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The multiple facets of opioid receptor function: implications for addiction

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Abstract

Addiction is characterized by altered reward processing, disrupted emotional responses and poor decision-making. Beyond a central role in drug reward, increasing evidence indicate that opioid receptors are more generally involved in all these processes. Recent studies establish the mu opioid receptor as a main player in social reward, which attracts increasing attention in psychiatric research. There is growing interest in blocking the kappa opioid receptor to prevent relapse, and alleviate the negative affect of withdrawal. The delta opioid receptor emerges as a potent mood enhancer, whose involvement in addiction is less clear. All three opioid receptors are likely implicated in addiction-depression comorbidity, and understanding of their roles in cognitive deficits associated to drug abuse is only beginning.

Introduction

Addiction stems from the progressive adaptation of the brain to repeated exposure to drugs of abuse. This complex brain disorder typically develops from an initiation phase, when the drug produces pleasurable, rewarding effects and is consumed recreationally. As the drug is used repeatedly, control of drug intake may be lost, leading to compulsive drug seeking and consumption. The addicted individual has entered a three-stage cycle, which involves binge/intoxication episodes followed by withdrawal and a negative emotional state that in turn leads to a craving/preoccupation step to seek the drug, back to the intoxication step (Figure 1). Neural circuits contributing to this vicious cycle have been extensively studied, and reviewed recently [1]. Less studied is the neurobiology of protracted abstinence, which involves the development of a negative mood that strongly limits full recovery from a history of drug abuse.

The opioid system, including the mu (MOR), delta (DOR) and kappa (KOR) opioid receptors interacting with a large family of endogenous opioid peptides, is broadly distributed along the neurocircuitry of addiction. In this review we will focus on a selection of recently studied opioid receptor roles in addiction, and more generally psychiatric

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research. A picture emerges where opioid receptors not only regulate drug reward, but also broadly contribute to emotional and cognitive processes whose dysfunction favors the development of addictive behaviors.

1. Mu opioid receptor and reward: the social dimension

The MOR is essential to mediate rewarding properties of opiates (morphine, heroin), as well as non-opioid drugs of abuse and natural stimuli [2, 3] (Figure 1). Among these, social behaviors, which are recognized as intrinsically rewarding [4] and represent a major determinant of emotional well-being in humans [5], involve this receptor. In humans, neural sensitivity to social rejection [6] and social hedonic capacity [7] show significant association with a common variant of the MOR gene (A118G), although the functional significance of this polymorphism remains debated [8] and may implicate genetic-epigenetic interactions [9]. Recent animal research supports a key role for MOR in social attachment and anhedonia in mice [10], as well as affiliative behaviors in prairie voles [11].

Social anhedonia is raising increasing interest in drug abuse research [12]. As addiction develops, hedonic homeostasis is compromised and reward processes gradually shift, leading to increased motivation for drugs of abuse at the expense of naturally rewarding stimuli [13]. Social dysfunction and isolation are frequently encountered in addicted individuals and used as diagnostic criteria. A growing body of evidence suggest a possible overlap in the neural circuitry underlying “social pain” and physical pain, which are both modulated by opiates, and MOR activity may well be at the center of the intriguing relationship between these two unpleasant experiences [14]. Future experiments will likely substantiate this hypothesis.

2. Mu opioid receptor and social reward along life: implications for addiction?

Evidence is accumulating that reward processes are highly dynamic during ontogeny, particularly in the area of social behaviors, and MOR likely contributes to these processes all along life. Maternal attachment was reduced in MOR gene knockout (KO) pups [15], stressing a very early role of MOR in parent-infant affiliative behavior. Consistently, MOR gene variants correlated with the quality of parental attachment in infant primates (C77G, [16]) and humans (A118G, [17]). Recent studies also suggest that MOR-mediated responses vary with age, particularly during adolescence as social behaviors become particularly important [18]. Social play, acting as a natural reinforcer in adolescent rats and mice, induced a conditioned place preference (CPP) and was potentiated by activation of MORs in the nucleus accumbens (NAc) [19] (Figure 2). Further, MOR stimulation by morphine substituted for social peer exploration (with different sensitivity across inbred strains) in adolescent but not adult mice [20]. Also, heroin self-administration and seeking [21], as well as emotional responses to opioid withdrawal [22, 23] differed between adolescent and adult rodents. Together, the latter studies show increased reinforcing effects of mu opiates and decreased aversive effects of opioid withdrawal in adolescent animals, which is consistent with the notion that susceptibility to initiate addictive behaviors is higher during this life period [24].

