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Review article

A mu-opioid feedback model of human social behavior

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ABSTRACT

Since the discovery of pain relieving and rewarding properties of opiates such as morphine or heroin, the human mu-opioid system has been a target for medical research on pain processing and addiction. Indeed, pain and pleasure act mutually inhibitory on each other and the mu-opioid system has been suggested as an underlying common neurobiological mechanism. Recently, research interest extended the role of the endogenous mu-opioid system beyond the hedonic value of pain and pleasure towards human social-emotional behavior. Here we propose a mu-opioid feedback model of social behavior. This model is based upon recent findings of opioid modulation of human social learning, bonding and empathy in relation to affiliative and protective tendencies. Fundamental to the model is that the mu-opioid system reinforces socially affiliative or protective behavior in response to positive and negative social experiences with long-term consequences for social behavior and health. The functional implications for stress, anxiety, depression and attachment behaviors are discussed.

1. Introduction

Pain and pleasure are essential forces of human social-emotional behavior. There is continuous competition between the processing of-, and action preference for pain avoidance and achievement of pleasure. Whilst formerly often considered opposite processes, more recent evidence suggests a common underlying neurobiological system (Fields, 2006; Le Magnen et al., 1980; Leknes and Tracey, 2008). An example of where pain and pleasure directly interact on a neural level is reward related analgesia where anticipation or acquisition of a reward diminishes pain (Fields, 2006; Leknes and Tracey, 2008).

One underlying system playing a crucial role in pain regulation as well as reward processing, is the endogenous opioid system (Fields, 2004; Fields and Margolis, 2015; Leknes and Tracey, 2008). The discovery of the endogenous opioid system is relatively recent, the use of opium however can be traced back to Sumerians in 3000 BCE. Morphine, the most active ingredient of opium, is still a universally used painkiller despite side effects including respiratory depression, dependence and tolerance (Merrer, 2009). Opiates such as morphine and heroine do not only have pain relieving properties but can also generate strong appetitive motivational actions and do have addictive potential (Fields, 2004). The role of the opioid system in addiction and its potential in the treatment of pain conditions made especially the mu-opioid receptor (MOR) system a target for medical research.

Early animal research indicated a promising role for opioid modulation in other areas than pain, such as social bonding (Herman and Panksepp, 1978; Panksepp et al., 1978) and threat learning (Good and Westbrook, 1995; McNally, 2009; McNally and Westbrook, 2003). Human research supports these findings, suggesting a key modulatory role for the MOR system in human social-emotional behavior and processing, which is especially relevant with regard to the current opioid crisis in North America. Crucially, evidence points towards an inhibitory role of the MOR system in the attention allocation to-, processing, and acquisition of threat related associations (Bershad et al., 2016; Eippert et al., 2008; Haaker et al., 2017; Ipser et al., 2013; Løseth et al., 2018) and further, indicates that opioid modulation affects the hedonic processing of social reward (Buchel et al., 2018; Chelnokova et al., 2014; Eikemo et al., 2017, 2016). Opioid modulation of both social threat and reward is not only relevant from a perspective of fundamental research with regard to its role in healthy social functioning (including emotion regulation, motivational processes and social bonding), but also with respect to clinical implications. Experience of early childhood adversity is related to long-term changes in endogenous opioid functioning and increased vulnerability for addiction and mood disorders later in life

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(Kennedy et al., 2006; Savulich et al., 2017). Further, a high comorbidity has been reported between long-term opioid use and increased anhedonia, pain and anxiety (Garland et al., 2019).

With the recent increase of attention to the role of the MOR system in human social-emotional behavior, the paper assesses the current state of research from the perspective of an opioid mediated continuous reinforcement model of social behavior. In short, if an individual experiences chronic stress or trauma during their life, opioid modulation of social behavior might shift from reinforcing actively social- to socially-avoidant behavior, characterized by altered sensitivity to reward, pain, threat and stress.

1.1. From pain and pleasure to social behavior

The Motivation-Decision Model of Pain (Fields, 2006) states that through unconscious decision processes, anything that has higher relevance for survival than pain receives action preference over pain related reflexes and therefore is potentially inhibiting nociception. This allows for an adequate response to environmental stimuli that require attention. Therefore, a salient reward cue may activate antinociceptive effects in the descending pain modulatory system and produce pleasure related analgesia allowing for reward pursuit. The second important environmental cue that can potentially gain action preference above pain reflexes as well as reward driven behavior is threat. Threat-perception may lead to stress induced analgesia (Ribeiro et al., 2005), enabling the individual to respond effectively to potential danger in their environment.

Both these processes are known to be driven by opioid modulation (Fields, 2006; Leknes and Tracey, 2008; Rebouças et al., 2005; Szechtman et al., 1981) through mediation of the hedonic value of affective cues. This in turn can promote goal directed approach-avoidance behaviors allowing for pain and threat avoidance as well as the pursuit of reward. Indeed, enhancing mu-opioid activity by administration of an opioid agonist (see Table 1 for a relevant overview of MOR system agonists and antagonists), can increase pleasantness for different reward stimuli (Eikemo et al., 2016), as well as decrease aversiveness of negative experiences such as pain (Fields, 2004). Blocking the mu-opioid system, on the other hand, results in decrease of pleasurable experience from rewards (Buchel et al., 2018; Chelnokova et al., 2014; Eikemo et al., 2016) and disrupts placebo- and reward induced analgesia (Rutgen et al., 2015). Importantly, either of these affective experiences are linked to changes in opioid activity in brain structures involved in social-emotional processing such as the amygdala, the periaqueductal gray (PAG), the orbitofrontal cortex (OFC), the nucleus accumbens (Nacc) and the ventral pallidum (VP) (Buchel et al., 2018; Leknes and Tracey, 2008; Ribeiro et al., 2005).

