Sexual orientation in all its aspects

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Boosted by his research and extensive reading on the influence of biology on sexual orientation, Jacques Balthazart summarises existing knowledge on the subject in a scientific article (1) in which he describes what is known based on animal models as well as on what is currently understood about the influence of hormones, genetics and epigenetics on sexual orientation in humans.

Jacques Balthazart's book caused a stir when it was published in 2011 and has been the subject of much debate ever since. It is certainly true that "The Biology of Sexuality - We are born homosexual, we don't choose to be so" (see article: Are we born homosexual?), clearly expresses the researcher's message and it is one that does not find favour with everyone. Jacques Balthazart, emeritus head of the Behavioural Neuroendocrinology Research Group in the GIGA-neurosciences centre of the University of Liege, has been studying this question for many years, both on animal models in his laboratory and in the literature on the subject. "One of the main differences that exists in terms of the sexual behaviour of men and women is sexual orientation: a large majority of women are interested in men and a large majority of men are attracted by women", explains Jacques Balthazart. "Therefore there is a huge difference between the sexes in terms of sexual attraction with the exception of a small section of the population of between 2% and 10% of individuals who are homosexual and who are therefore interested in having a same-sex partner." Struck by the fact that this sexual difference continued to be attributed to education or to deliberate choice, the scientist wanted to put down on paper, current biological knowledge on homosexuality, in a way that was accessible to all. "Repeated claims are made that homosexuality is caused by some deficiency in the mother's role, the absence of a father or an unresolved Oedipus complex etc. But apart from this, there are thousands of scientific articles that show an influence of prenatal hormones, genetics or even epigenetics", continues Jacques Balthazart.
Embryonic hormones at the heart of the controls of sexual orientation

In the context of a special volume of *Philosophical Transactions of the Royal Society B* (1) on the multiple origins of sexual differences in the brain, the coordinator of the volume asked Jacques Balthazart to carry out a review of the literature on the biological factors that influence sexual orientation. "In this article, I explain what we know about animals and that could have an impact on humans as well as what is actually known about humans", says the scientist.

In his laboratory, Jacques Balthazart studies how male (*testosterone*) and female (*oestradiol*) sex hormones act on the brain to control sexual behaviour. In order to do this, the researcher and his team used various animal models such as quail, canaries, rats or mice. "We realised that hormones act during very early life, that is to say, *in utero*/ovo, or during the first days of life, to irreversibly define how males and females will react to sex hormones as adults. This is what is known as the organising effects of hormones on the brain", explains the scientist. Hormones will therefore influence the structure of the brain so that it will be organised in such a way as to produce male or female sexual behaviour. By means of several experiments, the researchers were able to demonstrate that it is possible to deliberately reverse sexual orientation in animals such as rats by manipulating sex hormones at birth or slightly before. The females then show male behaviour and males show female behaviour when they are at the reproductive age.

In the west of the US, there is an animal model that is well known in terms of homosexuality. "*This came to light after fertility problems were identified in these sheep*" explains Jacques Balthazart. "*Research on this sheep population shows that the homosexual rams do not present hormonal problems in adulthood but that their sexually dimorphic nucleus - responsible for sexual behaviour and located in the brain preoptic area - is smaller than in the other males and..."
is of similar size to that present in the females”. Significantly, this nucleus is essentially regulated by embryonic hormones…If the embryo is exposed to an high level of testosterone, it will develop a male-sized nucleus. If there is not much testosterone at this stage of development, the size of the sexually dimorphic nucleus will be smaller like those of the females.

**When the hormonal balance is upset by illness**

In humans, this difference in the size of the sexually dimorphic nucleus had already been observed as far back as 1993. "This is old information but still remains relatively unknown, especially in France where the influence of biology on homosexuality is rarely spoken about”, the Professor continues, "This area of the brain was histologically examined in humans based on examination of the brains of individuals who died from the AIDS epidemic. But observation of this difference does not constitute formal proof because it is difficult to be sure about an individual’s sexual orientation before their death and some say that the reduced size of the sexually dimorphic nucleus is a consequence and not a cause of homosexuality”. In rats and sheep, scientists have proved that it is a consequence of the action of prenatal hormones and that the size of this nucleus is correlated to the sexual orientation of these animals. It is therefore tempting to think that the same mechanisms could apply in humans…