Researchers now face the difficult task of clarifying the molecular basis of dynamic MOR function along development, and the significance of age-dependent MOR-mediated reward in the overall lifetime risk of addiction.

3. Kappa opioid receptor and aversive states: stress and addiction

In addiction research, dynorphin/KOR activity is definitely considered a major anti-reward system, producing dysphoric effects and antagonizing rewarding effects of drugs of abuse and social stimuli [25]. Accordingly, KOR activation in the NAc decreased social play in adolescent rats [19], and mediated selective aggression towards novel conspecifics in prairie voles, thereby supporting pair bond maintenance [26]. In addition, it is well established that social or physical stressors, as well as prolonged exposure to drugs of abuse increase activity of the dynorphin/KOR system, notably through corticotropin-releasing factor (CRF) signaling [27, 28]. Enhanced tonic KOR function, in turn, may represent one mechanism underlying the pro-addictive effect of stress, notably by promoting relapse [27]. More generally, stress-induced KOR activation has strong pro-depressant effects, and KOR blockade is considered a promising strategy to treat depressive disorders [29].

Most recent studies have addressed brain sites and neurotransmitters involved in KOR-mediated aversive states and modulation of drug reward, and there is strong evidence that serotonergic signaling is involved. Local infusion of the KOR antagonist nor-BNI in the dorsal raphe nucleus (DRN) blocked U50,488 CPA, as well as social stress-induced reinstatement of cocaine CPP [30]. Further genetic approaches established a key role for KORs expressed by DRN serotonergic neurons projecting onto the NAc, and showed that this particular KOR population produces aversion and potentiates cocaine reward via p38 α MAP kinase signaling [31, 32]. Beyond cocaine and the DRN, stress-induced activation of KOR in the amygdala potentiated nicotine CPP [33], and future studies will determine whether stress/KOR-mediated effects on drug reward extend to most drugs of abuse.

In conclusion, an endogenous dynorphin/KOR tone emerges under stressors, which typically intensify while addiction develops, contributing to negative emotional states of acute withdrawal and protracted abstinence (see Figure 1 and section 5 below). A recent observation supporting this view is that pharmacological KOR blockade had no effect on alcohol self-administration in naive rats, but reduced this behavior in rats previously made dependent on alcohol [34].

4. Delta opioid receptor and emotions: potential impact on addiction

The exact role of DOR in brain function has emerged only recently, with the availability of genetic tools and highly selective drugs [35]. The importance of DOR activity to reduce levels of anxiety and attenuate depressive-like states is now well established [35] (Figure 1).

However, DOR implication in drug reward and addictive behaviors is the subject of debate [36]. KO mice studies indicate that DOR contributes to nicotine, but not morphine, D9 tetrahydrocannabinol (THC) or 3,4-methylenedioxy-N-methylamphetamine (MDMA) CPP. Further morphine self-administration was maintained in DOR mutant mice, suggesting altogether that reward processes are not, or only weakly regulated by DOR (reviewed in [35]). Importantly, DOR KO mice drank more alcohol while reducing their innate anxiety levels [37]; activation of DORs in the ventral tegmental area diminished alcohol consumption [38], and the delta agonist TAN-67 reduced levels of anxiety and depressive-like behaviors in alcohol- and cocaine-withdrawn mice (see [35]). These data together point at a role for DOR in emotional comorbidity associated with addiction (see section 5 below). Future investigations will determine whether this observation generalizes to other drugs of abuse.

Finally, a recent analysis of DOR KO mice suggests that DOR activity facilitates association of morphine effects with the context, but not other cues [39, 40]. In hippocampal interneurons, the drug-context association engages opioid peptide-mediated activation of the

DOR [41], whose implication in context-dependent memory processes, and potentially context-induced relapse, requires further investigations.

5. The opioid system in emotional comorbidities of addiction

Addiction-depression comorbidity is highly prevalent in humans [42]. Animal research indicates that antidepressant medication reverses anhedonia in rats undergoing spontaneous nicotine or amphetamine withdrawal, suggesting shared biology between depression and depressive symptoms of acute drug withdrawal (see [43]). Recently, a mouse study reported the development of emotional deficits during protracted abstinence to morphine. Social withdrawal and despair-like behavior increased along a 4-week abstinence period [44]. Morphine-abstinent mice showed durable modifications of the serotonergic system, and treatment with fluoxetine (a specific serotonin reuptake inhibitor) during abstinence prevented the development of emotional dysfunction [44, 45].

