Review

The brain opioid theory of social attachment: a review of the evidence

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Summary

The psychology of close human relationships is increasingly well understood and our understanding of the neurobiology of the onset of pairbonding behaviour in a range of species has benefited from the use of rodent-based models. However, the human literature has suffered from a lack of focus upon the unique nature of primate social bonds and has so far failed to adequately identify the neurobiological and behavioural mechanisms which maintain these complex, diverse and enduring social networks. One neurobiological mechanism that has been overlooked is the endogenous opioid system. Though less explicitly researched than the more familiar oxytocin/vasopressin system, there is considerable evidence that the opioids play a fundamental role in sociality, especially in the primates. This review summarises our current understanding of the evidence for the role of this system in prosocial behaviour in non-primate mammals, nonhuman primates and humans. An important conclusion is that the opioid system may play a more central role in sociality in primates (including humans) than in other mammalian taxa.

Keywords: endogenous opioid system, β-endorphin, OPRM1, prosociality, relationships.

1. Introduction

Human relationships are characterised by their diversity, complexity and longevity. In particular, a range of pairbonds, including but not limited to parental, romantic, best friend and grandparental, may trade off, complement

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or antagonise each other as they contribute to an individual's social network. While replicated to some extent in other primates, human relationships appear to reach unique depths of emotional, cognitive and physical intensity. The ability to form functional relationships has implications for future mental and physical health as well as increased social and communicative skills, while dysfunctional bonds can lead to a range of psychopathologies, addictions and anti-social behaviours (e.g., Uchino, 2006; Reblin & Uchino, 2008). While the psychology of human close relationships has attracted considerable interest for a number of years, it is only recently that attention has focussed on the biochemical underpinnings of these behaviours. Building on evidence from rodent research, roles have been identified for various neuropeptides (including oxytocin, vasopressin, dopamine and serotonin) in the onset of human parental and romantic pairbonds (e.g., Panksepp, 1999; Lorberbaum et al., 2002; Bartels & Zeki, 2004; Fisher, 2004; Aron et al., 2005; Acevedo et al, 2008). However, while this research has undoubtedly been valuable, it has tended to overlook an important class of neuroendocrines that play a central role in social bonding, at least in the primates, namely the endogenous opioids (Keverne et al., 1989). In this review, we focus on the role that endorphins might play in nonhuman primate and human social bonding. Before doing so, however, we first address the evidence from nonprimate mammals and the issues that arise from focussing on rodent-based models of social bonding.

2. The problem with rodents

Although there has been a considerable amount of research on the neurochemical bases of sociality (focussing in particular on the oxytocin/vasopressin axis) using rodents (Carter et al., 1995; Insel & Young, 2000), there are good grounds for arguing that rodents may not be the best models for understanding behaviour and its neurobiological underpinnings in primates. Firstly, there is no direct evidence of common physiological mechanisms for pairbonding behaviour between rodents and humans. This is given added weight by the recent finding that there are striking differences in the historical rate of encephalisation between those taxa whose descendants now have bonded social systems (e.g., primates, equids) and those that, like rodents, do not (e.g., felids, ruminants) (Shultz & Dunbar, 2010). The increased contribution of cortical areas in the behaviour of primates in general (and humans

in particular) compared to rodents suggests that different neurophysiological processes might be involved (Keverne, 1996; Young & Wang, 2004; Bales et al., 2007). Secondly, while pairbond maintenance among the cognitively less advanced mammals relies to a great extent on hormonal control and sensory stimuli, in primates the maintenance of close relationships seems to be controlled to a much greater extent by cognitive and meta-cognitive mechanisms associated with an extended period of offspring dependency and a reduction in the olfactory areas as well as the expansion of the neocortex (Keverne, 1996; Curley & Keverne, 2005). Thirdly, it is not even clear whether vasopressin (at least) is actually related to pairbonding even in rodents: Fink et al. (2006), for example, have shown, in a detailed phylogenetic analysis, that the vasopressin AVPR1a receptor gene is unrelated to monogamy in the vole family as a whole.

On a more general note, there is the striking contrast between the limited number of relationships (mostly short term mating pairbonds) in rodents and the diversity, longevity and complexity of primate relationships. Shultz & Dunbar (2007) argued that anthropoid primates, including humans, have extended the intensity and persistence of monogamous relationships to all areas of their social life. This requires a mechanism that is de-coupled from the stimuli of either sexual interaction or parturition so as to facilitate the maintenance of less intense but stable bonds between social group members (Depue & Morrone-Strupinsky, 2005). A focus on the neurobiological mechanisms of relationship onset within a limited group of species which exhibit only restricted forms of pairbonding behaviour must inevitably be inadequate (Dunbar & Shultz, 2007). Rather, if we are really to understand how and why primate relationships work in the way they do, then research is required into the mechanisms of relationship maintenance in the full range of relationships that characterise these species. In short, if we are to understand the neurobiology of human relationships, we need to explore the mechanisms involved in more appropriate comparative species, namely the nonhuman primates.

3. An alternative neurochemical candidate

One important family of neuropeptides that has been largely overlooked in the discussions of relationship formation is the endogenous opioid peptides. Following their discovery in the early 1970s, endorphins were proposed as

the neurochemical mechanism motivating romantic and parental behaviour in humans based upon the similarities between the characteristics of opioid drug addiction and romantic relationships (Liebowitz, 1983; Panksepp, 1999). However, perhaps due to the difficulty of working with opioids, attention shifted in the 1990s to oxytocin and vasopressin following the discovery of their role in rodent pairbonding. Meanwhile, however, the endogenous opioid system's involvement in the maintenance of dyadic social and maternal/infant pairbonds has been confirmed in nonhuman primates (Fabre-Nys et al., 1982; Keverne et al., 1989; Misiti et al., 1991; Martel et al., 1995; Kalin et al., 1995). More importantly, there is direct experimental evidence from humans suggesting that involvement in a romantic or supportive relationship explicitly elevates pain thresholds (Master et al., 2009; Younger et al., 2010), suggesting that endorphin titres may be higher during active relationships. Given this, it may now be appropriate to re-focus attention on the suggestion that the endogenous opioids are one of the missing links in the story of primate and human bonding. While oxytocin, vasopressin, dopamine and serotonin may be implicated in their *onset*, the endogenous opioids may play the maintenance role which is vital for, amongst other things, stable long-term relationships and the rearing of psychologically healthy, socially adept human beings.

4. The brain opioid theory of social attachment

The Brain Opioid Theory of Social Attachment (BOTSA) is based upon the strong behavioural and emotional similarities exhibited by those involved in intense, close relationships and those addicted to narcotics (Panksepp, 1999; Insel, 2003). Individuals who develop a dependence on a relationship (i.e., love) and individuals who develop a dependence on exogenous opiates (such as morphine) experience three distinct phases in the development of the relationship. The first involves an initial stage of euphoria followed by addiction. Endorphins are linked to consummatory reward which elicits feelings of pleasure, liking and gratification motivating the individual to seek out the rewarding behaviour. This is associated with both high rates of self-administration in rats and nonhuman primates and, in humans, an increase in feelings of interpersonal warmth, euphoria, well-being and bliss associated with endogenous opioid release (Stein & Belluzzi, 1978; Koob, 1992;

Ferrante, 1996; Comings et al., 1999; Depue & Morrone-Strupinsky, 2005). The second stage is one of tolerance-habituation. In relationships, this involves the move from 'romantic' to 'companionate' love, or from attraction to attachment (Liebowitz, 1983). Finally, there is a powerful third phase of withdrawal if the object of dependence is removed. In social relationships, these are the emotions and behaviours associated with separation distress or depression (see below: Liebowitz, 1983).

