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Review

Central control of penile erection: A re-visitation of the role of oxytocin and its interaction with dopamine and glutamic acid in male rats

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ABSTRACT

Oxytocin is a potent inducer of penile erection when injected into the central nervous system. In male rats, the most sensitive brain area for the pro-erectile effect of oxytocin is the paraventricular nucleus of the hypothalamus. This nucleus and surrounding regions contain the cell bodies of all oxytocinergic neurons projecting to extra-hypothalamic brain areas and the spinal cord. This review shows that oxytocin induces penile erection also when injected in some of these areas (e.g., ventral tegmental area, ventral subiculum of the hippocampus, posteromedial cortical nucleus of the amygdala and thoraco-lumbar spinal cord). Microinjection studies combined with intra-cerebral microdialysis and double immunofluorescence studies suggest that oxytocin in these areas activates directly or indirectly (mainly through glutamic acid) mesolimbic dopaminergic neurons. Dopamine released in the nucleus accumbens in turn activates neural pathways leading to the activation of incerto-hypothalamic dopaminergic neurons in the paraventricular nucleus. This activates not only oxytocinergic neurons projecting to the spinal cord and mediating penile erection, but also those projecting to the above extra-hypothalamic areas, modulating directly or indirectly (through glutamic acid) the activity of mesolimbic dopaminergic neurons controlling motivation and reward. Together these neural pathways may constitute a complex hypothetical circuit, which plays a role not only in the consummatory phase of sexual activity (erectile function and copulation), but also in the motivational and rewarding aspects of the anticipatory phase of sexual behaviour.

Contents

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1. Introduction

Penile erection is a male sexual response that plays a key role in reproduction of mammals including man, and that can be also observed in contexts different from those strictly related to reproduction. Depending on the context in which penile erection occurs, different central and peripheral neural and/or humoral mechanisms participate in its regulation (see Meisel and Sachs, 1994; Argiolas and Melis, 1995, 2004, 2005; Sachs, 2000, 2007; McKenna, 2000; Giuliano and Rampin, 2000, 2004; Andersson, 2001; Melis and Argiolas, 1995a, 2003; Hull et al., 2002). Among central neurotransmitters and neuropeptides that control penile erection, the best known are dopamine, serotonin, excitatory amino acids, nitric oxide, adrenocorticotropin, oxytocin and opioid peptides. They can facilitate or inhibit penile erection by acting in several brain areas, i.e., the medial preoptic area, the paraventricular nucleus of the hypothalamus, the ventral tegmental area, the hippocampus, the amygdala, the bed nucleus of the stria terminalis, the nucleus accumbens, the medulla oblongata and the spinal cord (Table 1) (see Meisel and Sachs, 1994; Witt and Insel, 1994; Stancampiano et al., 1994; Argiolas and Melis, 1995, 2005; Argiolas, 1999; Bancila et al., 2002; Giuliano and Rampin, 2000, McKenna, 2000; Andersson, 2001; Hull et al., 2002; Coolen et al., 2004).