Other arguments about the influence of embryonic hormones on human sexual orientation can be added to the list. There are illnesses which affect the embryonic hormonal balance which are associated with a change in sexual orientation. For example, hyperplasia of the adrenal glands consists of an abnormal development of these glands which then no longer secrete cortisol but which produce androgens instead. "The girls affected are often exposed to much higher levels of male hormones than normal during the course of their embryonic life. This results in a masculinisation of genital structures. Some are born with a fusion of the lips or a clitoris the size of a penis etc.”, explains Jacques Balthazart. Very often, these anomalies are corrected at birth and the children in question are raised as little girls. But, in terms of behaviour, they are more inclined to play at more masculine games, and, at an adult age, the incidence of female homosexuality in these in these young girls is in the order of 20% to 40% according to studies. "It could therefore be thought that this excess of androgens during prenatal life leads to a masculinisation of sexual preferences”, continues the scientist. "And the higher the levels of secretion of prenatal androgens, the more homosexuality incidence increases. It is one of the arguments for the influence of hormones on sexual orientation in humans”.

Finally, an entire series of human characteristics are influenced by prenatal hormones and can be correlated to the sexual orientation of individuals. A series of factors are masculinised by prenatal testosterone. The relative length of the 2nd and 4th fingers of the right hand, for example. "Men generally have a shorter 2nd finger than the 4th”, explains Jacques Balthazart. "And homosexual women also statistically have a shorter 2nd finger than the 4th which would suggest that they have been exposed to an excess of testosterone. Of course this does not work on an individual level but it has been statistically confirmed".
Unfortunately, it is very complicated to obtain formal proof of the influence of embryonic hormones on sexual orientation. In fact, there is an enormous amount of variation because hormonal disturbances can occur at different stages of embryonic life. This proof could eventually be obtained thanks to a study of individuals from the embryonic stage up to the age of 25. "In an ideal world, it would be necessary to take blood samples from embryos and observe the sexual orientation these individuals have at an adult age. This is both ethically unacceptable and nobody has the means to conduct such a study", states the scientist.

The concordance of sexual orientation in twins

In parallel with the study of the influence of hormones on sexual orientation, much research has focussed on the influence of genetics on homosexuality. "We know that this influence exists because, if we look at family lines where a first individual is seen to be homosexual, the probability that other members of the family will be homosexual also is increased compared to the average observed for the population", explains Jacques Balthazart. Naturally, we could all tell ourselves that it is simply a question of education or family environment, but this would be to ignore a certain number of studies conducted on dizygotic and monozygotic twins. "The concordance of sexual orientation of twins is higher in "real" twins than in "false" twins", states the Professor. "There is a 65% rate of concordance of sexual orientation in monozygotic twins but only 18% in dizygotic twins". But genetics does not explain everything because there is "only" 65% concordance in two people who have a virtually identical genome…Whether they involve hormones, genetics or epigenetics, the biological factors do not by themselves provide a full explanation for the biological origins of homosexuality, but together, they constitute a set of arguments showing that the biological influence is very important.
The X chromosome in the spotlight

With regard to the genes involved in a predisposition to homosexuality, different research groups have been focussing on the question but no clear evidence has yet been established. "It seems that there is not only one gene responsible but that there are many and they are not very penetrating, that is to say that while they do not directly determine sexual orientation, they can influence it", indicates the researcher. However, scientists agree to say that masculine sexual orientation is inherited from the mother. In fact, when there is a homosexual male in a family, there is a higher chance that other men will be homosexual in the maternal branch of the family. From this starting point, researchers have hypothesized that the genes responsible for sexual orientation are likely to be found on the X chromosome. "They realized that at the end of this chromosome, there is an area called XQ28 in which they found genetic markers associated with homosexuality", says Jacques Balthazart. "Another study shows that this zone contains a gene known as MAGE A11, which controls sensitivity to testosterone in males. This gene could be modified in some individuals and affect the sensitivity of their brain to testosterone". But this has yet to be demonstrated.