BOTSA predicts that social isolation results in low levels of endogenous opioids, motivating the individual to seek social contact. Social contact duly results in the release of endogenous opioids, consummatory reward and an associated feeling of euphoria and contentment (Nelson & Panksepp, 1998). However, the relatively quick degradation of endogenous opioids in vivo and the fact that some, such as β-endorphin which is specifically implicated in social contact (Keverne et al., 1989), do not lead to tolerance means that the individual must continue to interact with the object of reward to prevent the symptoms of withdrawal.

It has been claimed that endogenous opioids are implicated in a wide range of prosocial behaviours, including sexual behaviour, maternal nurturance, separation-distress, gregariousness, social bonding, play and social memory. One suggestion is that the endogenous opioid system's involvement in the social domain has evolved as a result of its primitive role in the body's pain and reward mechanisms — these pathways having been exapted to reinforce the pain of social isolation and the reward of social contact respectively (Panksepp et al., 1997). Recent work focusing on (i) the close neural relationship between the experience of physical pain and emotional pain due to relationship breakdown and (ii) the mediating effect of romantic interaction on physical pain lend support to this theory (Master et al., 2009; Way et al., 2009; Younger et al., 2010).

Initial evidence for BOTSA came from two distinct sources: Liebowitz's anecdotal account based on his psychiatric work and Panksepp's experimental work on separation distress and play in nonhuman mammals (e.g., Liebowitz, 1983; Panksepp, 1999). However, due to the difficulties of assaying levels of CNS endogenous opioids (these do not pass readily through the blood-brain barrier: Bloom, 1983; Dearman & Francis, 1983; Kalin & Loevinger, 1983; Boecker et al., 2008), further empirical evidence for this phenomenon has been difficult to obtain. The exception to this is the comparative work on grooming and infant/mother behaviour in nonhuman primates, but this has received surprisingly little attention in the wider context

of social bonding. Table 1 summarises the relevant studies that are reviewed in the following sections.

5. The endogenous opioid peptide system: peptides, receptors and genetics

The endogenous opioid peptides can be divided into three groups; the endorphins (including β-, α-, δ- and γ-endorphin and the recently identified tetrapeptides endomorphin-1 (EM1) and endomorphin-2 (EM2): Kackler et al., 1997; Zadina et al., 1997), the pentapeptide enkephalins and the dynorphins, and their respective receptors, the mu (μ), kappa (κ), delta (δ) and nociceptin receptors. While only the endomorphins have been found to exhibit both high affinity and selectivity for a single receptor (the μ opioid receptors (MOR)), the other endogenous opioids do show higher affinities for some receptors than to others. β-endorphin shows a particular affinity for the MOR and δ receptor (DOR), the enkephalins for the DOR and the dynorphins for the κ receptor (KOR) (Lord et al., 1977; Bodnar & Klein, 2006; Kieffer & Evans, 2009).

While they all have their origin in the brain's pain control mechanisms, endogenous opioids are implicated, essentially as neurotransmitters, in a wide range of physiological, behavioural and neurobiological systems, with these functions mainly reflecting the densities of the receptor types and their differing patterns of dispersal throughout the motor, limbic, reward, endocrine and sensory areas of the brain, as well as the gastrointestinal tract, placenta and ovaries (Leng et al., 1985; Autelitano et al., 1986; Kieffer & Evans, 2009). Here, they are involved in the control of pain, consummatory reward, addiction, sexual activity, mental illness, affective states, memory and learning, digestion, parturition, respiration, appetite and thirst, renal function, temperature regulation, metabolism, immunity and cardiovascular regulation (Taube et al., 1976; Stein & Belluzzi, 1978; Leng et al., 1985; Ferrante, 1996; Zubieta et al., 2003; Bergdorf & Panksepp, 2006; Bodnar & Klein, 2006; Bodnar, 2007; Dishman & O'Connor, 2009; Koepp et al., 2009; Parra-Gamez et al., 2009).

β-endorphin, the most potent endogenous opioid peptide, is implicated in the regulation of physical and emotional stress and pain, consummatory reward (including the reward of social interaction), parturition, hypothermia,

Table 1. Summary of the empirical papers which provide evidence with respect to the BOTSA.

Relationship type/interaction	Study type	Receptor/opioid type	Subject category/species	Reference
Mother/infant	Plasma assay/dissection	β-endorphin, met-enkephalin	Rat	Petraglia et al. (1985)
Mother/infant	Neuroimage (Autoradiography)	β-endorphin, general receptor.	Rat	Hammer & Bridges (1987)
Mother/infant	Antagonist/agonist	General	Rat	Bridges & Grimm (1982)
Mother/infant	Antagonist/agonist	General	Rat	Grimm & Bridges (1983)
Mother/infant	Antagonist/agonist	General	Rat	Panksepp et al. (1994)
Mother/infant	Antagonist	General	Rat	Roth & Sullivan (2003)
Mother/infant	Antagonist/agonist	General	Rat	Carden et al. (1996)
Mother/infant	Antagonist	General	Rat	Byrnes et al. (2000)
Mother/infant	Antagonist	General	Chicks	Panksepp et al. (1980)
Mother/infant	Agonist	β-, γ-, α-endorphin, met-enkephalin	Chicks	Vilberg et al. (1984)
Mother/infant	Agonist	General	Puppies	Panksepp et al. (1978)
Mother/infant	Antagonist/agonist	General	Guinea pigs	Hermann & Panksepp (1978)
Mother/infant	Knock out	μ-receptor	Mice	Moles et al. (2004)
Mother/infant	Antagonist	General	Sheep	Shayit et al. (2003)
Peer directed	Antagonist/agonist	General	Dogs	Knowles et al. (1989)
Peer directed	Agonist	General	Rats	Panksepp et al. (1979)
Peer directed	Pain proxy/antagonist	General	Mice	D'Amato & Pavone (1993)

Table 1. (Continued.)

Relationship type/interaction	Study type	Receptor/opioid type	Subject category/species	Reference
Peer directed	Agonist	General	Rats	Panksepp et al. (1978, 1997)
Peer directed	Neuroimage (Autoradiography)	General	Rats	Vanderschuren et al. (1995a)
Sexual	Agonist/antagonist	General	Rats	Gessa et al. (1979)
Play	Neuroimage (Autoradiography)	General	Rats	Panksepp & Bishop (1981)
Play	Neuroimage (Autoradiography)	General	Rats	Vanderschuren et al. (1995b)
Play	Antagonist/agonist	General	Rats	Panksepp et al. (1985), Panksepp (1999)
Play	Agonist	General	Rats	Vanderschuren et al. (1996)
Play	Antagonist/agonist	μ-, κ-, δ-receptor	Rats	Vanderschuren et al. (1995c)
Peer directed	Antagonist/agonist	General	Talapoin monkeys	Meller et al. (1980)
Peer directed	Antagonist/agonist	General	Talapoin monkeys	Fabre-Nys et al. (1982)
Peer directed	CNS assay	β endorphin	Talapoin monkeys	Keverne et al. (1989)
Peer directed	Antagonist	General	Rhesus macaques	Martel et al. (1995)
Peer directed	Antagonist	General	Squirrel monkeys	Winslow & Miczek (1988)
Mother/infant	Antagonist/agonist	General	Rhesus macaques	Kalin et al. (1988, 1995)
Mother/infant	Antagonist	General	Rhesus macaques	Martel et al. (1993, 1995)
Mother/infant	Agonist	General	Crab eating macaque	Misiti et al. (1991)
Mother/infant	Genetic	μ receptor	Rhesus macaques	Barr et al. (2008)
Mother/infant	Antagonist	General	Rhesus macaques	Graves et al. (2002)
Peer directed Sexual/romantic	Ethnographic	General	Human	Liebowitz (1983)

Table 1. (Continued.)