Recent animal and human research provide evidence that this function of the MOR system extends from such basic approach-avoidance mechanisms to more complex social behavior. Through the modulation of hedonic value the MOR system indirectly influences motivational aspects and emotional learning which in turn drive more complex social behaviors such as social rejection, empathy, anxiety, bonding and touch (Eippert et al., 2008; Haaker et al., 2017; Hsu et al., 2013; Nummenmaa et al., 2016; Rutgen et al., 2015). An increasing number of studies investigate the influence of opioid modulation on these social-emotional behaviors, which we will review in the upcoming paragraphs.

Table 1
Overview of a selection of MOR receptor agonists and antagonists and their binding mechanisms to the three opioid receptor types (mu, delta and kappa opioid receptors). The selection is based on information relevant to understand the described research in this paper. CNS = central nervous system.

Drug	Type	Binding mechanisms
Morphine	Agonist	Opioid agonist with high affinity to the mu-opioid receptor and lower affinity to kappa- and delta-opioid receptors in the CNS.
Buprenorphine	Agonist	Partial agonist to the mu-opioid receptor and antagonist to the kappa-opioid receptor in the CNS.
Naltrexone	Antagonist	Competitive opioid antagonist with high affinity to the mu-opioid receptor and lower affinity to kappa- and delta-opioid receptors in the CNS.
Naloxone	Antagonist	Competitive opioid antagonist with high affinity to the mu-opioid receptor and lower affinity to kappa- and delta-opioid receptors in the CNS.

2. Mu-opioid modulation of social-emotional behavior

2.1. Social rejection and empathy

Social pain, defined as the experience related to the damage or loss of close social relationships or a self-devaluation through rejection or negative evaluation is suggested to be modulated by opioid mechanisms. The pain of social rejection has been associated with increased MOR activity in areas of the brain considered part of the physical pain modulation circuitry (cf. Fields, 2004), including the bilateral amygdala, midline thalamus, the subgenual anterior cingulate cortex (sgACC) and the right ventral striatum (Hsu et al., 2013). Crucially, administration of buprenorphine reduces perceived social rejection in humans (Bershad et al., 2016) and separation distress is decreased after morphine administration and increased after naloxone administration in rodents (Herman and Panksepp, 1978). Moreover, increased MOR activity in areas involved in pain processing during rejection is not only related to reduced feelings of rejection, but also with increased resilience traits (Hsu et al., 2013), thus serving a protective function.

A recent study gave first insight into the underlying opioid driven neurochemical base of empathy for pain (Rutgen et al., 2015). The authors demonstrated that administration of naltrexone compared to placebo, did not only block the effect of placebo analgesia on self-perceived pain as one could expect, but crucially, also reduced the effect of placebo analgesia on other-perceived pain (Rutgen et al., 2015). Thus, a common opioid centered neurobiology seems to modulate physical pain, social pain and empathy for pain.

2.2. Fear and stress

Similar to the adequate response to pain, adaptive responses to threat and stress are important to assure safe navigation and health in our everyday life. Key brain structures involved in threat processing, including the nuclei of the amygdala, thalamus, ACC and PAG are densely innervated with mu-opioid receptors and suggested to be involved in opioid mediated modulation of anxiety (McNally et al., 2004; Poulin et al., 2006). Evidence from rodent research indicates an inhibitory role for endogenous opioids in the acquisition of threat associations and further a facilitatory role for unlearning such associations. Indeed, administration of MOR agonists decrease efficacy of threat conditioning whereas administration of opioid antagonists enhance threat conditioning and disrupt extinction (Good and Westbrook, 1995; McNally et al., 2004; McNally and Westbrook, 2003; Westbrook et al., 1991).

In humans, the endogenous MOR system can also inhibit the acquisition of conditioned threat associations (Eippert et al., 2008; McNally, 2009), since blocking the MOR system resulted in enhanced processing in pain and threat-related pathways, including the amygdala, rostral ACC and PAG and enhanced behavioral conditioned responses (Eippert et al., 2008). Crucially, these findings were recently extended towards social learning as threat conditioning through observational learning was sustained after naltrexone administration as reflected by enhanced stress responses in the amygdala, midline thalamus and PAG (Haaker et al., 2017). These results thus support the idea that the MOR system shapes aversive learning based on first-hand as well as indirect, social experiences (Eippert et al., 2008; Haaker et al., 2017).

