Neuro-oestradiol, a two-speed sexual hormone

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Oestradiol, which controls sexual behavior and is known to act in the long-term, has also been shown to be able to act rapidly, much like a neuro-transmitter. In a study published in the *Journal of Neuroscience*, researchers at the University of Liege have demonstrated that this rapid action has a direct effect on the motivational phase of the sexual behavior of male quail but not on copulation. Thus, the "long-term" mode of action serves to prepare the brain for the breeding season. It makes it possible to set up the nervous system so that it will be ready to react when required to do so. The "short-term" mechanism acts like a switch that turns on the system when the environmental and social conditions are favorable.

![Diagram of oestradiol production and action](image)

Classified as a female *hormone* due to its high circulating concentration in females, *oestradiol* (or estradiol, E2) is a form of *oestrogen*. However, this *steroid* hormone is also present in males and plays an important role in reproduction. Ironically, in spite of the high concentration of the hormone in females, oestradiol is produced from testosterone which is typically considered as a male hormone. An *enzyme* known as aromatase transforms testosterone into oestradiol in both the ovaries and testicles as well as in many other tissues including the brain. Although oestrogens are generally perceived as being associated with reproduction, they have different effects and act in numerous tissues in humans and animals. They notably play a role in bone and mammary tissue, growth, skin-flexibility, cognitive functions such as memory, neuro-protection and even hormone-dependent cancers.

**Synchronising reproduction and season**

In the male, oestrogens produced in the brain (sometimes called "neuro-oestrogens") are involved in the control of sexual behaviour. "They act through genomic mechanisms by binding to intracellular receptors and interacting with the DNA of cells in order to modulate the transcription of target genes", explains Charlotte
Cornil, Research associate at the F.R.S.-FNRS in the Behavioral Neuroendocrinology Laboratory of Prof. Jacques Balthazart, at GIGA-Neurosciences of the University of Liege. This type of action produces effects on sexual behavior within a relatively long time-frame. "The behavioral effects appear after several days", explains Charlotte Cornil. "This type of action is perfectly in line with the role commonly ascribed to oestrogens in the synchronization of sexual behaviour with the appropriate season", continues the researcher. Indeed, animal reproduction is generally controlled so that the youngs are born at the time of year that is the most favorable for their survival and growth. The environmental stimuli make this control possible and constitute signals for organisms. "For example, light affects the growth of the gonads and therefore the secretion of testosterone. This is followed by an increase in the brain production of oestradiol which itself acts on the nervous system", indicates Charlotte Cornil. So, to summarize: seasonal variations lead to variations in the secretion of testosterone upon which the production of oestrogens depends and which in turn has an effect on sexual behavior!

When oestradiol moves into second gear

In addition to these delayed effects caused by the genomic action of oestradiol, this hormone also acts faster by taking a non-genomic route. "This mode of action does not involve the modulation of the expression of genes",
specifies Charlotte Cornil. "Here oestradiol interacts with membrane receptors located on the cell surface and triggers rapid changes in cell function". As an example, this type of action by oestradiol in neurones causes a variation in the frequency of action potentials, that is to say, their firing rate.

Charlotte Cornil and Aurore Seredynski, a PhD student in the laboratory, in collaboration with Gregory Ball of the Johns Hopkins University of Baltimore (Maryland, USA), wanted to know if the rapid mode of action of oestradiol (by the non-genomic route) had an effect on the sexual behavior of Japanese quail, which is the laboratory's preferred model.

"Sexual behavior can be divided into two main phases", continues Charlotte Cornil. "The first, called the appetitive or motivational phase, includes the approach and courtship behavior which allows partners to get closer to each other. The second phase, the consummatory phase, is the behavioral sequence during which the partners copulate". While the consummatory phase is easy to assess, the motivational phase is measured by the frequency of contractions of the cloacal gland of the male quail. Birds do not have external genitalia. The sperm is transferred from the male to the female when the animals place their cloacae (posterior orifices) in contact. The frequency of the cloacal contractions in response to the sight of a female is one of the signs of sexual motivation in the male used in the laboratory setting.