Relationship type/interaction	Study type	Receptor/opioid type	Subject category/species	Reference
Sexual/romantic	Ethnographic	General	Human	O'Donnell et al. (1967)
Sexual/romantic	Ethnographic	General	Human	Lex (1990)
Sexual/romantic	Ethnographic	General	Human	Albertin & Iniguez (2008)
Sexual/romantic	Ethnographic	General	Human	Simmons & Singer (2006)
Sexual/romantic Peer directed	Ethnographic	General	Human	Hawkins & Abrams (2007)
Sexual/romantic	Neuroimage (fMRI)	General	Human	Younger et al. (2010)
Mother/infant	Ethnographic	General	Human	Bernstein et al. (1984)
Mother/infant	Ethnographic	General	Human	Fiks et al. (1985)
Mother/infant	Ethnographic	General	Human	Lief (1985)
Mother/infant	Plasma assay	β-endorphin	Human	Franceschini et al. (1989)
Mother/infant	Behavioural	General	Human	Miller & Holditch-David (1992)
Mother/infant	Behavioural	General	Human	Feldman et al. (2003)
Affective states	Neuroimage (PET)	General	Human	Koepp et al. (2009)
Affective states	Neuroimage (PET)	μ-receptor	Human	Zubieta et al. (2003)
Affective states	Pain proxy	General	Human	Jamner & Leigh (1999)
Affective states	Pain proxy/ antagonist	General	Human	Depue & Morrone-Strupinsky (2005)
Peer directed	Pain proxy	General	Human	Baron (2008)
Peer directed	Pain proxy	General	Human	Barra (2003)
Peer directed	Pain proxy	General	Human	Kaskatis (2006)

Table 1. (Continued.)

Relationship type/interaction	Study type	Receptor/opioid type	Subject category/species	Reference
Peer directed	Pain proxy	General	Human	MacDonald (2007)
Peer directed	Pain proxy	General	Human	Cohen et al. (2009)
Peer directed	Antagonists	General	Human	Gillberg (1988, 1995)
Peer directed	Plasma assay	β-endorphin	Human	Leboyer et al. (1994)
Peer directed	Antagonists	General	Human	Bouvard et al. (1995)
Peer directed	Antagonist	General	Human	Panksepp & Lensing (1991)
Peer directed	Antagonist	General	Human	Kolmen et al. (1995)
Peer directed	Antagonist	General	Human	Chabane et al. (2000)
Peer directed	Genetic	μ-receptor	Human	Troisi et al. (2010)
Peer directed	Genetic	μ-receptor	Human	Way et al. (2009)
Peer directed	Plasma assay	β endorphin	Human	Kaada & Torsteinbo (1989)
Mental health	Neuroimage (PET)	μ-receptor	Human	Kennedy et al. (2006)
Mental health	Neuroimage (PET)	μ-receptor	Human	Love et al. (2009)
Mental health	Plasma assay/pain proxy	β-endorphin	Human	Tordjman et al. (2009)
Mental health	Neuroimage (PET)	μ-receptor	Human	Prossin et al. (2010)
Mental health	CSF assay	β-endorphin, met-enkephalin	Human	Stanley et al. (2010)
Mental health	CSF assay	β-endorphin	Human	Nagamitsu et al. (1997)

respiratory depression and digestion; the enkephalins in pain regulation, consummatory reward, parturition, digestion and risk of addiction; and EM-1 in the appetitive and consummatory aspects of male sexual behaviour (Taube et al., 1976; Stein & Belluzzi, 1978; Leng et al., 1985; Petraglia et al., 1985; Comings et al., 1999; Bodnar & Klein 2006; Dishman & O'Connor 2009; Parra-Gamez et al., 2009).

Psychologically, endorphin activation is experienced as a mild opiate 'high' associated with light analgesia (Hughes et al., 1975; Belluzzi & Stein, 1977; Holaday, 1983; Blalock, 1998; Nelson & Panksepp, 1998; Stephano et al., 2000), and through this plays its role in reward as well as in pain control. Zubieta et al. (2001) demonstrated that painful stimuli result in opioid activation in the amygdala, thalamus, hypothalamus and nucleus accumbens) and deactivation in the dorsal anterior cingulate cortex (dACC), periaqueductal grey area (PAG) and Brodman areas 8 and 9 of the prefrontal cortex. Recently, pain sensitivity has been shown to be specifically associated with opioid binding in the insula and the orbitofrontal cortex, with individual differences in pain tolerance being a function of opioid receptor availability (Mueller et al., 2010). Endorphins have also been explicitly identified as being responsible for the psychological experience of affect: deactivation of μ-opioid receptor sites (those explicitly targeted by β-endorphins) is specifically associated with negative affect states (Zubieta et al., 2003), and there is opioid receptor activation in both the hippocampus and amygdala in response to positive affect (Koepp et al., 2009). Thus, while largely inactive or 'silent' under normal circumstances, this system is activated by a number of biologically relevant stimuli, including social stimuli (Herz, 1995).

β-endorphin-releasing neurons are found at especially high densities in the hypothalamic nuclei, as well as in the heavily innervated mesolimbic structures involved in reward (Bodnar & Klein, 2006). Their receptor sites occur widely in the brainstem, basal ganglia and corticolimbic regions (Stephano et al., 2000), as well as the dorsomedial and anterior hypothalamus, the medial preoptic area, the septum, nucleus accumbens and the stria terminalis (Strand, 1999), the amygdala (Herbert, 1993) and in the frontal lobes. The role of endorphins in the reward system is emphasised by the fact that there is a particularly high density of opioid receptors in the orbitofrontal cortex, an area of the prefrontal cortex that is explicitly associated with both reward and, importantly, sociality (Powell et al., 2010; Lewis et al., 2011).

Of the three key receptors, the μ-receptor (or mu-opioid receptor, MOR) exhibits the widest range of applications, and indeed genetic variation, and knockout studies indicate that it is the most vital receptor for the regulation of pain (Hall et al., 2003; Chen et al., 2010). Receptor density can be variable depending on age and circumstance (the postnatal and early infant stages are particularly important to its development). The developmental trajectories of the different receptor types are independent of each other, with each reaching adult densities at different times after birth (Vanderschuren et al., 1995a; Carden et al., 1996; Hol et al., 1996).

A range of other neurotransmitters and hormones, including oxytocin, prolactin, serotonin, noradrenaline, estradiol, testosterone, progesterone and dopamine, interact with the endogenous opioids to enable, mediate or suppress their influence (Taube et al., 1976; Gold et al., 1978; Dupont et al., 1979; Meites et al., 1979; Taché et al., 1979; Ellingboe et al., 1980; Leng et al., 1985; Hammer & Bridges, 1987). Dopamine is known to suppress the influence of endorphins despite their joint, albeit distinct roles, in the reward system, while β-endorphin's interaction with oxytocin prevents tolerance to its rewarding effects which may be crucial for any role β-endorphin might play in relationship maintenance (van Ree et al., 1979; van Ree, 1983; Kovacs et al., 1987; Depue & Morrone-Strupinsky, 2005). Further, sex differences in the physiological and behavioural impact of the endogenous opioids (Zubieta et al., 2002) may be mediated by the gonadal hormones: testosterone improves their analgesic effects, whereas the impact of oestrogen is more variable, and, in some cases, it may even adopt a role as an opioid antagonist (substances that bind to the opiate receptor sites and block out the endogenous opioids themselves, thereby preventing the opiate-like analgesic effect). Further, the fluctuations in estradiol levels which accompany the follicular and luteal phases of the female cycle appear to impact on the affinity of the MOR for opioid peptides which can lead to diurnal fluctuations in the functionality and impact of the endogenous opioids (Ikeda et al., 2005; Zubieta et al., 2005; Bodnar & Klein, 2006; Bodnar, 2007).

Sex and age differences in the impact of the endogenous opioids are also affected by the distribution and density of receptors and the affinity of these to the opioids (Matsukura et al., 1978; Bodnar & Klein, 2006; Bodnar, 2007). Both receptor density and affinity are sex dependent and, because of this, antagonist-based treatments for alcoholics appear to be of greater efficacy in female subjects than in males (Zubieta et al., 1999; Bodnar & Klein, 2006).

