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Euro Neuropharmacology 2018: Interaction of Oxytocin and neuropeptide S in anxiety and social fear - Inga D Neumann - University of Regensburg.

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Abstract:

Oxytocin is a neuropeptide hormone and it is generally produced in the hypothalamus and released by the posterior pituitary. It plays an important role in social bonding, sexual reproduction, childbirth, and the period after childbirth. Oxytocin is derived by the enzymatic cleavage encoded by the human OXT gene. It is synthesized as an inactive precursor protein. This precursor protein includes the oxytocin carrier protein neurophysin I.The inactive precursor protein undergoes hydrolysis into smaller fragments via a series of enzymes. Upon hydrolysis that releases the active oxytocin nonapeptide which is catalyzed by peptidylglycine alpha-amidating monooxygenase (PAM). The activity of the PAM enzyme system depends upon vitamin C. Ssodium ascorbate stimulates the production of oxytocin from ovarian tissue over a range of concentrations in a dose-dependent manner. Many of the similar tissues where PAM is found are also known to store higher concentrations of vitaminC. Oxytocin is metabolized by the oxytocinase, leucyl/cystinyl aminopeptidase. Amastatin, and puromycin have to inhibit the enzymatic degradation of oxytocin and degradation of various other peptides, such as vasopressin, met-enkephalin, and dynorphin A. Hypothalamus is made in magnocellular neurosecretory cells of the supraoptic and paraventricular nuclei, and stored in Herring bodies. Later, It is released into the blood from the posterior lobe of the pituitary gland. The axons have collaterals that innervate neurons in the nucleus accumbens, where oxytocin receptors are expressed. The endocrine effects of hormonal oxytocin and the cognitive or behavioral effects of oxytocin neuropeptides are coordinated through its common release through these collaterals. Oxytocin and arginine vasopressin are neuropeptides synthesized in the hypothalamus and secreted from the posterior pituitary gland. Oxytocin described for its key role in stimulating uterine contractions and milk let down after birth and AVP is central to water homeostasis by regulating urine concentration at the level of the kidney. In addition to these physiologic functions, both peptides are now understood to mediate numerous social behaviors in mammals. Oxytocin is also produced by few neurons in the paraventricular nucleus that project to other parts of the brain and to the spinal cord. Oxytocin receptor-expressing cells are located in amygdala and bed nucleus of the stria terminalis. After seeing the effects of oxytocin on social behavior in mammals, researchers began to investigate effects could also be observed in humans. Other research discovered that people with conditions that involve difficulties in social behavior which have lower levels of oxytocin in their blood compared with people without these conditions. Results from the earlier animal research, scientists began to examine the effect of giving oxytocin to humans as a nasal spray. Recommending oxytocin as a medication might improve some social behaviors in people who have difficulties in these areas. A Key part of social behavior is understanding what other people are thinking and feeling. This ability is known as “theory of mind,” as it involves in making a sense of what is going on inside someone else’s head. If we can understand others’ thoughts or beliefs, and how this might be different from our own thoughts or beliefs, then we can better predict how we should interact with them or how they will behave in the future. This information can be transmitted without words, through body language. We sometimes watch depressed ones slump their shoulders forward. However, most emotional information comes from the face, particularly from the eye and mouth regions.

Oxytocin has a single receptor (OXTR) encoded on chromosome 3, whereas vasopressin has three types of receptors, AVPR1a and AVPR1b (also called V3) and V2, on chromosome 20. AVPR1a is present on vascular smooth muscle, in the liver, and on neurons; AVPR1b/V3 is detectable in the anterior pituitary; and the V2 receptor is found primarily in the kidneys. Outside of the brain, oxytocin receptors are detectable in humans in high concentrations in the uterus, gradually increasing in number over the course of pregnancy. Tissue taken from hysterectomy or cesarean section at different gestational time points in pregnant women has shown a rapid regulation of oxytocin receptor expression around the onset of labor, facilitating uterine contractions Many other tissues and organs, including ovaries, testis, mammary glands, kidneys, thymus, pancreas, adrenal, and even adipose tissue, have been shown to express oxytocin and vasopressin receptors in different species; some studies revealed that exogenous synthesis of oxytocin can take place at certain peripheral sites. When considering OXT as an anxiolytic treatment, chronic neuropeptide effects should be of major. Studies performed reveal that chronic OXT effects strongly depend on the dose and duration of application, are likely to vary between male and female subjects and are dependent upon the innate level of anxiety. For example, in male mice, chronic icv infusion of OXT (10 ng/hour) over 2 weeks induce a robust increase in anxiety-related behavior in two independent behavioral tests, whereas a tenfold lower dose did not alter anxiety. In contrast, in ovariectomized, steroid-treated female rats, 5 days of icv OXT (10 ng/hour) reduced anxiety levels. In support of such sex differences, 7 days icv OXT (20 ng/hour) in male rats did not affect anxiety-related behavior. Studies proved that OXT system in general anxiety and social fear, in addition to its many prosocial effects. Differing activities of the brain OXT system, including gene expression patterns and local release, which are determined by genetic and epigenetic factors, underlie differences in emotional and social behaviors. High central OXT availability, for example, seems to be associated with an anxiolytic and prosocial, socially competent phenotype. A gradual shift of the activity scale toward the left, e.g., by diminished OXT–OXT-R interactions, is associated with elevated nonsocial anxiety, lack of social preference, and social fear. However, before the OXT system can be considered a safe treatment target, various molecular, neuronal, and brain net-

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work variables need to be studied after acute, repeated, or chronic OXT application in animal and human studies. Moreover, biological markers of the activity and responsiveness of the endogenous OXT system need to be validated and employed to distinguish potential OXT responders and nonresponders to avoid disadvantageous effects in the latter.

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