**A dichotomous effect on sexual behavior**

"We administered a treatment directly into the 3rd cerebral ventricle of male birds. Some animals received an aromatase inhibitor combined or not with oestradiol", explains Charlotte Cornil. The results of this study which was published in the Journal of Neuroscience (1) reveal that the treatment was rapidly followed by an effect on sexual motivation but had no effect on the consummatory phase. Individuals who had received the aromatase inhibitor alone showed a remarkable drop in the frequency of contraction of the cloacal gland in response to the presentation of a female while those treated with the inhibitor and oestradiol showed a frequency of contraction similar to that of the control individuals. However, in both cases, the treatment did not influence the copulation of individuals. "This was a real surprise, we expected to observe effects on both phases because they are very much connected", indicates the scientist. Supplementary tests confirmed these results.

Is this effect on the motivational phase really due to the non-genomic action of oestradiol? In order to test this idea, the researchers coupled the hormone with a molecule that is incapable of crossing cell membranes: bovine serum albumin. "We obtained the same result, which indicates that the effect on sexual motivation is initiated at the cellular membrane and not in the cell nucleus", reveals Charlotte Cornil. The same hormone has therefore developed complementary mechanisms - Slow, genomic, and rapid, non-genomic - to regulate different components of sexual behavior. "Our observations suggest that the genomic mode of action serves to prepare the brain for the breeding season. It enables the nervous system to be set up such that it can react when required to do so", explains the researcher. "The non-genomic mechanisms act as a switch that turns on the system when the environmental and social conditions are appropriate", continues Charlotte Cornil.
Another line of research in the behavioral neuroendocrinology laboratory is the study of the control of aromatase. Here too, different studies have shown that in parallel with the genomic mechanisms which control the activation of this enzyme, the aromatase can be activated or inactivated a lot more rapidly by simple phosphorylation (addition of a phosphate group to a protein or small molecule). Continuing their collaboration with Gregory Ball, Charlotte Cornil and Catherine de Bournonville, a PhD student in the laboratory, wanted to know more about the rapid changes in aromatase activity that occur in vivo following sexual interactions in quail. "To ensure rapid changes in local oestradiol concentration, aromatase must also quickly change its activity", specifies Charlotte Cornil.

Scientists dissected six aromatase-expressing cell populations in the brains of male quail which had been previously exposed to the sight of a female or that had copulated. "We noticed that aromatase activity drops rapidly after copulation but also after simple visual contact with the female", indicates Charlotte Cornil. The results of this study have been published in the journal Psychoneuroendocrinology (2).

"We have not yet solved the mystery of this early drop in aromatase activity. But if we take into account our previous study, we can hypothesize that, as the rapid action of oestradiol affects sexual motivation but not performance, oestradiol needs to be rapidly synthesized in order to allow the animals to get closer to each other but is no longer required afterwards when other neurotransmitters take over, which might explain the drop in aromatase activity after just seeing the female", explains the researcher.
A hormone that ressembles neurotransmitters

More and more studies tend to show that oestradiol is capable of rapid action. This is true to such a degree that scientists are asking the question as to whether this hormone should not be placed in the same category as "neurotransmitters" instead of continuing to consider it as a chemical messenger which exerts a long-term action (3). Indeed, while hormones are molecules secreted into the blood and act on distant targets, neurotransmitters are synthesized in the synapses where they act directly. The two studies mentioned here reinforce the idea that oestradiol, with its non-genomic action, behaves more like a neurotransmitter.
Regulation of reproduction by the combined action of the genomic and non-genomic effects of estrogen. When the concentrations of circulating testosterone (T) are weak (winter-time), the local concentration of estrogen in the brain is also weak. There is therefore no activation of behavior by the steroids (neither a genomic nor a non-genomic effect). The nerve circuits which control behavior (represented here by the connections joining the median preoptic nucleus [MPN] to the periaqueductal grey nucleus [PGN; premotor relay] and also to the spinal cord) are present but non-functional. The secretion of testosterone by the testicles increases under the influence of the longer days of spring and leads to the transcription of aromatase (ARO).


(3) Jacques Balthazart, Gregory F. Ball. *Is brain estradiol a hormone or a transmitter? Trends in Neurosciences* 2006 • 29, 241-249. Read the article: Oestradiol, sex dan sun.