Individual differences in the affinity of receptors for specific endogenous opioids, or even in receptor density, can often be a consequence of genetic polymorphism. The MOR *Oprm1* gene has been found to be highly polymorphic with at least 10 polymorphisms within the coding region. The DOR *Oprd1* is relatively polymorphic, whereas *Oprk1* (KOR) does not contain any active polymorphisms. Links have been found between *Oprm1* genetic polymorphisms and the effectiveness of analgesia, the propensity to develop alcohol and drug addiction and a range of mental disorders including schizophrenia and epilepsy. Similarly, there are possible links between *Oprd1* polymorphisms and the tendency to exhibit eating disorders. Further, the frequency of polymorphisms appears to be geographically distinct. For example, the frequency of the minor allele (G) of the A118G polymorphism of the *Oprm1* gene, associated with a threefold increase in β-endorphin binding at the MOR, is as high as 45% in Asian populations but between 5 and 25% in European and African-American populations (Ikeda et al., 2005; Mayer & Höllt, 2006; Troisi et al., 2010; Way & Lieberman, 2010).

6. Endogenous opioids and social behaviour in non-primate mammals

Within non-primate mammals, the endogenous opioids have been implicated in the regulation of a range of social behaviours including maternal/infant bonding, sexual behaviour, gregariousness, kin relationships, separation anxiety and play.

While β-endorphin has been widely implicated in pregnancy and parturition (the shift in hormonal balance associated with pregnancy increases the secretion of β-endorphin and the density of opioid receptors: Keverne, 1996), it may also play a role in maternal/infant bonding. Circulating β-endorphin, released from the pituitary and, potentially, the placenta, increases during pregnancy, reaching a peak at delivery in both rats and humans. While plasma-based endogenous opioids are likely involved in the control of stress and pain during birth, the presence of increased concentrations of both MORs and β-endorphin in the medial pro-optic area (MPOA) during pregnancy (an area implicated in pairbonding behaviour in rats) suggests that it may also have a role in preparing the mother for developing an attachment to her offspring (Petraglia et al., 1985; Hammer & Bridges, 1987).

The picture during lactation, when one would expect β-endorphin levels to remain high as a reflection of a developing bond, is less clear: densities remain high in areas of the pituitary but return to baseline in the MPOA (Petraglia et al., 1985; Hammer & Bridges, 1987). A study of the role for endogenous opioids in lactation suggests that levels only remain high during the early period of lactation, the first 10 days, following which they fall (Byrnes et al., 2000). Blockade of the opioid receptors during lactation leads the mother to prolong her nursing bouts suggesting that the endogenous opioids may play a complex role at this stage: maintaining the mother/infant bond while promoting the cessation of lactation by promoting a decrease in mother/infant proximity (Byrnes et al., 2000). Indeed, there is considerable physiological and anatomical evidence to suggest that endorphins (and the β-endorphins and the κ-opioid-receptors, in particular) may have an inhibitory effect on oxytocin activation in the pituitary during lactation in mammals (Bicknell et al., 1988; Zhao et al., 1988; McDonnell et al., 1994; Franchini et al., 2003; Morris et al., 2010).

Maternal behaviour in the rat has been found to be disrupted by administration of an endogenous opioid agonist (a substance that creates the same feelings as an endorphin) like morphine and promoted by naloxone (an opioid antagonist) (Bridges & Grimm, 1982; Grimm & Bridges, 1983). These results are predicted both by BOTSA and by Panksepp's work on social distress: administration of opioid agonists should create feelings of social comfort, reducing the need to seek out social contact, while the administration of antagonists, would motivate the individual to seek such contact (Panksepp et al., 1994). However, the role for endorphins in rodent maternal behaviour is complex. When using the measure of pup retrieval, naloxone does not inhibit the mother rat's motivation to retrieve her pups but does affect her ability to do so competently — the onset of retrieval is delayed or the pups are dropped before reaching the nest. In contrast, low doses of morphine do not reduce her competency despite equivalent dosages inhibiting separation distress in infants (Panksepp et al., 1994). Further research is required to study both the impact that varying dosages of opioids have upon maternal behaviour and whether different aspects of maternal behaviour (e.g., retrieval, crouching, licking and cleaning) are affected to differing extents by morphine and naloxone administration.

While the role for endorphins in motivating maternal behaviour remains ambiguous, that for their role in motivating attachment in infants is more robust. The most convincing evidence comes from the literature on separation

distress (considered in detail below). However, a recent study has confirmed another area in which endogenous opioids facilitate infant attachment behaviours: the development of maternal preference. Roth & Sullivan (2003) showed that administration of naloxone inhibits a rat pup's ability to learn its mother's odour, a behaviour which is critical for pup survival. Endogenous opioids have also been implicated in the regulation of learning and memory, and Roth & Sullivan posit that they are critical to the learning and expression of this behaviour. Their conclusion is supported by Shayit et al.'s (2003) work on sheep: administration of naloxone within the first four hours following birth prevents lambs developing a mother-specific preference, whereas controls preferentially approached and maintained proximity to their mothers as opposed to an 'alien' ewe.

One of the key predictions of BOTSA is that absence of social contact will lead to extreme withdrawal symptoms akin to withdrawal from narcotics. One key piece of evidence to support this prediction comes from the literature relating to separation distress. In a range of mammals, including rats, mice, chicks, sheep, guinea pigs, dogs, non-human primates and humans, separation from the mother leads the young to emit distress vocalisations which are alleviated when pup and mother are reunited. There is considerable evidence from a range of species that administration of morphine reduces these vocalisations, while naloxone increases them even in the presence of conspecifics, in line with the predictions of BOTSA (chicks: Panksepp et al., 1980; puppies: Panksepp et al., 1978a,b; Guinea pigs: Hermann & Panksepp, 1978; rats: Carden et al., 1996; sheep: Shayit et al., 2003). Further, tests using a range of neuropeptides, including β-, γ- and α-endorphin and met-enkephalin, oxytocin and vasopressin, showed that while all the endorphins were capable of suppressing distress vocalisations, by far the most potent was β-endorphin; in contrast, met-enkephalin failed to show any affect (Panksepp et al., 1978a,b; Vilberg et al., 1984; Panksepp et al., 1997). This latter study implicating β-endorphin as the most important endogenous opioid in the regulation of social distress, has gained further support from a study analysing the impact of the absence of MOR (the receptor for which β-endorphin has the highest affinity) on distress vocalisations. In this study, Moles et al. (2004) found that μ-receptor knockout mice pups (*Orpm*−) vocalised much less frequently than normal (or wild type) *Orpm*+ pups when isolated from their mothers; moreover, administration of morphine had no

effect upon the frequency of distress vocalisations despite significantly reducing it in *Orpm+* mice. Further, the ability of *Orpm−* mice to recognise their mother's odour was impaired: only 36% of these could do so, compared to 100% accuracy in *Orpm+* mice, implying an inability to selectively approach their own mother.

Endogenous opioids — and explicitly β-endorphin — have been implicated in a number of social behaviours which are associated with the rewarding, rather than pain-related, aspects of the endogenous opioid system. These pro-social rewarding behaviours include the maintenance of social cohesion, gregariousness, male copulatory behaviour, maintenance of kin relationships, memory and social play. Dogs administered with morphine showed a marked reduction in social tail wagging despite 24 h of social deprivation, whereas naloxone treated dogs who had not been socially deprived showed an increase (Knowles et al., 1989). Social tail wagging is one mechanism by which dogs maintain group cohesiveness following separation. Rats administered with morphine maintain significantly lower levels of proximity with conspecifics than control animals (Panksepp et al., 1979). (However, one note of caution that should be sounded is that neither of these studies controlled for the sedating effects of morphine.) In contrast, mice allowed to interact with siblings show higher pain tolerance (a proxy for endogenous opioid release) than mice allowed to interact with non-siblings (D'Amato & Pavone, 1993). Administration of naloxone reverses this effect in sibling dyads but not in non-sibling dyads — which was interpreted by these authors as implying that interaction between non-siblings does not lead to opioid release.