The last biological factors influencing sexual orientation which are being studied by scientists are the epigenetic factors. "Epigenetics involves the modification of histones, protein-based constituents of chromosomes, or parts of the DNA which permanently change the expression of certain genes", explains the researcher. "We know that the synthesis of sexual hormones and their actions are controlled by epigenetic factors. In addition, before these hormones appear in the embryo, dozens of genes are expressed in a differential manner in the male and female. This can only stem from a genetic control from sex chromosomes that induce the modification of the expression of other genes by epigenetic mechanisms", affirms Jacques Balthazart. In humans, initially, genital structures are non-differentiated at the early embryonic stage. It is only by means of the action of testosterone that the external genetic organs are formed. "When we consider the levels of testosterone in embryos, there is more in the males than in the females but there are superimpositions of these hormone levels. The females who have the most testosterone are at the same level as the males who have the lowest amount of the hormone", explains the Professor. If this was the only factor controlling the differentiation of
genital structures, there would be many individuals born with intersex genital structures but this is not the case. "In reality, testosterone only acts after being transformed by an enzyme and this transformation is epigenetically regulated differently in males and females. There is therefore more testosterone in active form (5-alpha dihydrotestosterone) in males, independently of the levels of testosterone". This explains why, despite the overlapping levels of testosterone, in almost all cases, a sex difference in genital structures is observed.

Concerning the question of the influence of epigenetics on sexual orientation, American researchers recently developed a mathematical model making it possible to analyse the contribution of the epigenetic phenomenon to the sexual orientation of males and females. "This model could help to partly explain the deviations that can occur in certain individuals".

**No formal proof but numerous arguments**

Finally, a last known factor at this stage contributes to the explanation of masculine homosexuality: the number of older brothers born of the same mother. "The more male children a woman has, the greater the probability that boys born later will be homosexual", states Jacques Balthazart. "This probability increases by 33% for each boy born of the same mother. This was demonstrated by Canadian researchers. Here too, it had been suggested that it was a question of family environment, but the data accumulated from 25,000 homosexual males made it possible to discount this argument". The most probable hypothesis which could explain this effect of older brothers is that the mother develops antibodies against a protein produced by the male foetuses. These antibodies modify the development and therefore the structure of these babies. "And the effect of these antibodies increases with each successive male embryo", continues the researcher.

In conclusion, several studies show a hormonal, genetic and epigenetic influence on sexual orientation. None of them can alone offer a complete explanation for homosexuality and each explanation in isolation can be disproved. "But when we look at all these studies, they constitute an array of arguments which suggest that biology has a great influence on sexual orientation and therefore homosexuality", affirms Jacques Balthazart. "It would be difficult to imagine that, from an evolutionary point of view, sexual orientation, which is crucial for the survival of the species, could go from being controlled by biological factors in animals, to being merely determined by education in humans", he continues. "In addition, homosexuality is present in all human societies with more or less the same frequency. The more tolerant a society is with regard to homosexuality does not lead to an increase in homosexual individuals".

In the face of arguments suggesting the influence of biology on sexual orientation, there are two types of reactions as Jacques Balthazart was able to experience. "For some people, it is a relief to be able to explain their sexual orientation from a biological point of view. This deculpabilises the parents or individual concerned with regard to the situation. Homosexuality is often more readily accepted when biology is seen to have a role in this sexual orientation", explains the scientist. Other people, however, do not want to entertain any biological explanation. "This is either because they prefer to assume that it is a deliberate choice, or because it is a problem for them that a medical approach is taken towards the phenomenon". The question of the origin of homosexuality is a complex and sensitive one. Scientific progress makes it possible to provide some answers but has not yet provided formal proof of a biological origin. And if this proof is obtained one day, will it put an end to the many debates surrounding homosexuality? Nothing could be less certain...
Schematic representation of the hormonal, genetic and epigenetic mechanisms that control sexual differentiation of the brain in mammals. The most detailed study of these mechanisms took place during analysis of the sexual differentiation of the sexual behaviour in rodents but the mechanisms can be applied in a wider sense to other phenomena. The presence of the SRY gene on the Y chromosome leads to the formation of testicles that produce testosterone (T) which, through its aromatisation (Arom) in œstradiol (E2) masculinises the brain. Direct genetic influences of genes located on the Y chromosome and epigenetic influences also affect this masculinisation. In females, the absence of the Y chromosome and therefore the SRY gene, leads to the formation of an ovary secreting few sex steroids during the life of the embryo. The associated hormonal and epigenetic influences result in a brain with feminine characteristics. This “normal” sexual differentiation in physiological conditions can be experimentally reversed by castrating the males at birth or by treating the females with exogenous testosterone or œstradiol.