A male or female brain? A question of estradiol!

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Sexual differentiation of the brain allows individuals to display male- or female-typical behaviour from puberty on. Although it has been well established that testosterone acts to masculinise the brain during embryonic development, scientists believed that estradiol was not involved in the feminisation of the brain until now. A theory that has been disputed by researchers at ULg who have proved the contrary in an article published in *The Journal of Neuroscience*.

Although the taboos surrounding sexuality have been falling away one by one since the end of the 20th century, transsexualism remains relatively repressed in western societies. Indeed, it is often considered to be just an oddity and yet, transsexualism is a real dissonance between the biological sex and the gender identity felt by an individual. Why do certain people, despite having a perfectly developed anatomy, feel like that they belong to the opposite sex? The origin of this disorder is still not well understood. One of the leads followed by scientists is the role of sex hormones during the development of the embryo. It seems that they are involved in the sexual differentiation of the human brain by programming gender identity and sexual orientation of an individual at the embryonic stage.

"Sexual hormones have two distinct roles", explains Julie Bakker qualified FNRS researcher at the Behavioural Neuroendocrinology Unit of the GIGA of ULg. "During development, that is up until puberty, these hormones contribute to the organisation of behaviour". Then, from puberty, they play a more active role in terms of sexual behaviour".

"Default" feminisation of the brain

According to the classic theory of the sexual differentiation of the brain, sex differences in the brain and behaviour of mammals develop under the influence of gonadal hormones. According to this theory, the development of the brain follows a "male" direction under the influence of testosterone secreted by the testes. "In the male, testes develop in the first months of embryonic development. They secrete testosterone which reaches the brain in the second trimester of development and leads to masculinisation", specifies Julie Bakker. In reality, paradoxically, to induce this masculinisation of the brain, testosterone must be transformed into estradiol - an estrogenic hormone considered to be a female hormone - by an enzyme
called "aromatase". It should be noted that the necessity of converting testosterone into estradiol is important mainly for the masculinisation of the brain in rodent species. However, we believe that it is testosterone and not estradiol that masculinises the human brain!

"In females, however, ovaries are not active during prenatal development. So there is no secretion of sexual hormones" continues the researcher. This supports the notion that in the absence of any gonadal hormones, female-typical neurological and behavioural characteristics develop, thus "by default".

**Of mice and men**

The main purpose of Julie Bakker’s research is to identify the neural circuits involved in reproductive behaviour and to analyse the mechanisms by which steroid hormones induce the sexual differentiation of the brain. In order to do so, and thanks to the support of the National Institute of Health (NIH) (USA) and the Nederlandse Organisatie voor Wetenschappelijk Onderzoek (NWO-VICI) (NL), the scientist combines research projects on transgenic mice and human subjects. "We work with transgenic mice that are no longer capable of synthesising certain hormones and we observe the repercussions that this has on their sexual behaviour and brain anatomy", explains Julie Bakker. “For research on humans, we conduct post mortem examinations on human brains as well as functional magnetic resonance imaging (fMRI)” studies on brains of different groups of patients suffering from disorders of sexual differentiation or who have a different gender identity than their biological sex.
For the mouse studies, Julie Bakker and her colleagues used ArKO mice, in which the gene encoding the aromatase enzyme has been deleted. Male mice are thus incapable of transforming testosterone into estradiol during their prenatal development and in adulthood, and adopt a similar behaviour to males that have been castrated in adulthood. These observations are in line with the classic theory of the sexual differentiation of the mammalian brain. However, Julie Bakker and her team obtained another result which questioned this theory: female ArKO mice also demonstrate anomalous sexual behaviour. Indeed, they express less lordosis behaviours and spend less time investigating the odors of potential mates. These results would thus suggest that estradiol plays a role in the development of sexual behaviour in females. A lead that Julie Bakker was eager to explore...

**An obsolete theory?**

In an article recently published in *The Journal of Neuroscience* (1), Julie Bakker and her colleagues described the experiments that enabled them to confirm the importance of estradiol in the development of the female brain. Indeed they succeeded in correcting the deficits in sexual behaviour in female ArKO mice, thanks to treatment with estradiol. An important point to highlight: "This treatment is effective after and not..."
beforebirth of female ArKO mice. More specifically, we succeeded to correct the sexual behaviour of ArKO females when the treatment was administered just before puberty in these animals", says Julie Bakker.

According to the researcher, in view of these new results, the classic theory of sexual differentiation of the mammalian brain needs to be revised. As with masculinisation, the feminisation of the brain would appear to be influenced by sexual hormones and does not proceed "by default". Furthermore, it is important to note the different "time windows" for the sexual differentiation of the male versus the female brain. Whereas in males, testosterone must act during embryonic development to induce the masculinisation of the brain, in females, the sexual differentiation seems to occur just before puberty...
The classic theory of sexual differentiation of the brain and behaviour. In the male embryo, testosterone (T) secreted by the testes enters freely into the brain, where it is converted into estradiol (E) by the aromatase enzyme. Under the influence of testosterone and estradiol, the brain thus becomes defeminised and masculinised. In the female embryo, the development occurs without any hormonal secretion; estradiol from the maternal circulation is bound with high affinity to alpha-fetoprotein (AFP), which protects the brain of female embryos from being defeminised and masculinised by this hormone.

(Bakker et al, Nature Neuroscience, 2006)
Tracking the route of estradiol in the neural circuits

In terms of research on the human model - which she is conducting in collaboration with the Nederlandse Instituut voor Neurowetenschappen (NIN) and the "Medisch Centrum Vrije Universiteit" in Amsterdam (Netherlands) - Julie Bakker has already her own ideas on putting these new results in perspective. "We could look at women who do not synthesise estrogen, such as women with Turner Syndrome for example, to see whether they have undergone a different sexual differentiation of the brain" explains the researcher. Turner syndrome is a chromosomal disorder. Affected women only have one X chromosome. Symptoms include small and non-functioning ovaries, and therefore a lack of estrogen secretion. "Initially, patients receive a treatment with growth hormones to reach a maximal size. Then, at puberty, an estrogen treatment begins in order to allow the young girls to develop", specifies Julie Bakker.
Female hormonal profile

**Classical theory**

*must be revised*

**Feminizing effects of estradiol**

- **P0**
- **P7**
- **P30**

**ORGANIZATION**

conception → Prenatal development → Birth

**INITIATION OF DEVELOPMENT**

Puberty

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Male hormonal profile

**Defeminizing and masculinizing effects of testosterone and estradiol**

- **conception**
- **Prenatal development**
- **Birth**
- **Puberty**
She is also trying to determine where estradiol acts in the female brain and the neuropeptide systems involved in the feminisation of the brain. "But also to determine the contribution of genes located on the X chromosome to the feminisation process since genes and hormones interact", concludes Julie Bakker. These studies should increase our understanding of how sex differences in brain and behaviour develop under the influence of gonadal hormones and sex chromosome genes and ultimately to understand why certain people feel like they belong to the opposite sex.