To address the sedation issue, two rodent studies used food to control for the possible sedating effects of morphine: in these studies, rats administered with a combination of opiates and oxytocin show a reduced interest in investigating locations which contain a conspecific ('social ports'), while there is no change in the frequency with which they investigate 'non-social ports' (food rewards), whereas rats administered morphine preferentially chose food over social rewards in maze tests (Panksepp et al., 1978a,b, 1997). Further, rats treated with met-and leu-enkephalin show enhanced learning and memory compared to controls, whilst those held in isolation for seven days exhibit an increase in opioid binding as a result of either increased receptor density or affinity (Stein & Belluzzi, 1978; Vanderschuren et al., 1995a). In

sexually inactive male rats, copulatory behaviour can be induced by the administration of naloxone, and it can be inhibited in sexually active rats by the administration of a non-sedating dose of an opioid agonist (despite the males still showing behavioural interest in the female rat, such as licking and inspecting the anogenital region) (Gessa et al., 1979).

Finally, one of the most potentially fruitful areas of research with respect to social relationships and reward has been in the sphere of rough and tumble play. This form of play is exhibited by a wide range of young mammals and manifests itself even if the individual has had no prior experience of the behaviour due to isolation, implying that it is a spontaneous neural urge. The most vigorous forms of play occur in already established social bonds, suggesting that it may be a mechanism for regulating and maintaining such bonds (Panksepp, 1999). In an early study, Panksepp & Bishop (1981) used autoradiographic mapping to show that social interaction, and specifically rough and tumble play, led to increases in endogenous opioid release in individuals involved in play as compared to socially isolated subjects. Further, this increase in endogenous opioid release was widespread within the brain but most profound in the amygdala, which is implicated in the mediation of social behaviours and emotion (Panksepp & Bishop, 1981). A replication of this study by Vanderschuren et al. (1995b) confirmed these findings, but extended the range of significant opioidergic activity to include the nucleus accumbens which is central to the regulation of reward processes in the brain. Other studies have shown that rats that have been socially isolated actively seek bouts of play in contrast to socially housed individuals who exhibit reduced motivation to play due to social satiation (Panksepp, 1999).

What is striking about the work on play is that, in contrast to gregariousness or social exploration, play behaviour is increased by administration of morphine and decreased by naloxone; furthermore, morphine facilitates dominance during play fighting while naloxone reduces it (Vanderschuren et al., 1996; Panksepp, 1999). Panksepp et al. (1997) argue that these results do not contradict the predictions of BOTSA: morphine may enable individuals to be confident enough in active social situations to play, while naloxone may promote negative feelings and a sense of psychological weakness which demotivates the individual from taking part in positive, highly active social interaction. This conclusion is supported by work which showed that naloxone-treated rats who are placed in a socially unthreatening situation (i.e., with an anaesthetised conspecific) begin to solicit play. An alternative

(or even complementary) explanation could be that morphine reduces the painful aspects of rough and tumble play — nipping, scratching and pinning — and, thus, encourages an animal to take part (Panksepp et al., 1985; Panksepp, 1999). In contrast, Vanderschuren et al. (1995c, 1996) argue that morphine may operate by powerfully increasing the reward of social play. While these results might appear to contradict BOTSA, the fact that the use of receptor-specific antagonist and agonists confirms a role for the MOR in social play at least lends further support for the key role that this receptor, in particular, plays in prosocial behaviours (Vanderschuren et al., 1995c).

7. Endogenous opioids and social behaviour in nonhuman primates

What is clear from the above review is that there is evidence for a role for the endogenous opioids in prosocial behaviour, even though the processes involved might be rather complex, and may even vary in effect with context. The evidence from nonhuman primates is less extensive but the results appear to be more robust, perhaps suggesting that endorphins have a greater and more consistent role to play in this group than in other mammals. Primates contrast with other mammals, especially rodents, in that they have been released from the hormonal and sensory control that typically underlies social bonding in mammals and have a correspondingly greater reliance upon neocortical rather than limbic system cognition. It has, therefore, been suggested that endogenous opioids might be the neurochemical 'glue' that, in conjunction with other cognitive mechanisms, enable nonhuman primates to maintain their complex social bonds over extended time periods independently of the hormone-stimulating processes of intercourse, pregnancy and parturition (Keverne, 1996; Panksepp, 1999; Curley & Keverne, 2005; Dunbar, 2010).

The first study exploring the role of endorphins in nonhuman primates social behaviour was intended to investigate whether, as in rats, the endogenous opioid system had a role to play in male sexual behaviour. This led to the conclusion that, while some results were in agreement with the findings in rats — morphine blocked copulation and naloxone elevated testosterone levels — others were ambiguous: in striking contrast to rats, administration of naloxone did not increase primate sexual behaviour. However, an incidental finding that naloxone-administered talapoin monkeys exhibited much higher rates of dyadic grooming than controls regardless of rank

(Meller et al., 1980) proved to be of more interest, given that, in nonhuman primates, grooming is important for the onset and maintenance of pairbonding during and after copulation, in reinforcing social bonds between mother and infant, in maintaining peace and social cohesion, in re-bonding individuals following aggression and in the maintenance and servicing of social bonds between allies (Fabre-Nys et al., 1982; Dunbar, 1992; Lehmann et al., 2007). Meller et al.'s fortuitous observation was, thus, the first confirmation that the endogenous opioids might be involved in the maintenance of social stability in nonhuman primates. Later studies have confirmed this finding: Fabre-Nys et al. (1982) replicated the earlier findings with respect to the impact of naloxone on grooming for both males and females and ruled out a role for dopamine or hormonal changes. Keverne et al. (1989) and Martel et al. (1995) confirmed a role for β-endorphin in this process by showing that (i) CNS levels of β-endorphin rose in previously isolated monkeys following grooming bouts and (ii) solicitations for grooming were, respectively, increased and decreased by administration of naloxone and morphine. However, when studying the impact of naltrexone on social behaviour in squirrel monkeys, Winslow & Miczek (1988) found that administration of the opiate antagonist reduced the initiation of social behaviour in dominant individuals but led to increased receipt of social initiatives by subordinate individuals. This suggests that, in nonhuman primates, the hormonal and physiological differences associated with rank may modulate the impact of the endogenous opioid system upon social behaviour, an echo of the role of dominance in relation to endorphin activation during play behaviour in rats (see above).

The other area of nonhuman primate social interaction that has provided evidence for the endogenous opioid system's involvement is that between mothers and infants. Administration of naloxone to infants leads to an increase in mother-directed behaviours — contact vocalisations (the 'coo'), bodily contact and suckling — and a decrease in social play with peers (paralleling the findings in rats). Interestingly, naloxone also leads to an increase in distress vocalisations despite the physical presence of the mother, perhaps because of the inability of the infant's endogenous opioid system to satiate its need for endorphins through physical contact (Kalin et al., 1988; Martel et al., 1995). In contrast, administration of morphine reduces contact ('coo') and reunion ('girning') vocalisations in infant rhesus monkeys (Kalin et al., 1988, 1995). Maternal behaviours are also impacted by endogenous opioids: morphine decreases and naloxone increases clinging between mothers and

infants during reunion episodes, while administration of heroin to mothers leads to self-isolation and indifference towards their offspring (Misiti et al., 1991; Kalin et al., 1995). However, administration of naltrexone to abusive rhesus macaque mothers failed to improve their behaviour towards their offspring despite increasing grooming episodes with peers and reducing maternal anxiety (as evidenced by a reduction in displacement activities) (Graves et al., 2002). The lack of involvement of opioids in maternal bonding behaviours in this instance seems to mirror the finding by Martel et al. (1993) that naltrexone reduces maternal attachment, a finding that contrasts with the studies by Kalin, Misiti and colleagues and is in opposition to the predictions of BOTSA. This would imply that the impact of the endogenous opioids on nonhuman primate maternal attachment behaviours is less clear cut than that relating to grooming or infant attachment and requires further investigation.