Social perception studies in humans support this idea. Blocking the

mu-opioid system with naltrexone resulted in an attentional bias to emotional faces and an increased identification of the emotional expressions anger and happiness (Wardle et al., 2015), emotions that are known to evoke approach motivation. This bias to detect socially relevant information is in line with the notion of Panksepp's BOTSA (Panksepp et al., 1978), that blocking the MOR system leads to emotional distress and subsequently results in behaviors that lead to social support and protection from potential threat. Administration of buprenorphine decreases the attentional bias for fearful faces (Bershad et al., 2016) and reduces fear recognition sensitivity (Ipser et al., 2013). Moreover, administration of the MOR agonist morphine decreases the subjective perception of anger in ambiguous as well as neutral faces (Løseth et al., 2018). In line with this protective role of mu-opioid activity in social threat perception, a recent study showed that buprenorphine also reduces the cortisol stress-response, which translates results so far only obtained in rodents (Bershad et al., 2015; Drolet et al., 2001; Ribeiro et al., 2005; Valentino and Van Bockstaele, 2015). This mechanism most likely underlies the observation that MOR activity can promote immediate anxiolytic and analgesic responses in humans after a traumatic event which is comparable to the analgesic response to inescapable shocks in animals (van der Kolk et al., 1985). At the same time, variation of the OPRM1 A118 G receptor gene was found to affect cortisol stress responses differentially in men and women, with women carrying the G allele (homo- and heterozygotic variant) showing a diminished cortisol stress response (Lovallo et al., 2015).

Overall, the reviewed evidence suggests a protective role of the MOR system in response to threat, pain or stress through dynamic regulation of psychological, physiological and endocrine responses. However, even though the protective, stress reducing effects of the MOR system are adaptive in the short-term, chronic exposure to stress can result in dysregulation of opioid mediated stress mechanisms that creates a shift toward MOR inhibition leading to tolerance and dependence – comparable to the effects of substance abuse (Valentino and Van Bockstaele, 2015). Indeed, early childhood adverse experiences are associated with altered reward processing and increased vulnerability to substance abuse disorders (Andersen and Teicher, 2009; Cohen and Densen-Gerber, 1982; Enoch, 2011), through dysregulation of opioid functioning (Gustafsson et al., 2008). Such dysregulation could in turn play an important role in psychopathologies such as PTSD, depression or (social) anxiety. These psychopathologies are related to hyper-reactivity of neural networks linked to social rejection and decreased reward responsivity (Lutz et al., 2018; Lutz and Kieffer, 2013a; Ribeiro et al., 2005). Similarly chronic opioid use can result in anhedonia and deficits in emotion regulation (Garland et al., 2019, 2017). Repeated confrontation with aversive social experiences can alter the sensitivity to social cues in the long-term through a similar shift in opioidergic mechanisms, towards increased sensitivity for negative social cues and dampened responding to positive social stimuli. Thus, although the protective, stress reducing effects of the MOR system are adaptive in the short-term, chronic exposure to stress can deplete this protective function, resulting in hyper- and hypo-reactivity of opioid-dependent neural networks.

2.3. Social reward, bonding & affiliation

We previously described the behavioral and underlying neural connection between the processing of rewarding and painful stimuli, with the indication that the MOR system is involved in attributing the hedonic value to pain and reward. Looking specifically at the processing of reward cues, research in rodents localized 'hedonic hotspots' in the brain reward circuitry. Areas in the rostrodorsal shell of the Nacc, the caudal ventral pallidum (VP), the parabrachial nucleus, the anterior orbitofrontal cortex and the posterior insula have been identified as the mu-opioid hotspots for the hedonic 'liking' of reward (Berridge, 2009; Berridge and Kringelbach, 2013; Castro and Berridge, 2017; Peciña et al., 2006). Research on social play, a social behavior which is intrinsically rewarding, highly important for social and cognitive development and crucial for peer-bonding, has been shown to be mediated by the MOR system (Guard et al., 2002; Trezza et al., 2010; Vanderschuren et al., 1995). Additionally, it has been suggested that the MOR system is involved in the motivational component of reward approach behavior, therefore, increasing the wanting of rewards. More specifically, the mu-opioid system might contribute to the motivation to obtain reward cues, since, after mu-opioid agonism in the medial Nacc shell, animals were shown to work harder for food reward (Peciña, 2008; Zhang et al., 2003).

These findings, on the one hand, are important to understand addiction behaviors, but on the other hand have also great relevance for research on appetitive responses to social interaction and affiliation mechanisms. The brain opioid theory of social attachment (BOTSA), which was developed on the basis of groundbreaking work from infant-attachment studies, indeed suggests such a central role of the MOR system in bonding and attachment (Panksepp et al., 1980). Human research so far, supports the idea that the MOR system is involved in the hedonic, and to a lesser extent motivational, aspects of social reward behavior. A recent neuroimaging study (Buchel et al., 2018) found a specific effect of MOR blockage on the hedonic value of reward in both pleasure ratings and reward related neural activation in the ventral striatum, lateral orbitofrontal cortex, amygdala, hypothalamus and medial prefrontal cortex. However, no effect was found on reward anticipation. Korb et al. (2020) showed that MOR blockade with naltrexone resulted in decreased physical effort as well as increased negative facial reactions in the reward anticipation phase compared to placebo. Further, in line with the idea that the MOR system regulates the hedonic value of reward, participants also showed reduced positive facial reactions during reward consumption. Subjective responses in terms of reward wanting and liking however were not affected by opioid blockade (Korb et al., 2020). Chelnokova et al. (2014) explored the question whether the MOR system is involved in the hedonic as well as motivational aspects of social reward directly, using a behavioral task assessing the 'liking' and 'wanting' of attractive faces. Interestingly they found that administration of the MOR agonist morphine increased specifically the liking of stimuli with high reward value, whereas blocking the mu-opioid system with naltrexone specifically decreased the liking of such. In line with the idea that the hedonic value influences the motivational component of reward, participants also invested more effort to keep seeing highly attractive stimuli under morphine but lessened their effort with naltrexone. Blocking the MOR system additionally increased the effort to stop viewing images that participants perceived low in reward value (Chelnokova et al., 2014). Further, it is reasonable to assume that with such an increase of the hedonic value of, as well as motivation for, reward stimuli, these are also better remembered. Looking at memory of social reward cues such as happy faces, administration of buprenorphine compared to placebo was indeed followed by a significant increase in memory for happy faces compared to other emotions (Syal et al., 2015).

