Neuro-endocrinology

2 BRIEFINGS

BRAIN DEVELOPMENT, FERTILITY AND KALLMANN'S SYNDROME

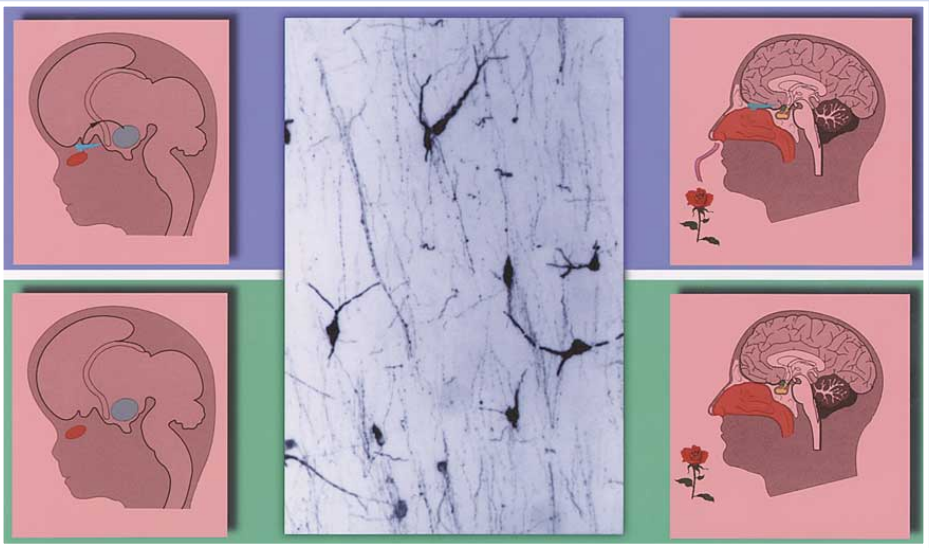
SUMMARY

Our nose is the early repository of our reproductive destiny! Surprising as this statement might appear, recent research has revealed that the nerve cells that control fertility have an olfactory origin. During early foetal life these cells migrate from the nose into the brain, along nerves that convey our sense of smell. Conditions, such as Kallmann's Syndrome, in which these neurones are imprisoned in the nose, lead to infertility in adulthood.

Nosy Neurones: a tale of sex and the sense of smell

In our daily lives we are surrounded by evidence of the powerful link between our sexuality and the sense of smell. Think only of the multi-billion pound perfume and deodorant industries! It appears that our reproductive processes are manipulated, not only by these expensive artificial odours, but by nature's own airbourne chemical signals, known as pheromones. In a recent article in "*Nature*", scientists have shown that human pheromones can alter the timing of ovulation in women. But what is the basis of the association between our fertility and the sense of smell. For an explanation we must look at the development of the brain centres that regulate these two functions.

Reproductive processes are ultimately controlled by highly specialised nerve cells (neuroendocrine neurones) in the brain. In the adult, these are located in an area at the base of the brain known



Centre panel shows widely distributed GnRH neurones and fibres (ribbon-like strands) in the hypothalamus of an adult. These neurones are absent from the hypothalamus of those with Kallmann's syndrome as they are imprisoned in the nose where they originated. Sufferers are, thus, infertile. This is because of severe abnormalities in the development of the olfactory bulbs (shown in bright blue in the upper panels: normal foetus, left: adult, right) of those with Kallmann's syndrome (bottom panels: Kallmann's foetus, left: Kallmann's adult, right). Because of this abnormality the developing GnRH neurones cannot migrate via this route from the nose (left panels, red oval) to the hypothalamus (left panels, blue oval). As well as being infertile Kallmann's sufferers have no sense of smell (right panels).

Neuro-endocrinology Briefing 2:
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as the hypothalamus. These neuroendocrine neurones make and release a ten amino acid peptide termed gonadotrophin releasing-hormone or GnRH. As the name indicates, the function of GnRH is to stimulate the release the two gonadotrophins, luteinising hormone and follicle stimulating hormone, from the pituitary gland (which lies just below the hypothalamus). The gonadotrophins are transported in the bloodstream to the ovaries of the female and the testes of the male where they regulate the production of the sex hormones, oestrogen and testosterone, and the production of mature eggs and sperm.

"Several thousand GnRH neurones embark on this long trek."

GnRH neurones are unique among neuroendocrine neurones in that they do not originate in the brain. It was extremely surprising when, a decade ago, scientists reported finding GnRH neurones in the developing nose of the embryonic mouse. There is now indisputable evidence from species, including man, that GnRH neurones originate outside the brain in the medial olfactory placode of the nose. They end up in the hypothalamus by migrating into the developing brain early in foetal life. Several thousand GnRH neurones embark on this long trek and finally reach their hypothalamic destinations by about the 16th day of pregnancy in the mouse and rat, the 70th in the sheep and 16th week of gestation in the human.

But how do the GnRH neurones navigate a successful course to the hypothalamus? And how do they know where to stop? Although we still have much to learn, we do know that the neurones migrate along the axons of the nervus terminalis and vomeronasal nerve as they invade the brain. The search is now on for the chemical "pole star" which guides them to their destination. The "stop" signal, however, appears to be rather imprecise. Thus, adult GnRH neurones do not end up in a neat clump but rather form a "smear" in the midline, close to the base of the hypothalamus. Somehow, this diffuse GnRH neuronal population is able to communicate so that the neurones are co-ordinated to secrete GnRH as a discrete bolus or "pulse". The intermittent nature of GnRH release is critical for the appropriate response of the reproductive organs. Hence, the *pattern* of pulsatile release regulates the activity of the ovary and testis and is responsible for the secretion of the reproductive hormones.

"GnRH neurones are found to be imprisoned in the nose."

But what of sex and smell?

In 1944, a geneticist and psychiatrist named Franz Kallmann was fascinated by a group of patients who exhibited both a lack of sexual development and sense of smell. Further investigation showed that these Kallmann's syndrome patients had abnormal, or absent olfactory bulbs and nervous connections to the centres of the brain that control the sense of smell. Because the vomeronasal and terminal nerves that form the axonal "bridge" between the nose and the brain were missing, the route along which the GnRH neurones normally migrate to the hypothalamus was absent. When the brains of those with Kallmann's syndrome are examined the GnRH neurones are found to be imprisoned in the nose, far from the site at which they can exert their influence on the reproductive system. Hence, Kallmann's syndrome patients remain in a reproductively immature state. Luckily, this infertile state can be overcome. Basic scientific investigations carried out by neuro-endocrinologists have informed the development of clinical treatments which can restore full fertility to Kallmann's sufferers. Treatment involves the use of a small portable, programmable pump which delivers GnRH as a series of discrete pulses at approximately two hourly intervals. After several months patients go through "puberty" and develop an adult physique. With continued treatment many have also been able to experience the joys of parenthood.

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Neuro-endocrinology Briefings are produced by the British Neuroendocrine Group

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