One possible new line of evidence has emerged from the pharmacogenetic literature. Analysis of the impact of variation in the highly polymorphic MOR gene *rh*OPRM1 in rhesus infants has shown that individuals who carry the minor G version of the C77G allele, a 'gain of function' variant, exhibit increased levels of attachment behaviours, and increased separation distress, when compared to carriers of the major A version (Barr et al., 2008). The pursuit of a similar study focusing on maternal genotypes may shed some light on the role for the endogenous opioids in maternal attachment behaviours.

What is interesting with respect to all these nonhuman primate studies is the nature of the predominant interaction which results in opioid release, namely a social interaction involving touch, irrespective of whether it involves mother/infant clinging or peer to peer grooming. It is becoming increasingly clear, as a result of evidence from both nonhuman primates and humans (see below), that touch plays a major role in the maintenance of social bonds as a consequence of opioid release (Dunbar, 2010).

8. Endogenous opioids and social behaviour in humans

While the evidence from non-primate mammals for the involvement of the endogenous opioid system in prosocial behaviour is reasonably extensive, and that from nonhuman primates with respect to grooming and infant attachment relatively robust, that from humans is noticeably lacking, despite

the fact that it was the behavioural parallels between intense social relationships and narcotic addiction which first alerted researchers to a possible role for endogenous opioids in social behaviour. This is, in all probability, due to the ethical and practical difficulties associated with both the assaying of opioid levels from human CSF and the administration of opioid receptor antagonists and agonists: the former can be unacceptably longlasting and the latter (e.g., morphine) can be addictive. As a result, the majority of studies have relied on proxies for endogenous opioid levels (e.g., pain threshold), indirect measures such as serum collection (which do not reflect CSF levels) and anecdotal reports from the psychiatric and addiction literature. What follows is a summary of those studies which have, indirectly, suggested a role for the endogenous opioids in prosocial behaviour followed by a consideration of the few studies, utilising functional scanning techniques and pharmacogenetic analysis, that have provided more direct evidence. Inevitably with respect to BOTSA, the conclusions of the first group of studies can only be speculative, although this should neither diminish their importance nor their potential as inspiration for further studies, while the latter can be argued to have provided more robust evidence even though they are scarce and invariably of small scale.

One of the first pieces of human evidence in support of BOTSA came from Liebowitz's psychiatric observations of romantic relationships (Liebowitz, 1983). He argued that romantic relationships share the same behavioural trajectory as narcotic addiction and that, just as individuals vary in their susceptibility to addiction, different subjects vary in their need to develop dependent relationships — from an inability to commit to any long term partnership to those who remain in abusive situations. He suggested that these differences were the result of differences in their neurochemical make up and explicitly identified the endorphin system its influence upon anxiety levels.

8.1. Addiction and prosocial behaviour

From this initial parallel between prosocial behaviour and addiction, it would appear to be a sensible step to consider those studies from within the addiction literature which refer to its impact on social behaviour. Without exception, ex-addicts report disruption to their close relationships and/or an inability to form new relationships (e.g., O'Donnell et al., 1967; Lex, 1990).

In their ethnographic study of a drug-using community in Spain, Albertin & Iniguez (2008) reported that drug use appeared to have replaced the need for close relationships in the addicts' lives:

> "*... a user is capable of relegating, abandoning or destroying important relationships when made to choose between these or the substance*" (ibid. 440).

> "*When you take* [drugs] *you don't need anybody; you are strong and you forget about people ...* " (ibid. 447).

> "*... drugs make you selfish ... if I can put everything into me*, [it is] *better than* [being] *among friends ...* " (ibid. 447)

Where close romantic relationships do persist, they are often based on a shared opiate addiction which leads to a commonality of purpose and direction but little else. Rosenbaum (1981) describes the attachment as functional rather than affective and, crucially, the relationship often ceases if one partner is rehabilitated (O'Donnell et al., 1967; Lex, 1990; Albertin & Iniguez, 2008). As a consequence, the dynamics of these relationships differ markedly from those of non-addict couples: addict couples often do not engage in sexual intercourse, reporting that "*... dope seems to take the place of sex ...*" and "*it got to the point where you don't need to have sex ...*" (Rosenbaum, 1981: 1201). They often remain in relationships which would be intolerable without opiates, and expressions of caring behaviour are largely drug related. This would imply that while non-addicts may be motivated to form relationships by the rewarding effects of endogenous opioid activation, drug addicts, who experience exogenous opioid satiation, enter relationships only for their practical reward (Simmons & Singer, 2006; Albertin & Iniguez, 2008). In line with the non-human literature we might also expect there to be evidence from the addiction literature that addiction impacts on the formation of the mother/infant bond. Certainly, evidence from the literature suggests that expectant addict mothers do comparatively little to prepare for their child's arrival; they also avoid skin to skin contact, as well as eye and vocal contact, immediately following birth, and, in the following months, focus almost exclusively on practical care and appear to exhibit much less enjoyment of their child than non-addict mothers — and are, as a result, more likely to have their cases referred to social services (Bernstein et al., 1984; Fiks et al., 1985; Lief, 1985). The avoidance of vocal

or physical interaction with the baby results in neglect of the infant's emotional, social and psychological development, with inevitable developmental consequences (Monnot, 1999).

While it is clear that opiate addiction is often associated with dysfunctional or completely absent social relationships, it is still unclear what implications this has with respect to BOTSA. Evidence of a link between dysfunctional parental and family relationships in an individual's early life and the propensity to addiction in later life may support the hypothesis that a lack of endogenous opioid release as a result of a lack of close relationships impacts on the development of the opioid system, motivating the individual to seek exogenous sources — which, in turn, negates the need for social contact (Nurco et al., 1998). This gains support from evidence that married individuals in emotionally close relationships are significantly less likely to develop addictions than those who are unmarried or in emotionally distant relationships, and that following treatment ex-addicts are keen to pursue relationships and re-build their social networks (Hawkins & Abrams, 2007; Heinz et al., 2009). However, the cause of breakdown of family relationships is less clear. If the catalyst for the breakdown is the addict withdrawing from their family, then this would support the notion that they do not require close relationships to satiate their need for opiate reward. However, if the catalyst is the withdrawal of the family from the addict as a result of mistrust or abuse, then this would not provide validation for BOTSA (Lex, 1990; Knight & Simpson, 1996; Hawkins & Abrams, 2007; Heinz et al., 2009). Likewise, is an addict mother's reluctance to interact socially with her child a consequence of opiate addiction inhibiting the motivation to develop and maintain close bonds or do addict mothers experience difficulty in bonding with their baby because of withdrawal symptoms, a lack of physical presence, aspects of their personality or a lack of a good parenting model (Bernstein et al., 1984; Fiks et al., 1985; Lief, 1985)? The key issue here is that, at present, we are relying on a body of evidence which, while valuable, was not collected with the aim of testing BOTSA. What is required is a focus on the nature of addicts' social relationships and the role of both exogenous and endogenous sources of opiates in these to enable the causal direction of these relationships to be clarified.