Based on the idea that social affiliation is at least partly driven by basic reward mechanisms, several studies support the idea of BOTSA (Herman and Panksepp, 1978; Panksepp et al., 1980), that the mu-opioid system plays an important role in supporting the formation and maintenance of social affiliation. For example, in human subjects we recently showed an increase of automatic facial responses associated with negative emotions (anger, sadness) in response to happy faces (Meier et al., 2016). Happy faces are considered powerful social reward cues and automatic imitation of happy facial expressions has been shown to promote social affiliation. We therefore suggested that blocking the MOR system disrupts the automatic behavioral response involved in social bonding (Meier et al., 2016). A study using positron emission tomography found an increase of MOR activation in response to social acceptance in areas related to reward and social salience processing, namely the ventral striatum, amygdala and insula. In addition, MOR activation in the ventral striatum was predictive for higher desire of social interaction (Hsu et al., 2013). Likewise, the feeling of

(interpersonal) warmth, part of the pleasurable feelings related to social bonding, has also been associated with MOR activity in humans (Depue and Morrone-Strupinsky, 2005). Schweiger et al. (2013), found that warmth-liking can induce trust, but that administration of naltrexone decreases warmth-liking. Interestingly, two further studies found that blocking the MOR system with naltrexone specifically decreased the feeling of social connection associated with warmth-liking, without modulating other affective (pleasantness etc.) or sensory component (Inagaki et al., 2016, 2015).

Taken together, the MOR system seems to promote the hedonic and motivational components of social reward, which in turn drives memory and decision-making towards the facilitation of social bonding and affiliation. Of interest is that patients with long-term prescription opioid use, and especially opioid drug misusers, show attenuated attentional and autonomic responses to natural rewards (e.g. food stimuli), and deficits in emotion processing (Garland et al., 2017, 2015; Lubman et al., 2009; but see Eikemo et al., 2019). This is in line with the idea that chronic opioid use is associated with a disruption and shift in the function of the endogenous MOR system (Garland et al., 2015; Valentino and Van Bockstaele, 2015). Similarly, even though not necessarily to the same extent, dysregulation of opioid mediated reward mechanisms, for example through experience of trauma or chronic stress (cf. section *2.2 Fear and Stress*) may thus lead to a reduction in the experience of pleasure and decrease the sensitivity to social cues that create opportunities to experience positive social interactions. Noteworthy is a recent study which showed that previously heroin addicted mothers on long-term opioid maintenance treatment (OMT), with low stress exposure and illicit drug use compared to the general OMT population, had intact and robust reward responsiveness to non-drug rewards (Eikemo et al., 2019). This indicates that, given relatively low psychosocial stress, long-term stable pharmacotherapy does not necessarily induce reduced reward responsiveness and anhedonia as reported in individuals who misuse opioid drugs (Garland et al., 2019; Lubman et al., 2009; Trøstheim et al., 2020). It could further indicate a recovery of reward systems under stable pharmacotherapy and socio-environmental conditions (Eikemo et al., 2019). Whether higher psychosocial stress exposure would modulate reward responsiveness in individuals on long-term opioid maintenance treatment remains to be seen.

2.4. Touch

A fundamental behavior implicated in social reward and relationship maintenance, in non-human primates as well as humans, is touch. Primate research showed that grooming, next to its function in hygiene, seems to be highly relevant for the formation and maintenance of social bonds (McGlone et al., 2014). In humans, touch has been shown to be a crucial factor in infant development (Field, 2010), it functions as safety signaling in parent – children interactions (Brummelman et al., 2018), and generally acts as a social buffer by reducing stress and altering the perception of pain and threat (Coan et al., 2006; Morrison, 2016). The mu-opioid system is suggested to mediate the positive effects of touch (Weller and Feldman, 2003). Research in non-human primates clearly shows modulation of grooming behavior through opioid mechanisms (Keverne et al., 1989). However, the fact that the animals are housed socially or isolated at different stages of these experiments makes a straightforward interpretation of the results difficult since the motivational state of the animal at time of drug administration might influence the measured outcome (c.f. Løseth et al., 2014). A study by Martel et al. (1993) showed that socially housed monkeys displayed gradually less grooming behavior towards their infant with naloxone administration over several weeks. Social grooming between adults decreased instantly from the first administration of naloxone. This suggests a certain amount of variability in the role of opioid modulation in mother-infant attachment and adult relationships and the relevance of touch therein (e.g. additional role of oxytocin in mother-infant attachment).