Oxytocin, the neurohypophyseal peptide well known for its hormonal role in lactation and parturition, is present in females and males, not only in neurons with cell bodies located in the paraventricular and supraoptic nuclei of the hypothalamus projecting to the neurohypophysis, but also in neurons projecting from the paraventricular nucleus and surrounding structures to extra-hypothalamic brain areas (i.e., the septum, the ventral tegmental area, the hippocampus, the amygdala, the medulla oblongata and the spinal cord). These neurons are thought to be involved in numerous central functions, such as memory, learning, affiliative and socio-sexual behaviours, including penile erection and copulatory behaviour (see Buijs, 1978; Sofroniew, 1983; Argiolas and Gessa, 1991; Pedersen et al., 1992; Carter, 1992; Wagner and Clemens, 1993; Ivell and Russel, 1995; Carter et al., 1997; Tang et al., 1998; Veronneau-Longueville et al., 1999). Indeed, oxytocin facilitates erectile function and male sexual behaviour in mice, rats, rabbits and monkeys (see Argiolas and Gessa, 1991; Carter, 1992; Pedersen et al., 1992; Argiolas and Melis, 1995, 2004; Argiolas, 1999). This may occur also in humans, since plasma oxytocin is increased by sexual stimuli, especially at ejaculation (Carmichael et al., 1987; Murphy et al., 1987) and by the manipulation of breast and of the genitalia, which usually occur during sexual intercourse (Tindall, 1974). A facilitative effect of oxytocin on male sexual behaviour was first demonstrated by the ability of intravenous oxytocin to decrease the latency to the first ejaculation and to retard sexual exhaustion of male rabbits paired with receptive females (Melin and Kihlstrom, 1963). However, the sexual effects of oxytocin were definitively recognized only in the eighties. Oxytocin given centrally in nanogram amounts was then found able to induce penile erection (Argiolas et al., 1985, 1986) and to improve copulatory behaviour (Arletti et al., 1985) in male rats, and to increase lordosis in female rats (Arletti and Bertolini, 1985; Caldwell et al., 1986), apparently by acting on uterine-type oxytocinergic receptors (see Argiolas and Melis, 1995, 2004; Argiolas, 1999; Melis and Argiolas, 2003; and references therein). Oxytocin improves sexual behaviour not only in sexually potent male rats (Arletti et al., 1985) but also in aged male rats (Arletti et al., 1990), and in dominant, but not in subordinate, male squirrel monkeys (Winslow and Insel, 1991). The pro-erectile effect of oxytocin is testosterone-dependent, since it is abolished by hypophysectomy and castration, and restored by supplementation with testosterone or its metabolites, estradiol and 5α-dihydro-testosterone given together (Melis et al., 1994a). The most sensitive brain area for the induction of penile erection by oxytocin is the paraventricular nucleus of the hypothalamus (Melis et al., 1986), from which all extra-hypothalamic oxytocinergic projections originate (see above). Here, oxytocin was found to be able to induce penile erection (and yawning) when injected at doses as low as 3 pmol (see Section 2.1 below). Oxytocin induced penile erection also when injected bilaterally into the CA1 field of the hippocampus, but not in the dorsal subiculum (see Section 2.3 below), the lateral septum, the caudate nucleus, the medial preoptic area, the ventromedial nucleus of the hypothalamus and the supraoptic nucleus (Melis et al., 1986). As to the mechanism by which oxytocin acts in the paraventricular nucleus to induce this sexual response, numerous studies suggest that oxytocin activates its own neurons. In line with this hypothesis, sexual interaction increases FOS, the gene product of the immediate early gene *c-fos* in paraventricular oxytocinergic neurons projecting to the spinal cord, which are involved in the control of penile erection (see Witt and Insel, 1994 and references therein), and sexual impotence (e.g., the inability of an adult male rat to copulate with an ovariectomized oestrogen–progesterone-primed receptive female) has been associated in the male rat with low levels of oxytocin mRNA in the paraventricular nucleus of the hypothalamus (Arletti et al., 1997).

Whether oxytocin influences the anticipatory phase or the consummatory phase of sexual behaviour is unclear at present. As oxytocin induces penile erection and the main effect of oxytocin on copulatory behaviour is a decrease in the post-ejaculatory interval in male rats (Arletti et al., 1985), it is reasonable to assume that the peptide improves sexual performance. However, as oxytocin also increases socio-sexual interaction (see Pedersen et al., 1992; Carter et al., 1997; Ivell and Russel, 1995), and oxytocin receptor antagonists prevent noncontact erections (Melis et al., 1999a), which are considered as an index of sexual arousal (see Sachs, 1997, 2000, 2007; Melis et al., 1998, 1999b and references therein), a possible role of oxytocin in sexual arousal and sexual motivation cannot be ruled out. This review summarizes published and unpublished results of recent studies, which show that oxytocin induces penile erection not only when injected into the paraventricular nucleus of the hypothalamus, but also in other extra-hypothalamic brain areas, such as the ventral tegmental area (Melis et al., 2007, 2009a; Succu et al., 2008), the ventral subiculum of the hippocampus and the posterior nucleus of the amygdala (Melis et al., 2009b, 2010), which are important constituents of the limbic system and are thought to play a key role in motivation and reward processes. These studies reveal that oxytocin participates in neural circuits, which include other neurotransmitters, such as dopamine and glutamic acid, and other brain areas other than the paraventricular nucleus, e.g., the ventral tegmental area, the nucleus accumbens, the hippocampus and areas yet to be identified. These circuits are likely to mediate an interaction between the mesolimbic and the incerto-hypothalamic dopaminergic system, and to play a role not only in the consummatory phase of male sexual behaviour (e.g., penile erection and copulation), but also in sexual motivation and sexual arousal, hence providing a neural substrate for explaining the motivational and rewarding properties of sexual activity.

2. Oxytocin influences penile erection by acting in different brain areas

2.1. The paraventricular nucleus of the hypothalamus

As recalled above the paraventricular nucleus of the hypothalamus was soon identified as the brain area most sensitive for the pro-erectile effect of oxytocin. When injected unilaterally in this nucleus, oxytocin was found active at doses as low as 3 ng (3 pmol) (Melis et al., 1986). Structure–activity relationship studies revealed