8.2. Human relationships, touch and the endogenous opioid system

We have already seen that, in nonhuman primates, social touch (grooming) is an important mediator of endorphin release. Evidence from the human

literature seems to support this. Connective tissue massage has been found to increase levels of plasma β-endorphin for up to an hour after cessation and induces a sensation of warmth and wellbeing in subjects (McKechnie et al., 1983; Kaada & Torsteinbo, 1989). Similarly, heightened levels of β-endorphin have been associated with acupuncture and this therapy has been found to have positive effects with respect to the rehabilitation of opiate addicts (Blum et al., 2000). Within the neonatal literature, it is clear that touch has an important role to play in establishing the parent/infant bond. Plasma β-endorphin levels increase in women after 20 min of nursing, while parent-received affectionate touch induced more settled behaviour (as represented by reduced heart rate and increased sleep) and smiles in pre-term infants than the practical contact received from nursing staff. Further, parents encouraged to practise 'kangaroo care' — skin-to-skin contact — exhibited higher sensitivity and lower negative intrusiveness towards their infants, the infant exhibited reduced negative emotions and, overall, the dyad exhibited increased reciprocity as compared to controls. In an intriguing study, Odendaal & Meintjes (2003) found that serum β-endorphin, oxytocin, prolactin and dopamine titres were all higher after the human subjects interacted affectionately with dogs than before in both the humans and the dogs, and were higher in the humans than after a control activity involving quite book-reading. In this study, blood samples were taken from the cephalic vein before immediately and after the intervention.

These results imply, firstly, that touch may be inducing a sense of well being within the infant-parent dyad which promotes bonding and, secondly, that it is the context of touch itself that is important, not merely its presence or absence (Franceschini et al., 1989; Miller & Holditch-David, 1992; Feldman et al., 2003). However, the drawback of all these studies is their reliance upon assaying serum rather than CNS levels of β-endorphin. Because endogenous opioids cannot cross the blood-brain barrier (Bloom, 1983; Dearman & Francis, 1983; Kalin & Loevinger, 1983; Boecker et al., 2008), plasma endorphin titres do not necessarily reflect the release of endorphins acting on the CNS via the neural system, and the ultimate neurobiological mechanism remains elusive as a result.

8.3. Endogenous opioids and group-based social behaviours

A role for the endogenous opioid system has been implicated in a number of human behaviours which may help to bond human groups on a larger

scale. One unique aspect of primate social behaviour is the extent of their social networks and, in humans, the need to maintain these social networks without the stimuli of pregnancy, parturition, sexual behaviour or adequate levels of grooming. This requires an alternative behavioural mechanism for the maintenance of social bonds (Dunbar, 2008; 2010). Recent research has suggested three possible mechanisms — music, laughter and group-based exercise, including dance — all of which may be linked to the release of endogenous opioids.

Panksepp (1999) argued that laughter is an engagement system which signals an individual's readiness to play, an invitation for continued social contact that is often expressed in the group context where it acts as a bonding mechanism. Recently, this suggestion has gained some support from a range of studies which assess the impact of laughter upon the ability to tolerate pain. In one series of studies, subjects who watched video or live comedy performances experienced elevated pain thresholds compared to controls who watched neutral or boring shows (Dunbar et al., submitted). A similar phenomenon may be at play when considering the impact of music upon human affective states and affiliation. There is evidence that solitary experience of music increases blood plasma endorphin levels and induces euphoric states (Blood & Zatorre, 2001; Stefano et al., 2004). However, music may also be a mechanism by which group level bonds can be maintained via the medium of performance. A recent study found that members of a capoeira dance group had elevated pain thresholds following their dance class compared to less physically active classes (Kaskatis, 2006). While caution should be exercised in respect of all these findings due to small sample sizes and the use of pain tolerance as a proxy for endogenous opioid release (and, in the latter case, the possibility that changes in opioid levels were the result of exercise rather than involvement in musical performance per se), overall they suggest that the endogenous opioids may be implicated in group level social bonding in humans.

PET scanning has recently confirmed a role for endogenous opioids in the phenomenon of the "runner's high" — the post-exercise euphoric state experienced by runners (Boecker et al., 2008). However, while this effect may lead to individuals being more open to affiliative behaviour following exercise — a hypothesis yet to be tested — it does not of itself allow us to conclude that physical exertion is a mechanism for group-level bonding (sensu Durkheim, 1915). However, some hints that it might do so are provided by

Cohen et al. (2009) who tested the pain tolerance of members of sweep-oar racing crews before and after 45-min training sessions under two conditions: alone and as six-man crews. They found that pain tolerance increased in both conditions but that this increase was significantly higher (almost double) following group as opposed to solitary exercise, indicating a social aspect to endogenous opioid activation. Whether this enhanced opioid activation leads individuals to be more prosocial and altruistic towards fellow group members remains to be seen.

8.4. Endogenous opioids, prosocial behaviour and mental health disorders

Finally, the last area of literature that suggests a role for endogenous opioids in human social behaviour is that relating to mental disorders. While the endogenous opioid system has been implicated in several disorders including schizophrenia, severe depression, obsessive compulsive, severe impulsive and eating disorders (Kennedy et al., 2006; Love et al., 2009; Bandelow et al., 2010; Stanley & Siever, 2010), here we focus upon two conditions whose symptoms initially suggest a specific dysfunction of the endogenous opioid system that manifests itself within the sphere of social and attachment behaviours: namely autism and Borderline Personality Disorder.

Autism involves serious impairments in social interaction and communication, often combined with a history of stereotyped behaviour and self-harm (both of which trigger endorphin release). Sufferers often exhibit reduced pain perception. In terms of social impairment, autistic individuals display limited reciprocal social interaction, difficulty interpreting nonverbal communication and impaired language. It has proved particularly difficult to find effective treatments for autism (Lam et al., 2006; Wink et al., 2010). Panksepp (1979, 1999; Sahley & Panksepp, 1987) was one of the first researchers to suggest that autistic individuals may be suffering from an overactive endogenous opioid system that effectively negates the need for them to interact socially to gain opioid reward. However, the empirical evidence to support this claim is ambiguous (see ElChaar et al., 2006; Lam et al., 2006; Wink et al., 2010). Several studies have found increased levels of CNS and circulating opioids in autistic subjects (Gillberg, 1988; Leboyer et al., 1994; Bouvard et al., 1995; Tordjman et al., 2009) and increases in prosocial behaviours following naltrexone treatment. Tordjman et al. (2009) reported absent or decreased behavioural pain reactivity in autistic subjects as

compared to healthy controls and heightened levels of plasma β-endorphin, which correlated with the severity of the autism (although caution needs to be exercised in this instance due to the nature of the endorphin assay). Panksepp & Lensing (1991) and Leboyer et al. (1992) reported increased desire to initiate social contact, verbalisation, eye contact and social exploration following treatment with naltrexone (a β-endorphin antagonist), while Kolmen et al. (1995) reported increases in the initiation of social communication. However, others have reported no difference — or even a reduction — in circulating levels of endogenous opioids as compared to controls and a lack of impact upon social behaviour following naltrexone treatment despite its leading to a decrease in hyperactivity, aggression and self harm and an increase in attention (Gillberg, 1995; Willemsen-Swinkels et al., 1995; Nagamitsu et al., 1997; Chabane et al., 2000). These differing conclusions may be due to methodological differences relating to sample size, issues surrounding the complexity of diagnosis and subject selection, dosage, the use of inappropriate controls and whether the study used a single or repeated dose protocol. In addition, studies which rely upon indirect measures of opioid system activity such as plasma assay rather than direct measures such as CSF assay or PET necessarily remain ambivalent. More recently, attention has shifted away from the endorphin system to focus on possible roles for glutamate, oxytocin and serotonin in this disorder. Nonetheless, some still argue — on the basis of the strong parallels between stereotypical autistic behaviours and the impact of morphine administration on the behaviour of animals — that the endogenous opioids are implicated in autism, albeit as a contributing rather than determining factor (Sher, 1997; Lam et al., 2006; Wink et al., 2010).

The suggestion that endogenous opioids are also implicated in Borderline Personality Disorder is relatively new. Nonetheless, initial findings appear more robust than those in the case of autism. Individuals who suffer from Borderline Personality Disorder often find difficulty in forming stable social bonds, are often involved in frequent and risky sexual contacts, exhibit attention-seeking behaviours, have a high incidence of drug addiction (45% of heroin addicts have Borderline Personality Disorder) and frequently self-harm. Sufferers tend to have particular difficulty perceiving the intentions of others (classifying individuals as either extremely good or bad, attributing malevolent intentions where none exist and misperceiving threats of abandonment) and exhibit extreme dependency coupled with aggression in their interpersonal relationships (Bandelow et al., 2010; Stanley & Siever, 2010).