There is relatively little human evidence investigating the role of the mu-opioid system in touch. In one study, 20 min of mother-infant skin-to-skin contact has been shown to reduce the peripheral levels of cortisol and beta-endorphins in the blood samples of the infants, presumably due to a decrease of hypothalamic-pituitary-adrenal axis activity (Mooncey et al., 1997). Nummenmaa et al. (2016) found increased binding potential, consistent with deactivation of endogenous mu-opioid activity in areas of social reward and affective processing (ventral striatum, amygdala, medial prefrontal, and orbitofrontal cortex) during social touch compared to a non-social control condition. An alternative mechanism underpinning their findings could be an upregulation of mu-opioid receptors. Finally, a study investigated the role of the mu-opioid system in perceived affective touch (activates C-tactile fibers in the skin which are suggested to mediate the pleasantness of touch) in healthy adults and patients with fibromyalgia (Case et al., 2016). Fibromyalgia is a chronic pain condition which has been related to decreased central MOR availability. Whilst in healthy participants MOR blockade with naloxone resulted in increased pleasantness ratings for touch, patients with fibromyalgia showed decreases in touch intensity ratings but no alteration of touch pleasantness (Case et al., 2016). On the other hand, a recent experimental study found no evidence for opioid modulation of c-tactile fiber mediated touch pleasantness, nor for the motivation to receive touch, after administration of morphine or naltrexone (Løseth et al., 2019). It is important to consider though that the application method of c-tactile optimal touch in the experimental context does not represent social, affiliative touch, nor is it a social buffering context, and might therefore not be opioid mediated (Ellingsen et al., 2016; Løseth et al., 2019). As an example for social buffering, Coan et al. (2006) showed that hand-holding between partners reduced negative affect and neural activation to the threat of physical pain, which speaks for opioid regulation of these effects.

In sum, there might be a role for the MOR system in touch. However, more research is warranted given the subjectivity and sensitivity of touch to context, as well as the variety in methods and measurements used in a range of different studies. Given that research on social reward showed that the MOR system might specifically reinforce positive *social* cues, future research should integrate the social aspect as a crucial component when investigating the interaction between MOR regulation and touch.

3. A mu-opioid feedback model of social interaction

Based on the reviewed evidence of the acute effects of opioid agonists and antagonists on human social-emotional behavior, we propose a mu-opioid feedback model of social interaction (Fig. 1). The model places opioid modulation of social pain, threat and reward processing in a theoretical framework of social behavior, suggesting an interactive role for MOR system in supporting affiliative or protective social motives through changes in neural sensitivity and behavior. Further, the model takes into account translational evidence on mechanisms and consequences of early trauma and chronic stress, which might cause a change in sensitivity to opioids that is comparable to substance abuse. The main purpose of this model is to provide a heuristic framework based on current evidence, to help disentangle complex opioidergic mechanisms of social-emotional behavior and therewith facilitate development and testing of new hypotheses.

On the one hand, the MOR system is a driving factor in building and strengthening our social connections. Panksepp et al. (1980) proposed that the role of the MOR system in social attachment behaviors could have developed from basic pain regulation systems that initiate behaviors which increase chances of survival. For example, distress vocalizations in young animals assure closeness and attention by their mother. Evidence for this hypothesis was collected on the basis of infant attachment behavior, where social distress could be relieved or induced by administration of MOR agonists or antagonists respectively (Herman and Panksepp, 1978; Panksepp et al., 1978). In humans, the limited neuroimaging evidence available shows that perception of rewarding

