Oxytocin

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Definition

Oxyotcin is a posterior pituitary, or neurohypophysial, hormone. Oxytocin was originally detected as early as 1895, and its uterine-contracting and milk-ejecting properties were first described in the early 1900's. The specific amino acid sequence and structure of oxytocin was first described and chemically synthesized in the early 1950's by du Vigneaud, for which he won the Nobel Prize in Chemistry in 1955. The subsequent development of specific agnonists and antagonists for oxytocin has provided the platform for research to further elucidate the role of this peptide on physiology and behavior (see Caldwell and Young, 2006, for further detail).

Oxytocin is a nonapeptide comprised of nine amino acids arranged in a ring structure. It is synthesized as part of a precursor preprohormone, which is cleaved to release the active, 9-amino-acid nonapeptide. Most oxytocin is synthesized in magnocellular neurons of the supraoptic nucleus (SON) and paraventricular nucleus (PVN) of the hypothalamus which project to the posterior pituitary, where oxytocin is stored and released into peripheral circulation. Oxytocin is also produced by parvocellular neurons of the PVN, which project to areas of the limbic system, including the hippocampus, amygdala, striatum, hypothalamus and nucleus accumbens, as well as to locus ceruleus, nucleus of the tractus solitarius, and spinal cord (Sofroniew, 1983; Swanson & Sawchenko, 1980). Centrally released oxytocin is believed to regulate behavior by acting as a neurotransmitter or neuromodulator. Oxytocin has been shown to be regulated by the female gonadal hormones estrogen and progesterone. A single oxytocin receptor, a member of the G-protein-coupled receptor family, has been isolated and identified (Kimura et al., 1992), which appears to transduce the primary actions of oxytocin.

Physiologic Actions of Oxytocin

Since the 1950's, research examining the role of oxytocin on the brain and behavior has flourished, although a majority of this research has examined the role of oxytocin within non-human animal models. The direct mammalian female reproductive roles of oxytocin were among the first to be identified. Peripherally, oxyotcin is known to stimulate such female mammalian functions as milk ejection during lactation and uterine contraction at parturition (Burbach et al., 2006).

A burgeoning literature indicates that oxytocin also plays a central role in the regulation of affiliative behaviors, social attachment, and stress responses within animal models. For example, oxytocin stimulates social motivation and approach behaviors, and facilitates formation of selective mother-infant attachment and adult pair-bonds (see Lim & Young, 2006 for a recent review). Oxytocin is also released both centrally and peripherally with stress (Nishioka et al., 1998; Wotjak et al., 1998), and appears to have an anxiolytic effect on endocrine and behavioral systems (Windle et al, 1997).

As compared with the animal literature, human research on the role of oxytocin is in its infancy. Studies of lactating mothers indicate that suckling and nipple stimulation are associated with an increase in oxytocin (Carter & Altemus, 1997). Studies evaluating associations between peripheral oxytocin levels and either affiliative or stress responses in non-lactating humans have, however, been more mixed.

Measurement Issues

Conflicting results within the limited human oxytocin literature may, in part, represent methodological issues associated with the peripheral measurement of this peptide. First, oxytocin is known to be released into peripheral circulation in a pulsatile fashion, where it has a half-life of about 16 minutes (Amico, Ulbrecht & Robinson, 1987). Thus, common use of venipuncture for single blood draw assessments of this hormone may provide an incomplete picture of regarding basal concentrations or variability of oxytocin over time or in response to laboratory tasks. Second, because oxytocin released centrally and peripherally are derived from separate neuronal populations within the hypothalamus, peripheral oxytocin may or may not reflect centrally released oxytocin.

The most common approaches to assessing peripheral oxytocin in humans includes the use of in-house radioimmunassays (RIAs; for one example, see Amico et al., 1985) or commercially-available assay kits, which include both RIA and enzyme immunoassay (EIA) approaches to hormone measurement. [For commonly used examples, see commercial kits available from Assay Design (Ann Arbor, MI) or Peninsula Laboratories (Can Carlos, LA)]. The use of commercially-available oxytocin assay kits are enjoying growing utilization in the human research literature. It is important to note, however, that commercially-available kits generally provide significantly higher estimates of circulating oxytocin levels as compared with those obtained with previously-described in-house RIAs. It is not known what factors drive this measurement difference. One possible explanation is that while previously studied in-house RIAs selectively target only the biologically active, 9-amino-acid nonapeptide, alternate assays may assess both active oxytocin as well as precursor molecules, or oxytocin prohormones. While oxytocin prohormones are not themselves believed to be biologically active, they may nonetheless represent plasma markers of oxytocin production and activity and, research would suggest, are more sensitive to circulating levels of estradiol. To date, little research has directly compared results obtained from these alternate oxytocin assays.

Relevant Human Research

Studies of lactating females support for the role of oxytocin in the modulation of cardiovascular and HPA stress responses. Suckling and nipple stimulation are associated with an increase in oxytocin as well as a decline in cortisol concentrations in plasma (Carter & Altemus, 1997; Chiodera et al., 1991). Lactation in human females also appears to decrease stress reactivity, dampening cortisol responses to physical (Altemus et al, 1995) and psychosocial (Heinrichs et al., 2001) stressors. Light et al. (2000) found that new mothers who showed endogenous increases in plasma oxytocin levels after holding their baby displayed blunted blood pressure in response to a subsequent psychosocial stressor. Heinrichs et al (2003) found that male subjects who received exogenous treatment with intranasal oxytocin in conjunction with social support exhibited lower cortisol responses, decreased anxiety, and increased calmness during a subsequent stress task (Heinrichs et al., 2003). Similarly, a series of studies conducted by Light, Grewen and colleagues indicate that endogenous peripheral oxyotcin release may be is associated with lower resting blood pressure and lower sympathetic activity in pre- and postmenopausal women (Light et al 2005a, 2005b; Grewen et al., 2005). In apparent contrast, however, Taylor et al. (2006) observed that postmenopausal women reporting gaps or difficulties in their social relationships displayed elevations in basal plasma oxytocin levels which were associated with elevated cortisol levels. These results may point to the need to measure and conceptualize dynamic or interactive aspects of peripheral oxytocin release and/or regulation, rather than rely solely on the interpretation of static peripheral oxytocin levels.

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