Press release

The 11st *Colloque Médecine et Recherche* of the *Fondation Ipsen in* the Endocrinology series: "Multiple origins of sex differences in brain. Neuroendocrine functions and their pathologies."

Paris (France), 29 November 2011 - Although the behavioural differences between males and females are plain to see, the mechanisms that underlie them are complex and not well understood. Reproductive and maternal behaviours, differences in cognitive skills and levels of aggression all result from an interweaving of genetic, epigenetic, developmental and hormonal influences; in humans these are overlaid with social and cultural programming. Perturbations of these processes may underlie conditions such as autism and attention deficit hyperactivity disorder, as well as rarer syndromes resulting from hormonal imbalances. Twelve scientists from Europe and the USA teased out these interactions at the annual Endocrinology colloquium hosted by Fondation IPSEN on Monday November 28th, 2011. The meeting was held in Paris and has been organised by Donald Pfaff (*Rockefeller University, New York, USA*) and Yves Christen (*Fondation IPSEN, Paris, France*).

At the start of embryonic life, the plan of the mammalian embryo is essentially female – male gonads differentiate only when one or more genes on the male-determining Y chromosome activate a cascade of reactions resulting in the local production of testosterone, which suppresses the female developmental path. The circulating sex hormones later influence the differential development of parts of the brain, particularly the hypothalamus, which regulates production of many hormones, including those involved in reproduction, lactation and maternal care and stress responses.

In most mammals, the adult female animal spends 95% of her time and energy on reproduction and maternal care, which has created considerable evolutionary pressure, particularly on the inter-related development of the hypothalamus and placenta, itself a source of hormones (Eric Keverne, *University of Cambridge, UK*). This pressure is further transmitted by the co-existence of three generations during gestation: the mother, foetus and the oocytes contained within the female foetus.

Sexual differentiation of the hypothalamus involves epigenetic regulation of gene transcription. Hormonal activation of genes induces changes in the chromatin structure in neurons, especially modifications of histones that determine whether or not a gene is transcribed (Pfaff). Another epigenetic mechanism, known as imprinting, identifies the parental origin of many genes involved in reproduction and sexually determined behaviour (Keverne; Catherine Dulac, *Harvard University, Cambridge, USA*). Imprinting is a major dynamic form of epigenetic regulation of hypothalamic function (Dulac) and enables coordinated gene expression in the hypothalamus and placenta (Keverne). In mice more than 1000 imprinted genes have been identified in areas of the brain regulating social, motivational and homeostatic functions (Dulac).

Apart from the hypothalamus, the differences between male and female brains has long been debated. Careful assessment of changes in the sizes of different brain structures between the ages of 3 and 30 years reveals that male and female brains are more alike than

different (Jay Giedd, *National Institute of Mental Health, Bethesda, USA*). In both sexes, some areas mature earlier than others but in general female brains mature earlier than male. Understanding the subtle differences in these changes may throw light both on behaviour and on illnesses more common to one sex than the other. At the microscopic level, sex-related differences in synaptic number and density are being found in the temporal lobe of the cortex (Javier DeFelipe, *Universidad Politécnica de Madrid, Spain*).

As well as directing the development of the male reproductive system, testosterone also has a powerful action on the foetal and neonatal brain, and consequently on promoting male-type behaviour, including toy preferences, sexual orientation, gender identification and some cognitive abilities (Melissa Hines, *University of Cambridge, UK*). The effect of social and cultural influences on this biological programming are being examined, particularly in a condition known as congenital adrenal hyperplasia, in which a genetic defect causes females to have some masculine behavioural characteristics and ambiguous genitalia as a result of producing androgens as well as oestrogen (Hines; Phyllis Speiser, *Hofstra North Shore LIJ School of Medicine, New York, USA*). Studies of brain development, cognitive functions and behavioural choices in affected women indicate that not all human behaviour is dictated by hormones (Speiser).