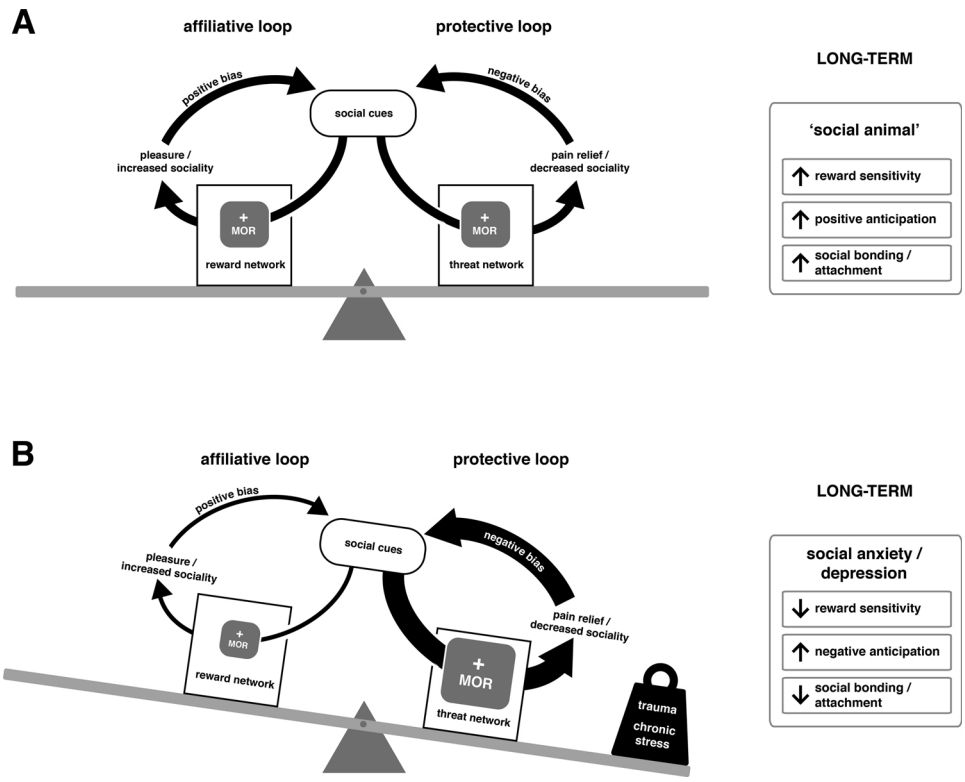

Fig. 1. Mu-opioid feedback model of social interaction. When a social interaction takes place, different social cues (e.g. reward, threat) of the interaction itself, including the context, trigger changes in MOR related activity in the brain to generate a hedonic interpretation of the social experience. If the social cue is positive, mu-opioid release in areas involved in reward and emotion processing create a pleasurable hedonic state motivating the individual to invest more time and effort into social interactions (affiliative loop). The individuals' anticipation and reward sensitivity for positive social cues facilitates creating strong social bonds with peers which act as a social buffer in the face of stress. If, on the other hand, the social cue is negative MOR activity in areas related to pain and threat processing help the individual to cope with the acute social pain by inducing pain relieving effects (protective loop). This is highly adaptive, it gives the individual time to regulate their behavior adequately to the situation and if necessary, to recover from the experience, but it also results in acutely decreased social reward sensitivity and social exploration. Dynamic shifts between the two loops allow for flexible behavior and a continuous social learning process, leading in the long-term to the well-adjusted 'social animal' (A). If the individual is confronted with frequent negative, potentially traumatic experiences, long-term changes in the neurochemical set-up of the MOR can create a shift in behavioral patterns toward the protective loop. The shift is characterized by chronically reduced sensitivity for social reward cues and an increase in anticipation for negative social cues such as threat or fear cues. This behavioral pattern makes it increasingly difficult to engage in future positive social interactions potentially leading to insecure attachment and difficulty to form strong long-term bonds (B). +MOR: change in mu-opioid receptor activity.

social cues has been associated to mu-opioid mediated activity in mesocorticolimbic structures (ventral striatum, lateral OFC, amygdala, hypothalamus, mPFC) (Buchel et al., 2018), with MOR activity in the ventral striatum after a positive social experience being predictive for interest in social interaction (Hsu et al., 2013). Therefore, if an individual interprets a social experience as positive through integration of social cues, context, etc., endogenous mu-opioids are released in areas related to reward processing, mediating the pleasant hedonic experience of social interaction. On a secondary level MOR activity decreases the individual's sensitivity for negative social cues and increases sensitivity for social reward cues (Ipser et al., 2013; Løseth et al., 2018; Syal et al., 2015). On a behavioral level this creates a positive feedback loop, resulting in increased social exploration and active affiliative behavior, creating space for additional positive social interactions due to positive anticipation of social reward cues. In the long-term, if an individual accumulates positive social experiences it leads to facilitation of strong long-term bonds with others which enacts as a strong social buffer in stressful situations (Machin and Dunbar, 2011) (Fig. 1A).

When encountering negative social cues that elicit a stress response, the release of opioids has a protective role which equally has been suggested to originate from pain regulatory mechanisms. In this case the pain regulatory mechanisms are aimed at decreasing painful experiences and eliciting behaviors associated with reacting to-, coping with-, and anticipation of potentially threatening events (Fig. 1A). On a more complex social-emotional level opioids modulate the behavioral response to social pain, stress and fear which protects against negative affect, also when seeing others in distress (Bershad et al., 2016, 2015; Haaker et al., 2017; Hsu et al., 2013; ; Rutgen et al., 2015). Opioids might therefore similar to oxytocin (Bos et al., 2015), facilitate helping behavior . Therefore, if an individual experiences an aversive social situation, MOR activity increases in areas related to pain and threat related processing including the amygdala, periaqueductal gray (PAG), thalamus, OFC, insula and the Nacc (Haaker et al., 2017; Hsu et al., 2015, 2013; Ribeiro et al., 2005; Zubieta et al., 2001). Moreover, Hsu et al. (2013) showed that greater MOR related activity in this network correlated with greater trait-resilience in the face of rejection, in support of the idea of a protective function of MOR activation. On a subjective level MOR related activity in response to pain is indeed associated with a decrease in sensory responses and negative affect (Zubieta et al., 2001).

This mechanism has however also negative repercussions for social behavior. Indeed, the effects of pain on pleasure and vice versa (Leknes and Tracey, 2008) as well as the effect of stress and cortisol on reward sensitivity (Berghorst et al., 2013; Montoya et al., 2014), indicate that sensitivity for social reward stimuli and therewith associated social exploration are dampened during an acute negative social experience. As previously mentioned, this response is highly adaptive allowing the individual to regulate their social pain and subsequent behavior to create new opportunities for positive social experiences (Fig. 1A). The experience of traumatic events or continuous exposure to stress however, leads to a chronic dysregulation of the MOR system resulting in less

responsivity to social reward and hypersensitivity to threat, both of these characteristics are strongly associated with social anxiety and depression (Garland et al., 2019; Lutz et al., 2018; Lutz and Kieffer, 2013b; Shurman et al., 2010). Thus, on the biopsychological and behavioral level, the individual enters a self-sustaining negative feedback loop with a strong bias toward anticipation of negative social cues. This bias feeds into the social experience creating a higher possibility of an actual aversive experience whilst reducing the probability of a positive social experience (Fig. 1B).