Stanley & Siever (2010) have argued that the symptoms of Borderline Personality Disorder are all the result of an inability to deal with interpersonal relationships. Bandelow et al. (2010) have hypothesised that these symptoms can be explained by an under-active endogenous opioid system, and in particular a reduction in receptor density rather than the insensitivity of these receptors to endorphins. Certainly, the pattern of behaviours exhibited by Borderline Personality Disorder sufferers would imply a set of individuals who are craving endogenous opioid satiation who often attempt to achieve this via exogenous routes. Indeed, sufferers exhibit lower baseline CSF β-endorphin and met-enkephalin titres compared to healthy controls (Stanley et al., 2010). However, while noting this, Stanley & Siever (2010) argue that receptor density may actually be increased or hyper-sensitised because receptors are up-regulated to compensate for low endogenous opioid levels.

Their hypothesis has recently been supported from a PET-scanning study that investigated the response of the endogenous opioid system to a sustained state of sadness in 18 female Borderline Personality Disorder sufferers. Baseline scans showed lower levels of opioid activation in Borderline Personality Disorder subjects, but higher levels of activation following exposure to a state of sustained sadness (Prossin et al., 2010). These results seem to mirror those observed behaviourally: a general sense of inner deadness (chronic dysphoria) which remains until the imposition of stress leads to impulsive behaviours, such as self-injury, sexual contact or the use of opiate narcotics and a resulting release of endogenous opioids and a heightened response from the hyper-sensitised μ receptors (Stanley & Siever, 2010).

8.5. Functional scanning techniques and pharmacogenetics

Although most of the work on humans relies on evidence gained from indirect assays, a small number of studies relating the endogenous opioid system and social behaviour has used more direct empirical methods. Koepp et al. (2009) used PET technology and the availability of opioid receptor-specific radiotracers to demonstrate that endogenous opioids were released (as indicated by reduced binding of the radiotracer) in the orbitofrontal, right amygdala and mesial temporal areas following the induction of positive emotion in subjects. This mirrored findings by Zubieta et al. (2003) that induction of negative states in volunteers increased the rate of opioid receptor radiotracer binding. Other studies suggest that the endogenous opioid system is implicated in the regulation of positive affective states, and hence may potentially

promote the formation of affiliative relationships, in humans: administration of naloxone increases self-reports of fear and anxiety in both sexes and decreases sensations of happiness in men, while in women naloxone reverses the heightened sensations of warmth and affection and ability to tolerate pain when viewing a film portraying the development of a close relationship (Jamner & Leigh, 1999; Depue & Morrone-Strupinsky, 2005).

More direct support comes from the pharmacogenetic literature. Sequencing of the polymorphic OPRM1 gene has found that possession of the minor G variant of the A118G allele (a 'gain of function' variant which leads to a threefold increase in receptor density and affinity) leads to an increase not only in the need for affiliation but also in the resultant neurobiological reward (Way et al., 2009; Troisi et al., 2010). Furthermore, such individuals experience the breakdown of relationships more keenly and have an increased dispositional and neural sensitivity to social rejection. More interestingly, the variance in allele frequency for this gene has recently been shown to correlate with differences on a collectivism versus individualism dimension across human populations (Way & Lieberman, 2010). Populations with high frequencies of the G allele typically live in much more socially cohesive (i.e., 'collectivist') societies.

Finally, a recent fMRI study has provided some direct empirical support for the endogenous opioid system's involvement in romantic relationships by exploiting its parallel role in the pain system. Individuals who viewed pictures of their romantic partner while being administered a painful stimulus reported reduced levels of pain compared to those viewing pictures of strangers. In addition to brain areas associated with pain detection, the reward centres of these individuals were also activated, leading the research team to conclude that this form of social interaction led to stimulation of the endorphin-based reward system which, in turn, led to a reduction in the experience of pain (Younger et al., 2010).

9. Conclusion

The aim of this review has been to assess the current evidence for a role for endogenous opioids in the processes of social bonding, and so to provide a counterweight to the current over-enthusiasm for the oxytocin/vasopressin

axis. We conclude that there is significant evidence for a role for the endorphin system in a range of mammalian bonding behaviours, including separation distress, play, gregariousness, grooming, infant attachment behaviours, positive affect and affiliative behaviours. The evidence relating to maternal attachment behaviours, group-based human social behaviours, autism and Borderline Personality Disorder is more ambiguous, but clearly provides enough of a smoking gun to encourage more detailed investigation. More importantly in our view, the evidence seems to suggest that while non-primate mammals may utilise the endorphin system to maintain infant/mother and sexual pair bonds, primates (and, hence, humans) may rely to a much greater extent on this system to maintain the complex, diverse and enduring social networks that are uniquely characteristic of this order. This has meant an expansion of the interactions which mediate endogenous opioid release including, in humans, those relating to synchronous group activities.

What is clear is that the human literature suffers not from a lack of evidence in support of the Brain Opioid Theory of Social Attachment (BOTSA) but from the lack of an ethically acceptable method of assaying CNS endorphins directly. PET scanning solves this problem to some extent, though it is currently exceptionally expensive and somewhat restrictive in the kinds of experimental designs that can easily be tested. Moreover, PET does not as yet provide scope for measuring opioid uptake in sufficient quantitative detail to allow dose-response comparisons of the strength of relationship quality between individuals or between species to allow us to correlate these with functional outcomes (e.g., relationship duration, reproductive fitness, etc). The alternative methodology offered by the use of naltrexone (a β-endorphin-specific antagonist) to confirm loss of effect circumvents some of these problems and has proved valuable in many cases. However, there may be ethical issues relating to the effect that blocking endorphin activation might have on subjects' on-going relationships.

On a broader social scale, the importance of a capacity for functional relationships for the cohesiveness of social communities may be especially important for species like nonhuman primates and humans that live in relatively large, bonded social groups. There is already considerable evidence that dysfunctional relationships, particularly in childhood, can lead to a range of anti-social behaviours, psychopathologies and addiction-based behaviours in adults (Uchino, 2006; Reblin & Uchino, 2008). An understanding of the role that the endorphin system plays in this process may not only help to

elucidate the processes of social cohesion but, in the human case, may also help suggest a range of actions that might mitigate the social impact of dysfunctional relationships, with resulting benefits to the individual and society at large. In addition, the increasing evidence linking endogenous opioids to genetic polymorphisms offers potentially important opportunities for understanding the population- and species-wise differences in behaviour.

One implication of the evidence reviewed here is that the current fashion for focussing on the oxytocin/vasopressin axis to the exclusion of everything else exposes us to the inevitable risk of underestimating the real complexity of the neurochemical mechanisms underlying social behaviour and, thus, of missing some of the subtleties and complexities involved. Although we have focussed here on the opioid (and specifically endorphin) system, this should not be taken as implying that we dismiss the other neuroendocrines as being unimportant. Our aim has simply been to redress the balance by establishing that there is sufficient evidence for the opioid system to warrant further study in conjunction with the other neuroendocrines. One of the potential confounds in studying the neurochemistry of social behaviour is the fact that several of the neuroendocrines have similar effects (e.g., the analgesic effects produced by both oxytocin and β-endorphin) and/or are known to be simultaneously implicated in a behavioural outcome (e.g., oxytocin and endorphins in autism). Indeed, given their roles as neurotransmitters, most of them probably are involved all the time as functional cascades with complex feedback effects. To undertake experiments that manipulate only one neuroendocrine without simultaneously controlling for the others risks erroneously attributing an effect to the wrong mechanism.

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