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Opioids and sexual reward

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ABSTRACT

Various lines of research indicate that sexual reward is mediated by opioids in both males and females. In the first part I review basic ideas about sexual reward in humans followed by a description of what is known in rodents, where most of the studies have been done. Although a direct method to measure opioid release during mating is not yet available, there is a substantial amount of indirect evidence in humans and animals indicating that opioids are released during the execution of sexual behavior. Studies using the conditioned place preference (CPP) method where the effects of opioids upon sex induced reward have been evaluated will also be described.
Evidence will also be presented indicating that the medial preoptic area (MPOA) plays a crucial role in the expression of opioid mediated sex-reward in males and females. This area is also important in other naturally occurring reward related behaviors such as singing. Opioids might be part of a system that mediates the rewarding properties of natural behaviors that are intrinsically rewarding.

1. Introduction

The study of reward states has become increasingly important to understand the mechanisms that trigger behavior. Behaviors required to maintain physiological balance and crucial for the survival of the individual and hence of the species, such as eating and drinking are one focus of attention. Other behaviors related to social aspects such as maternal behavior, playing, and sexual behaviors have been studied in attempts to identify the neurobiology of reward that triggers and directs behavior. If an animal displays a behavior that induces a reward state this would increase the probability that the behavior will be repeated again in the future. This is crucial in terms of evolution where adaptive behavior requires integration of external and internal stimuli. In fact, a recent review clearly puts this in perspective by analyzing the social behavior network and the mesolimbic reward system. These two systems have homology relationships in five major vertebrate lineages: mammals, birds, reptiles, amphibians and teleost fish, indicating that they were already present in early vertebrates. The authors proposed that both circuits are part of a larger social decision-making network (O'Connell and Hofmann, 2011). A crucial aspect of this proposal is that social behavior must be rewarding.

Reward elicits an approach behavior based on incentive motivation. Stimuli that activate approach behaviors are called positive incentives which usually have a hedonic value that will induce a positive affective (PA) state (Agmo, 1999; Di Chiara and Bassareo, 2007; Di Chiara and Imperato, 1988; Paredes, 2009; Paredes and Fernández-Guasti, 2008). The PA states in animals are not easy to measure. While in humans we can ask the individuals if a stimulus or a situation induces a physiological or psychological state associated with happiness or good feelings, in animals we have to rely on an operational definition based on approach behaviors (Agmo, 1999, 2007a; Di Chiara and Bassareo, 2007; Di Chiara and Imperato, 1988; Paredes, 2009, 2010; Paredes and Fernández-Guasti, 2008). So if an animal repeatedly approaches a stimulus we have to assume that this is because in the past the stimulus has produced in the animal a positive physiological state. There are also instances in which the animals can show a clear approach behavior without any previous experience. For example, the preference for a sexually receptive female or her odors is independent of previous sexual experience (see Agmo, 2003; Portillo and Paredes, 2004 and references therein), suggesting that some behaviors crucial for the survival of the species could be intrinsically rewarding (Paredes, 2009).

There is an extensive literature in which the rewarding effects of drugs have been investigated but less research has been devoted to the study of naturally occurring behaviors that produce a reward state. Although no direct method exists yet to measure opioid release during different behaviors, several lines of indirect evidence clearly suggest that endogenous opioids mediate the reward states in many naturally occurring behaviors, including sexual behavior. I will review this evidence, both in males and females which indicates that a common opioid system mediates sexual reward. The positive affective state mediated by opioids assures that the behavior will be repeated under appropriate conditions. If sex is intrinsically rewarding, the animals will repeat the behavior favoring reproduction and hence, the survival of the species.

2. Sexual reward in humans

To say that sexual behavior in humans is rewarding is obviously unnecessary (except of course in some pathologies such as dyspareunia),

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but it will be important to have in mind what is known about humans when we describe reward in animal studies. It should also be kept in mind that sexual behavior is not a basic need like food, drink, adequate temperature control or sphincter control. For example, if a human or an animal doesn't eat or drink it will get sick, and if this is prolonged the subject would eventually die. This is not the case if the human or animal doesn't engage in sexual behavior. The lack of sex might irritate some humans, and maybe animals too, but some humans voluntarily decide to abstain from sexual activity. Some abstain for religious reasons, and others consider sex to be unimportant or simply don't find the need to have sex. Some of these individuals are known as asexuals because they have no sexual attraction to either sex (Bogaert, 2004, 2006; Brotto et al., 2010; Brotto and Yule, 2011) (http://www.asexuality.org/home/). The few studies that have been published on this topic in humans indicate that asexuals represent 2–5% of the population, this percentage is about the same in men and women, and is not related to religion, education or lack of sexual experience. In fact many of the asexual individuals have had sexual experience with different partners but they have simply not been rewarding (Bogaert, 2004, 2006; Brotto et al., 2010; Brotto and Yule, 2011). This clearly reflects the individual variation in a very complex human behavior. Interestingly, a similar small proportion of individuals that do not mate despite the fact that they are repeatedly tested with receptive females have been described in other species (Portillo et al., 2006, 2013; Portillo and Paredes, 2003). It still needs to be determined if females from different species, with normal physiological hormone levels, will not display sexual behavior when repeatedly tested with sexually vigorous males.