Evidence from the clinical field, for instance that chronic pain as well as prolonged opioid drug (mis-) use are accompanied by a change in mu-opioid receptor functioning (Garland et al., 2019; Harris et al., 2007; Jones et al., 1988; Klega et al., 2010), reduced reward sensitivity and attenuation of emotion regulation capacities (Garland et al., 2017, 2015), and that early childhood trauma and PTSD increase vulnerability to addiction and mood disorders (Kennedy et al., 2006; Malcolm-Smith et al., 2013; Savulich et al., 2017), supports this line of thought. Further, research on the consequences of opioid use during pregnancy indicate a dysregulation of the central and autonomic nervous system in newborns with Neonatal Abstinence Syndrome (NAS), with consequences for basic behaviors such as sleep, feeding, stress reactivity and communication with the parent (Velez and Jansson, 2008). Crucially though, research highlights the importance of contextual factors, such as quality of caregiving or stability of the social environment, in the long-term development of these infants (Sarfi et al., 2011). Therefore, whilst pre-natal opioid exposure represents a heightened vulnerability and risk factor, quality of caregiving, and therewith early exposure to a stressful or secure environment, is a crucial predictor for attachment, resilience and development.

4. Clinical relevance

The reviewed evidence on social behavior and emotional processing gives reason to consider the role of opioids in clinical context, especially with regard to psychopathologies where changes in the ability to perceive pleasure or process threat are part of the symptomatic, such as social anxiety and depression (Colasanti et al., 2011; Lutz et al., 2018; Shechner et al., 2012).

In line with the idea of a protective role of MOR activity, research suggests that opiodergic neurotransmission is involved in anxiolytic responses by dampening negative affect and distress in an acutely stressful situation (Colasanti et al., 2011), which might be dysregulated in the case of social anxiety. Characteristics of social anxiety include hypersensitivity to threat and dampened social reward sensitivity (Shechner et al., 2012). As previously reported, pre-clinical as well as human experimental work clearly demonstrate a role for the mu-opioid system in fear learning (Eippert et al., 2008; Good and Westbrook, 1995; Haaker et al., 2017; McNally, 2009; Westbrook et al., 1991) and reward processing (Berridge and Kringelbach, 2008; Chelnokova et al., 2014; Peciña et al., 2006; Syal et al., 2015), therefore the MOR system could contribute to symptoms of social anxiety by changing sensitivity to threat and reward cues.

A distinct characteristic of depression is the decreased ability to perceive pleasure, which can be termed as reduced reward responsivity and increased sensitivity to social pain (Lutz et al., 2018). Neuroimaging evidence indicates that individuals with depression show an elevated MOR tone in the thalamus during baseline measurements, and they further lack the MOR deactivation in rostral ACC, ventral pallidum, amygdala and inferior temporal cortex in response to a sustained state of sadness that was found in healthy controls. Rather they showed an increase of MOR related activation in the inferior temporal cortex (Kennedy et al., 2006; Zubieta et al., 2003). In addition, individuals with depression showed a decreased MOR response in response to direct social rejection and they lacked the MOR mediated reward response in the Nacc that healthy controls showed (Hsu et al., 2015).

A further point to consider in this context is that the MOR system has a direct impact on the HPA axis, which plays a major role in aversive learning processes. Animal work, looking at the interactive role of the MOR system and corticotropin releasing factor (CRF) in the locus coeruleus, suggests a protective role of the MOR system with the occurrence of acute stressors, downregulating the effects of CRF and therewith promoting recovery after the stressor. Repeated stress however has been shown to shift the balance in the locus coeruleus toward inhibitory MOR regulation, resulting in long-term modifications of neural circuits supporting evidence of a link between post-traumatic stress disorder (PTSD) and vulnerability for substance abuse (Valentino and Van Bockstaele, 2015). The results are further in line with research suggesting that childhood trauma results in long-term changes in the mu-opioid system, accompanied by altered emotion regulation mechanisms, as well as heightened vulnerability for substance abuse and mood disorders later in life (Kennedy et al., 2006; Malcolm-Smith et al., 2013; Savulich et al., 2017), and adds to neuroendocrine models that explain how childhood adversity affects social-emotional behavior and impaired quality of caregiving in later generations (Bos, 2017)

5. Future directions

Research up to date clearly indicates a role for the mu-opioid system in a range of social behaviors. At the same time, looking at the reviewed evidence human research is only at its beginning. Models of social behavior in opioid research are largely based on animal work (Berridge and Kringelbach, 2015; McNally, 2009) which outlines the importance of translational research and designs to build strong, more causally conclusive evidence. In addition to what has been done so far, the use of sensitive measures (e.g. facial electromyography or eye-tracking) that test for subtle changes in behavior conserved in human and non-human animals such as the eye-blink startle-reflex (Haaker et al., 2019) could contribute valuable implicit behavioral data and provide a more in-depth perspective of the role of the MOR system in social behaviors. A continued issue is the non-standardized use of drug dosage in administration studies, as well as the fact that some of the agonists and especially all of the antagonists used do not have exclusive affinity to mu-opioid receptors. In future research, more well-powered studies including both, agonist and antagonist manipulation, are necessary to make conclusions on a bidirectional level. Further, research suggests modulation of behavior and physiological responses in humans and non-human primates through functional polymorphisms of the OPRM1 receptor gene, including attachment (Barr et al., 2008), cortisol stress reactivity (Lovallo et al., 2015; Schwandt et al., 2011), sensitivity to social rejection (Way et al., 2009; however see Persson et al., 2019) or hedonic capacity (Troisi et al., 2011). It should be noted though that effects tend to be small and have been criticized to not always hold in well powered replication studies (c.f. Jern et al., 2017; Persson et al., 2019). Therefore, (replication) studies with large enough sample sizes are necessary to further disentangle the role of functional OPRM1 receptor gene variations.