Male-type behaviour seems to be expressed to an extreme in people with autism, which is in any case far more prevalent in males. Foetal testosterone levels affecting brain development, arousal, and social and communication behaviour seem likely to be significant in the development of autistic behaviour but genetic predisposition and stress early in life probably also contribute (Pfaff; Simon Baron-Cohen, *University of Cambridge, UK*). Attention deficit hyperactivity disorder is also far more common in boys than girls, although to some extent this may reflect a bias in diagnosis (James Swanson, *University of California, Irvine, California, USA*). This condition may also have developmental origins, with risk factors including stress in pregnancy and maternal obesity, and some abnormalities in circadian rhythms are being found in affected children. Prenatal stress, particularly pre-eclampsia and growth restriction, seems to be a significant factor for developing major depressive disorder and increased risk for cardiovascular disease in later life, a combination that affects women more than men (Jill Goldstein, *Brigham and Women's Hospital and Harvard Medical School, Boston, USA*). The stress disturbs the development of the foetal hypothalamus/pituitary/adrenal axis, resulting in deficits in sex-specific stress response circuits, endocrine regulation and parasympathetic cardiac regulation.

Testosterone is not the only hormone affecting brain and behaviour – the serotonin system is also implicated in aggression and in psychiatric conditions marked by high impulsivity and aggression, which tend to be more common in males than females (Francesca Ducci, *King's College, London, UK*). Several variants in genes involved in this system have been linked to aggression and stress reactivity in studies of families, people with Conduct Disorder and Antisocial Personality Disorder, and violent Finnish prisoners. High risk in males with these variants is associated with testosterone levels, childhood trauma and other forms of stress, and alcohol use.

So far no mention of the female hormone, oestrogen. As foetuses of both sexes are bathed in maternal oestrogen, this hormone seems to have little effect on the sexual differentiation of the brain. At the other end of life, however, the decline in oestrogen levels in post-menopausal women has been associated with higher risk of stroke, neurodegenerative disease and osteoporosis (Phyllis Wise, *University of Washington, Seattle, USA*). Some studies have found that post-menopausal oestrogen therapy can be deleterious, but a re-

examination in animal models of stroke is showing that oestrogen has a strong anti-inflammatory action in both stroke and sepsis, provided it is replaced straight after its withdrawal.

Yet again, the speakers at this colloquium have demonstrated the complex factors involved in the regulation of human behaviour. Behavioural differences between the sexes in humans result from a tapestry of influences: genes, hormones, stress in pregnancy, life events, social and cultural programming all contribute to the wide spectrum of behaviours seen in both sexes. Out of the deeper understanding that serious conditions, ranging from autism and attention deficit hyperactivity disorder to stress reactivity, depression and extreme aggression, all have their roots in this intricate network should come leads to their prevention and treatment.

La Fondation Ipsen

Established in 1983 under the aegis of the Fondation de France, the mission of the Fondation Ipsen is to contribute to the development and dissemination of scientific knowledge. The long-standing action of the Fondation Ipsen aims at fostering the interaction between researchers and clinical practitioners, which is indispensable due to the extreme specialisation of these professions. The ambition of the Fondation Ipsen is to initiate a reflection about the major scientific issues of the forthcoming years. It has developed an important international network of scientific experts who meet regularly at meetings known as Colloques Médecine et Recherche, dedicated to six main themes: Alzheimer's disease, neurosciences, longevity, endocrinology, the vascular system and cancer science. Moreover, in 2007, the Fondation Ipsen started three new series of meetings. The first series is an annual meeting organized in partnership with the Salk Institute and Nature and focuses on Biological Complexity; the second series is the “Emergence and Convergence” series with Nature, and the third with Cell and the Massachusetts General Hospital entitled “Exciting Biologies”. Since its beginning, the Fondation Ipsen as organised more than 100 international conferences, published 72 volumes with renowned publishers and 219 issues of a widely distributed bimonthly newsletter Alzheimer Actualités. It has also awarded more than 100 prizes and grants.

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