It is also clear that some people consider that few things cause a reward or positive affective state as intense as the one experienced at orgasm (Agmo, 2007b). Abundant evidence indicates that for humans sexual behavior is rewarding, including both classical studies (Kinsey et al., 1948) and recent reviews that can be consulted by the interested reader (Agmo, 2007b; Pfaus et al., 2012). The point that I will try to address in the present manuscript is the role of opioids in the rewarding aspects of sexual behavior. Again, although no direct evidence exits about what substance mediates the PA state in humans it is well documented that administration of opioids like heroin or morphine produces sensations similar to those produced by an orgasm (Mirin et al., 1980; Pfaus and Gorzalka, 1987; Sathe et al., 2001). Acute administration of heroin is usually described as producing immediate euphoria with orgasm-like sensations followed by a period of relaxation and sedation (Mirin et al., 1980; Pfaus and Gorzalka, 1987). On the other hand, chronic opiate usage is associated with erectile dysfunction, absence of or delay ejaculation, decreased sexual desire and difficulty to experience orgasm (Sathe et al., 2001). These effects are probably due to the effects that opioids have in the endocrine system, since the chronic effects of opiod administration increase GH and prolactin and decrease LH, testosterone, estradiol, and oxytocin levels (Vuong et al., 2010).

The administration of an opioid antagonist like naloxone or naltrexone facilitates the reappearance of sexual desire in addicts. In healthy subjects, naltrexone produces a significant increase in the number of orgasms compared to subjects given placebo. The intensity of arousal was also significantly greater in the naltrexone-treated subjects than in the control group. This evidence suggests that endogenous opioids modulate the orgasmic response and the intensity of sexual arousal in men (Sathe et al., 2001).

Indirect evidence that opioids participate in sexual reward comes from the study of analgesic effects associated with vaginal stimulation in women. It is clearly established that opioids have analgesic effects in humans and animals (Bodnar, 2011, 2012). Based on studies showing that the administration of beta-endorphin induced profound analgesia, sedation, and euphoria in patients with intractable pain (Oyama et al., 1980) and that vaginal stimulation also produced potent analgesia in female rats (Komisaruk and Wallman, 1977; Ross et al., 1979) Komisaruk and colleagues evaluated whether vaginal self-stimulation in women could produce analgesia. Adult women used a pressure transducer to receive vaginal self-stimulation to produce a report of pressure or pleasure. In those women that perceived the vaginal self stimulation as pleasurable pain tolerance and the pain detection threshold increased by 37% and 53%, respectively. In a second study, the vaginal self-stimulation applied to produce orgasm induced an increase of pain tolerance and the pain detection threshold by 75% and 106%. The tactile threshold remained unaffected in various control conditions, and in women who reported that vaginal self-stimulation was neither pleasurable nor uncomfortable these thresholds showed only a slight increase (Whipple and Komisaruk, 1985). The significant increase in pain threshold occurred when the stimulation was applied to the anterior wall of the vagina or when the women applied pleasurable self-stimulation to the anterior vagina wall, the posterior vagina wall or the clitoris (Whipple and Komisaruk, 1988). To our knowledge, no study has directly evaluated sex-associated analgesia in men but there are several anecdotal descriptions indicating that sexual stimulation and ejaculation in men is associated with analgesia (Kinsey et al., 1948; Pfaus and Gorzalka, 1987).

3. Sexual reward in rodents

Most of the research in this area has been done in laboratory animals, especially rats. When the studies correspond to other species they will be specifically mentioned. Although some of the results of studying sexual reward may be generalized to all species, including humans, the extrapolation of results between animals and humans has to be cautiously considered. There is an extensive literature that has evaluated the effects of opioid agonists and antagonists on different aspects of sexual behavior in male and female rats and other species. A detailed review of that literature is beyond the scope of the present manuscript and there are a couple of excellent early reviews on the topic (Agmo and Paredes, 1988; Pfaus and Gorzalka, 1987). However, it could briefly be mentioned that there is general agreement that administration of an opioid agonist inhibits sexual behavior in males and females without affecting motor activity, while administration of opiate antagonists have produced conflicting results. Some studies have described a reduction in the number of intromissions and in ejaculation latency; others found only an increase in the postejaculatory interval without affecting other parameters. Still, other studies have reported no effects of opioid antagonists upon sexual behavior (Agmo and Paredes, 1988; Pfaus and Gorzalka, 1987). Two endogenous opioid peptides have been isolated recently that bind to the μ receptor with high affinity and selectivity (Fichna et al., 2007; Hackler et al., 1997; Pan and Kastin, 2007; Zadina et al., 1997). Endomorphin 1 (EM-1) and 2 (EM-2) have the same effects upon sexual behavior as those observed using synthetic opioids. Infusion of EM-1 into the MPOA inhibited lordosis behavior in a dose dependent manner and administration of EM-1 and EM-2 into the third ventricle or MPOA also inhibited lordosis (Acosta-Martinez and Etgen, 2002). In both studies the inhibitory effects upon lordosis were blocked by specific μ receptor antagonists (Acosta-Martinez and Etgen, 2002; Sinchak and Micevych, 2001). In males, the administration of EM-1 in the third ventricle inhibited several parameters of sexual behavior. It increased ejaculation latency, the inter-intromission interval and reduced the number of ejaculations during the test (Parra-Gamez et al., 2009). When EM-1 was infused in the MPOA an increase in mount and intromission latencies as well as an increase in pursuit of the female was observed. When the endogenous opioid peptide was infused in the medial amygdala (Me) an increase in the number of mounts was observed. The effects on male sexual behavior were completely blocked by pretreatment with naloxone confirming that endogenous opioid peptides modulate sexual behavior (Parra-Gamez et al., 2013). In the following section I will focus on the evidence that clearly suggests that opioids are released during sexual behavior contributing to the rewarding properties of mating.