Protracted abstinence has been little investigated in animal research, and further studies will be important to investigate the dynamics of molecular and circuit adaptations involved in this key aspect of addiction (Figure 1). MOR, DOR and KOR are distinct, yet central players for both reward processing and emotional control, and likely contribute to the negative emotional states of protracted abstinence (Figure 1) [42, 46]. The analysis of how and where opioid receptors modulate monoaminergic transmission along a history of drug abuse, for example, is only beginning (serotonin and KOR, see section 3).

6. The opioid system, decision-making and addiction

Increasing evidence shows neurocognitive deficits in the development of addictive behavior. Recreational drug use initially engages both goal-directed and impulsive actions [47], and these gradually evolve while addiction develops. Executive controls decline so that behaviors shift from goal-directed to habitual behaviors and drug consumption becomes compulsive. The implication of opioid receptors in poor decision-making of addicted individuals has been substantiated recently.

Goal-directed behavior is controlled by hedonic and incentive properties of rewarding stimuli. Naloxone blockade experiments showed that endogenous opioids are required for the processing of both properties of natural rewards, and that these controls occur in distinct brain regions (ventral pallidum or the shell of the NAc for the former, baso-lateral amygdala, BLA, for the latter) [48]. Further, receptor blockage using specific antagonists indicated that MOR, but not DOR or KOR, controls incentive learning in the BLA [49] (Figure 2).

Decision-making, i.e. choosing between several goal-directed behaviors, involves comparing both (i) reward value of actions goals and (ii) likelihood of reward when performing these actions. A recent study in the mouse showed that MOR in the NAc core is essential for the first aspect, while DOR in the NAc shell is necessary to encode the second [50]. In humans, naltrexone impaired decision-making processes, in both alcoholics and healthy controls [51], but the precise opioid receptor mechanism remains to be determined.

Regarding inhibitory controls, a mouse genetic study showed that MOR and DOR oppositely regulate motor impulsivity, and suggested that MOR reduces while DOR increases inhibition [52]. Pharmacological studies in rats also supported a role for MOR in several measures of impulsivity [53] and for DOR in response inhibition [54]. In human, PET imaging revealed that high MOR activity (both basal and stress-induced) correlates with high impulsiveness [55], in accordance with animal data. At present, no study has addressed MOR gene polymorphisms [8] in relation to these behaviors.

Therefore, both MOR and DOR regulate normal goal-directed processes and impulsivity. These activities could contribute to both addiction vulnerability and the development of pathological drug consumption. MOR, but not DOR or KOR, blockade in the NAc shell attenuated deleterious effects of amphetamine on inhibitory controls [56], and repeated MOR activation progressively increased levels of impulsivity during prolonged heroin self-administration [57]. Importantly, a recent study established a causal relationship between MOR function and the emergence of a compulsive-like behavior. In this study wild type mice developed compulsive-like morphine oral self-administration, but this was not observed in knock-in animals expressing a mutant MOR designed to desensitize and internalize in response to morphine [58].

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Highlights

- The mu opioid receptor is a main player in social and developmental rewards
- Blocking the kappa opioid receptor may prevent relapse and social aversion
- The delta opioid receptor is a mood enhancer, with a debated role in addiction
- All three receptors may regulate addiction-related mood and cognitive disorders

Perspectives

Beyond a central role in drug reward, recent evidence now indicates that opioid receptors play key roles in the many facets of substance use (Figure 2). MOR is a main actor in brain processing of rewarding properties of social stimuli, an area of investigation attracting increasing attention in psychiatric research. Dissecting specific underlying neuronal circuits will be necessary to achieve an integrated view of brain mechanisms encoding the multiple forms of reward, and their adaptations during the course of addiction. KOR is now recognized as a key player in stress-induced addictive-like behaviors, and blocking KOR is a promising strategy to prevent relapse and alleviate negative affect in addiction. Also, all three opioid receptors appear as distinct, key players in emotional comorbidities of addiction. Finally, MOR and DOR are implicated in goal-directed actions and inhibitory controls. Improving our understanding of specific MOR, DOR and potentially KOR functions in compulsive behaviors associated with addiction will require the use of sophisticated recent animal models [59]. More generally, the development of translational studies is strongly needed to understand the specific function of each receptor, particularly DOR and KOR, in addicted patients.

