Psychoneuroendocrinology (2013) 38, 2448—2461

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Presence of a pair-mate regulates the behavioral and physiological effects of opioid manipulation in the monogamous titi monkey (*Callicebus cupreus*)

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Received 14 November 2012; received in revised form 7 March 2013; accepted 13 May 2013

KEYWORDS
Mu opioid receptor;
Morphine;
Naloxone;
Attachment;
Social behavior;
Titi monkey;
Cortisol;
HPA axis;
Monogamy

Summary The role of opioid receptors in infant—mother attachment has been well established. Morphine, a preferential μ opioid receptor (MOR) agonist, attenuates separation distress vocalizations and decreases physical contact between infant and mother. However, there is little research on how opioid receptors are involved in adult attachment. The present study used the monogamous titi monkey (*Callicebus cupreus*) to explore the role of opioid receptors in the behavioral and physiological components of pair-bonding. In Experiment 1, paired male titi monkeys ($N = 8$) received morphine (0.1, 0.5, or 1.0 mg/kg), the opioid antagonist naloxone (1.0 mg/kg), vehicle, or a disturbance control and were filmed with their pair-mate for 1 h. In Experiment 2, the same eight males received morphine (0.25 mg/kg), naloxone (1.0 mg/kg), vehicle, or a disturbance control and were filmed for an hour without their pair-mates. All video sessions were scored for social and non-social behaviors. Blood was sampled immediately prior to drug administration and at the end of the hour session. Plasma was assayed for cortisol, oxytocin, and vasopressin. In Experiment 1, opioid manipulation had no effect on affiliative behaviors; however, morphine dose-dependently decreased locomotor behavior and increased scratching. In Experiment 2 in which males were separated from their pair-mates, naloxone increased locomotion. Morphine dose-dependently attenuated the rise in cortisol, while naloxone potentiated the increase of cortisol. The cortisol increase following naloxone administration was greater when a male was alone compared to when the male was with his pair-mate. Naloxone increased vasopressin but only when the male was tested without his pair-mate. The present study found that the absence of a pair-mate magnified naloxone's effects on stress-related hormones and behaviors, suggesting that the presence of a pair-mate can act as a social buffer against the stress-inducing effects of naloxone.

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0306-4530/$ — see front matter
http://dx.doi.org/10.1016/j.psyneuen.2013.05.009

1. Introduction

The role of the opioid system in infant–mother bonds is well established (Herman and Panksepp, 1978; Panksepp et al., 1980; Kalin et al., 1988, 1995; Nelson and Panksepp, 1998). Infants separated from their mother or primary attachment figure emit stereotyped separation vocalizations (Panksepp et al., 1980; Hoffman et al., 1995; Mason and Mendoza, 1998). Preferential MOR agonists (such as morphine and oxymorphone) attenuate these distress vocalizations in young that develop selective attachments to their mothers, such as guinea pigs (Herman and Panksepp, 1978), dogs (Panksepp et al., 1978a), monkeys (Kalin et al., 1988), and chickens (Panksepp et al., 1978b, 1980). In contrast, non-specific opioid antagonists such as naltrexone or naloxone, either have no effect or intensify these vocalizations (Herman and Panksepp, 1978; Panksepp et al., 1980; Kalin et al., 1988; Nelson and Panksepp, 1998). Polymorphisms of the *OPRM1* gene coding for the MOR in monkeys have also been found to affect separation vocalizations (Barr et al., 2008).

Nelson and Panksepp (1998) have argued that individuals seek to obtain an optimal opioidergic tone, which can be modulated by an attachment figure. Disruptions to opioidergic activity through separation from an attachment figure result in behavioral and physiological changes such as separation vocalizations and activation of the hypothalamic–pituitary–adrenal (HPA) axis. In addition to its effects on separation vocalizations, exogenous opioid manipulation has also been shown to affect the HPA axis (Wand et al., 1998). Acute administration of MOR agonists decreases cortisol concentrations in humans (Zis et al., 1984), macaque monkeys (Broadbear et al., 2004), and sheep (Parrott and Thornton, 1989), while naloxone and naltrexone increase cortisol concentrations in humans (Wand et al., 1998), nonhuman primates (Fabre-Nys et al., 1982), and sheep (Parrott and Thornton, 1989). It is hypothesized that distress vocalizations emitted during separation act to attract the mother, thereby reinstating an infant's ideal opioidergic tone and HPA homeostasis (Panksepp et al., 1980; Nelson and Panksepp, 1998).

In addition to opioids regulating infant–mother attachments, opioids also appear to have a role in affiliative behavior in adult, nonhuman, Old World primates living in large social groups. In talapoin monkeys and macaques, morphine administration decreases the number of grooming solicitations and the amount of grooming received, while naloxone administration increases grooming solicitations and the receipt of grooming (Fabre-Nys et al., 1982; Keverne et al., 1989; Martel et al., 1995). Receipt of grooming results in a release of β-endorphins (Keverne et al., 1989), which primarily bind to MORs (Goodman et al., 1983). It has been proposed that morphine administration results in overactivation of MORs, which ends in an adjustment in an animal's behavior to maintain a homeostatic level of MOR activation by decreasing the amount of grooming received (Nelson and Panksepp, 1998). In contrast, administration of naloxone or naltrexone is predicted to increase the amount of grooming received, which would compensate for the decrease in MOR activation.

The role of opioids in affiliative behavior among adult animals has also been explored in the formation and maintenance of monogamy. The filial-like attachment bond formed between adults in monogamous species enables the possibility of exploring the potential contribution of opioids in this unique social system (Mason and Mendoza, 1998). The neurobiology of adult attachment has focused primarily on neuropeptides such as oxytocin (OT) (Williams et al., 1994; Carter et al., 1995; Smith et al., 2010; Young et al., 2011a; Schneiderman et al., 2012) and vasopressin (AVP) (Winslow et al., 1993; Jarcho et al., 2011; Young et al., 2011a; Gouin et al., 2012) as well as the neurotransmitter dopamine (Aragona et al., 2003; Curtis et al., 2006; Young et al., 2011a). In the monogamous prairie vole, systemic administration of the opioid antagonist naltrexone, or local administration of the specific MOR antagonist CTAP into the dorsal striatum, prevents pair-bond formation (Burkett et al., 2011). Shapiro et al. (1989) found that morphine can reduce side-by-side contact in prairie voles at high doses that also affect locomotor behavior. However, opioid blockade with naloxone or naltrexone has repeatedly failed to increase physical contact in prairie voles whereas it does in nonmonogamous primates (Shapiro et al., 1989; Burkett et al., 2011; Resendez et al., 2012). One of the questions we are concerned with is whether the differences between voles and macaques are due to their social structure or phylogenetic status. The manner in which opioid receptors influence affiliative behaviors may vary depending on the neurophysiological differences found in monogamous versus nonmonogamous species or those found in rodent versus primate species. The present study attempts to answer this question through the use of a monogamous primate species.

The titi monkey (*Callicebus cupreus*) is a socially monogamous nonhuman primate that forms strong, heterosexual pair-bonds (Mason, 1966), and therefore acts as an excellent nonhuman primate model to examine whether the opioid system is involved in adult attachment. Titi monkeys spend a significant amount of time in physical contact and proximity

Table 1 Social composition information.

♂ Subject	♀ Pair-mate	# of offspring	Offspring sex	Offspring age (years)
29775	37133	0	–	–
30410	36993	0	–	–
31716	29852	1	♂	1.5
32878	34866	0	–	–
34438	37623	0	–	–
34531	36163	1	♂	0.6
35383	30557	0	–	–
36187	35292	1	♀	0.1