Next, based on the proposed mu-opioid feedback model of social interaction we will suggest research questions from two different angles to be investigated in the future, starting with a fundamental research perspective, followed by a consideration of the effects of trauma and chronic stress. Our model proposes, on the basis of existing experimental research, that the MOR system modulates the sensitivity to social threat and reward, and crucially also learning processes related to threat and reward cues that drive more complex social behavior.

To begin with, several fundamental research questions remain unanswered. Human studies demonstrated an inhibitory role for the MOR system in the acquisition of threat related associations (Eippert et al., 2008; Haaker et al., 2017). With regard to threat related mechanisms, generalization of fear to cues to neutral or safe stimuli is a common phenomenon in anxiety and PTSD (Lissek et al., 2008) and considering the MOR system's role in fear conditioning it is likely that opioids contribute to threat memory formation. As a first suggestion, we

hypothesize that the MOR system inhibits generalization of fear cues to other modalities. At the same time rodent research suggests a facilitatory role of mu-opioid modulation in threat extinction learning (McNally, 2009; McNally and Westbrook, 2003). Threat extinction is a crucial emotion regulation strategy which is often impaired in mood disorders such as anxiety or PTSD. We therefore suggest that it is timely to test whether the MOR system also facilitates threat extinction in humans.

Next, in the context of social reward, animal and human research indicate that the MOR system is important for both the hedonic value and the motivational aspect of reward (Chelnokova et al., 2014; Eikemo et al., 2017; Peciña, 2008). At the same time, Buchel et al. (2018) found that the hedonic component is opioid dependent, whereas reward anticipation is not. In our model we suggest that by modulation of reward (and threat) sensitivity a bias toward new social cues is created, influencing both anticipation and the motivational aspect to engage with these. To disentangle further, to what extent endogenous opioids contribute to 'wanting' of reward and whether these mechanisms are dopamine dependent, it would be valuable to study the interaction of dopamine and endogenous opioids in reward processing and motivation using joint administration of a MOR agonist with a dopamine antagonist. First human evidence from a recent study using dopamine and opioid antagonists in two separate samples suggests that both the opioid and dopamine system are relevant in the reward anticipation phase, whereas during the reward experience only the opioid system significantly modulated behavioral outcomes (Korb et al., 2020).

Moreover, considering the crucial role of the MOR system in pain – reward processing and the regulation of both, looking at opioid modulation approach – avoidance mechanisms could contribute interesting data in disentangling the mu-opioid system's role in social-emotional functioning. Unpublished, preliminary work of our own suggests that blocking the MOR system resulted in heightened threat reactivity in a context that allowed for threat avoidance. With approach-avoidance characterizing both appetitive motivation as well as fear of punishment, previous research (Terburg et al., 2012, 2011; Terburg and van Honk, 2013) has made the link to social dominance which is related to high reward drive and reduced anxiety related behaviors. With the mu-opioid release being involved in the increase of specifically high reward liking and evidence showing MOR agonist administration results in a decrease of perceived anger (Løseth et al., 2018) and other threat cues (Bershad et al., 2015; Ipser et al., 2013), future research should investigate whether the MOR system facilitates dominant behavior in social contexts.

Finally, within the framework of the proposed mu-opioid feedback model of social interaction and the reviewed evidence from rodent and human literature, investigating the mu-opioid modulation of acute and chronic stress seems promising. From a fundamental perspective it would be interesting to start with testing in humans whether stress-induced analgesia is opioid dependent. Next, considering the proposed mu-opioid feedback model of social interaction, it would be timely to investigate whether differences in threat and reward processing in individuals who have experienced early trauma or chronic stress are opioid mediated. Evidence from such research would not only be informative regarding the efficacy of opioid mediated pain regulation in different populations, but could contribute knowledge about a biological mechanism underlying the psychological processing of traumatic events and the persistence of automatic behavioral tendencies that contribute to symptomatic of affective disorders (e.g. PTSD, social anxiety).

6. Conclusion

With the MOR system being an underlying factor of the continuous, competitive regulation of pleasure and pain, it is crucial to investigate its role in social-emotional behaviors as it contributes to our ability to respond in an adaptive manner to social experiences. Based on existing evidence we propose a mu-opioid feedback model of social interaction which suggests a distinct role of the MOR system for regulating affect and behavior in social interactions and takes into account long-term consequences for social behavior and health. In an acute social interaction, the MOR system creates a hedonic interpretation of the experience which triggers a neurobiological and behavioral response that either serves affiliative purposes or helps to protect from negative experiences. In the short term the protective response to negative experiences is highly adaptive. With chronic exposure to stress though, long-term changes in the MOR neuro-chemical set-up can create a shift in behavioral patterns with implications for social anxiety and depression. Our proposed model is an attempt to provide a theoretical framework of opioid modulation of social-emotional behavior, based on which new hypotheses can be formed and tested.

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