symptoms in Prader–Willi syndrome. The often abnormal position of the baby in the uterus at the onset of labour, the high percentage of infants with asphyxia and the high proportion of children born prematurely or post-maturely may all be related to abnormal fetal hypothalamic systems, as the fetal hypothalamus plays a crucial role in labour. Abnormal luteinizing hormone-releasing hormone neurons are thought to be responsible for the decreased levels of sex hormones, resulting in non-descended testes, undersized sex organs and insufficient growth during puberty. A lack of growth hormone-releasing hormone may also contribute to the short stature of patients with Prader–Willi syndrome. In addition, the aberrant control of body temperature and daytime hypersomnia may result from hypothalamic disturbances. The number of oxytocin neurons – the putative satiety neurones – in the hypothalamic paraventricular nucleus is markedly decreased in Prader–Willi syndrome. This is presumed to be the basis of the insatiable hunger and obesity of patients with the syndrome. © Growth hormone, growth hormone-releasing hormone, hypothalamus, insatiable hunger, obesity, oxytocin, perinatal problems, Prader–Willi syndrome

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In 1956, Prader, Labhart and Willi described a syndrome in children that was characterized by mental retardation (mean IQ of 65), gross obesity, severe infantile hypotonia, hypogonadism and hypogenitalism (1). Serum levels of testosterone are usually low in males with Prader–Willi syndrome, whereas levels of serum oestradiol, luteinizing hormone (LH) and follicle-stimulating hormone in females with the syndrome are usually low, but may also be in the normal range. The abnormalities of sexual development in Prader–Willi syndrome are mainly due to a defect in the hypothalamic–pituitary–gonadal axis (2–4). In addition, patients with the syndrome have mental retardation, behavioural problems, such as fits of temper, depression and sudden aggression, and a variety of minor malformations, including a small forehead, almond-shaped eyes, triangular mouth, small hands and feet, short stature and decreased pigmentation of skin and hair.

Dysfunction of various hypothalamic systems may be the basis of a number of the symptoms of Prader–Willi syndrome, including those associated with the reproductive system, appetite and obesity, and short stature.

Timing and nature of birth

Severe fetal hypotonia is often noticed by the mother during pregnancy. In addition to the baby’s underactivity, its position in the uterus at the onset of labour is often abnormal (either a transverse, face or breech presentation). These abnormal presentations result in a high percentage of assisted deliveries. In addition, the percentage of asphyxiated infants is at least eight times higher than in the general population (5). It has often been presumed that the fetal position is caused by hypotonia, the child being too weak to move itself into the correct position. However, there are other congenital disorders affecting the hypothalamus and pituitary – in which hypotonia is not reported – that are also accompanied by abnormal presentation of the fetus at birth, such as anencephaly and septo-optic dysplasia (De Morsier syndrome).

The fetus plays an active role in the course of its own delivery. Fetal hypothalamic systems seem to be crucial for a normal birth process. Human anencephalics do not have a neurohypophysis, and release of oxytocin and vasopressin is impaired (6, 7). In anencephalics, expulsion takes twice as long as normal, and the birth of
the placenta takes three times longer than normal (8). In patients with septo-optic dysplasia, in which the fetal hypothalamic–hypophyseal system is often damaged (9), perinatal problems are also frequently found. The timing of birth in children with Prader–Willi syndrome is also often abnormal; a relatively high percentage of such children are born either prematurely or post-maturely (5). An abnormality of the hypothalamus, which plays a central role in the child’s timing of its own birth, may explain these phenomena. In anencephaly, a high percentage of children are born prematurely or post-maturely, indicating the crucial function of the fetal brain in the timing of birth (10).

Effects on the reproductive system

Abnormal function of hypothalamic LH-releasing hormone (LHRH) neurones is thought to be responsible for decreased levels of sex hormones in children with Prader–Willi syndrome. This results in non-descended testicles in boys, and undersized sex organs in boys and girls, as well as decreased levels of sexual behaviour and insufficient growth during puberty. The onset of menstruation is often late in girls, if it occurs at all. It is not known whether the suggested abnormality in LHRH production is due to the absence of LHRH neurones or to their abnormal location. Another possibility is that these neurones produce too little or an abnormal form of the hormone.

Effects on appetite and weight

The birth weight of children with Prader–Willi syndrome is often below normal, but from 2 years onwards they tend to grow fatter than other children. Appetite control is exacerbated when there is more severe mental retardation. The obesity may be caused by an increased drive to eat and by an impaired mechanism of satiety. Both functions are controlled by the hypothalamus. Animal experiments have shown that the parvocellular oxytocin neurones of the hypothalamic paraventricular nucleus (PVN) are crucial for the regulation of food intake. In the rat, these neurones project into brainstem nuclei; for example, the nucleus of the solitary tract and the dorsal motor nucleus of the vagus nerve (11). Small lesions in the rat PVN are responsible for overeating and obesity (12), suggesting that the PVN usually has an inhibitory effect on eating and weight. In addition, stimulation of the medial parvocellular subdivision of the rat PVN significantly increases gastric acid secretion (13). Central administration of oxytocin or oxytocin agonists inhibits food intake and gastric motility in the rat, whereas these effects are prevented by an oxytocin receptor antagonist (13–16).

We have investigated whether a disorder of the PVN or, more particularly, of its putative satiety neurones – the oxytocin neurones – might be the basis of the insatiable hunger and obesity in Prader–Willi syndrome.

The thionine-stained volume of the PVN is 28% smaller in patients with Prader–Willi syndrome, and the total cell number of the PVN is 38% lower, than in controls (17). Immunocytochemistry revealed that the immunoreactivities of oxytocin and vasopressin are decreased in patients with Prader–Willi syndrome (Fig. 1), although individual variation was high. A large and highly significant decrease (42%) in the number of oxytocin-expressing neurones was found in all five patients with Prader–Willi syndrome studied (Fig. 2). The volume of the PVN containing the oxytocin-expressing neurones was 54% lower in Prader–Willi syndrome. The number of vasopressin-expressing neurones in the PVN did not change significantly (Fig. 2). The finding that the thionine-stained PVN volume, total cell number and oxytocin cell number were low in patients with Prader–Willi syndrome indicates a disorder of hypothalamic development. These findings are consistent with the hypothesis that oxytocin neurones in the PVN may have a physiological role as ‘satiety neurones’ in ingestive behaviour in man, as well as in rats (17), and suggest that it may be possible to curb the patients’ appetites by administration of oxytocin.

Other effects of hypothalamic dysfunction

Effects on vasopressin neurones

Out of seven patients studied with Prader–Willi syndrome, two stained weakly (17) or not at all (18) for vasopressin neurones, depending on the antibody used. These two patients also did not stain with antibodies against 7B2, a neuroendocrine chaperone that prevents premature activation of the enzyme prohormone convertase (PC) 2. As the precursor of vasopressin was present in these two patients with Prader–Willi syndrome, and no PC2 activity was found in the supraoptic and paraventricular nucleus, it is presumed that they had a disturbance in the processing enzyme that also affects the 7B2 gene from the paternal allele (18; author’s unpublished data). The finding that vasopressin expression is occasionally diminished in patients with Prader–Willi syndrome is consistent with the demonstration by Miller et al. (19) that in 20% of patients there is a complete absence of the posterior pituitary bright spot on magnetic resonance imaging (MRI), indicating a disturbed function of the hypothalamic–hypophyseal system. Such a defect has also been found in patients with hypothalamic diabetes insipidus. Whether a vasopressin defect is indeed present in patients with Prader–Willi syndrome who lack the posterior pituitary bright spot on MRI should be investigated by a combination of pre- and post-mortem observations.

Temperature control and sleep disturbances

The observation of aberrant control of body temperature in Prader–Willi syndrome is also interpreted as a hypothalamic disturbance (20).
Fig. 1. Thionine-stained sections of the PVN, showing no clear qualitative differences between controls (A) and patients with Prader–Willi syndrome (B). The staining of oxytocin (C and D) and vasopressin (E and F) was generally lower in patients with Prader–Willi syndrome (D and F) than in controls (C and E). Two patients with Prader–Willi syndrome had either intense or weak oxytocin staining (G) but only negligible vasopressin staining (H) in the PVN. The bar represents 50 μm. Reproduced with permission from Swaab et al. (17).
Effects on stature

Short stature and delayed skeletal maturation are the most frequent features of Prader–Willi syndrome, occurring in 90% of patients (24). This short stature is probably only partly due to hypogonadism: patients also have blunted growth hormone (GH) responses to pharmacological stimuli and to GH-releasing hormone (GHRH), suggesting that hypothalamic dysfunction is an important factor in short stature (25, 26). The possibility that short stature is due to a deficit above the level of the pituitary is reinforced by the fact that GH treatment stimulates growth in patients with Prader–Willi syndrome. In addition, weight gain is decreased after GH treatment, and levels of insulin-like growth factor I are increased (4, 24, 27). In GH-deficient children with Prader–Willi syndrome, the overall mean height SD and weight SD changed from −2.2 to −0.8 and from 3.5 to 2.4, respectively, after 2 years of GH treatment (24). GHRH is produced in the arcuate nucleus (28), and preliminary results indicate that GHRH production in this region may be decreased in at least some patients with Prader–Willi syndrome (author’s unpublished data).

Conclusions

Most of the signs and symptoms of Prader–Willi syndrome seem to have their basis in dysfunction of hypothalamic systems: obstetric problems and inatellite hunger appear to be due to a lack of oxytocin, hypogonadism to LHRH deficiency, and short stature to a lack of GHRH. Aberrant temperature control and sleep disturbance may also be due to hypothalamic dysfunction. This possibility should be confirmed by quantitative immunocytochemistry on autopsy material from patients with Prader–Willi syndrome.

References