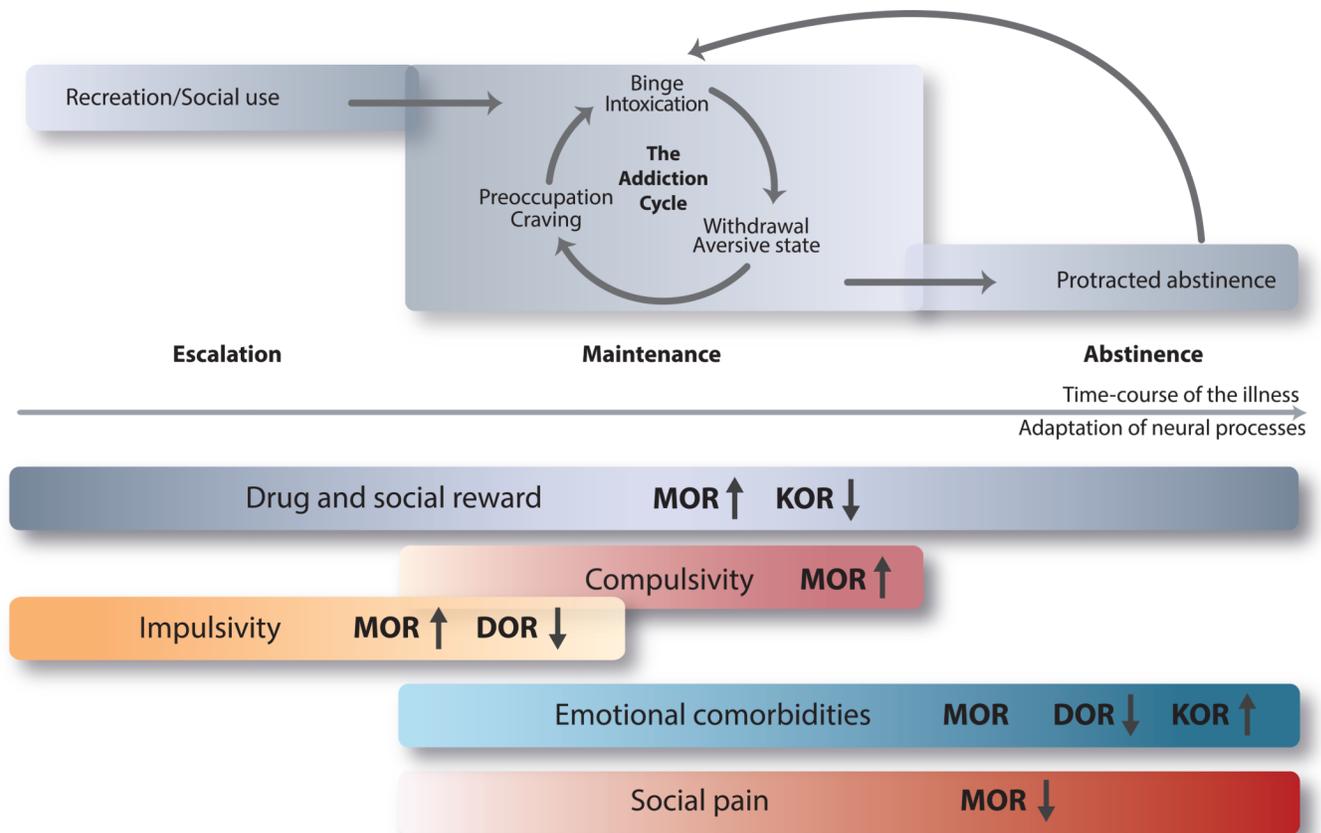


Figure 1. Opioid receptors are key players in most brain processes underlying addiction
Top. In addicted individuals, recreational drug use switches to compulsive drug intake. The addiction cycle typically includes intoxication/withdrawal/craving episodes [1]. Exiting the vicious cycle requires strict maintenance of abstinence. Drug abstinence in former addicts is characterized by a negative affect, which strongly contributes to relapse [44]. **Bottom.** The mu and kappa opioid receptors (MOR and KOR) exert opposing control over drug and social reward, with MOR enhancing and KOR reducing reward processing. MOR and delta (DOR) opioid receptors oppositely regulate inhibitory controls, with MOR and DOR activities increasing and decreasing motor impulsivity, respectively. MOR-mediated reward and impulsivity likely contribute to initiate drug use. The three opioid receptors fulfill distinct roles in addiction-related emotional disorders, with pro- and antidepressant-like activity for KOR and DOR, respectively, and a complex role for MOR [42]. The MOR may also be a key player in brain pathways encoding social pain. Arrows indicate the effects of opioid receptors activities.

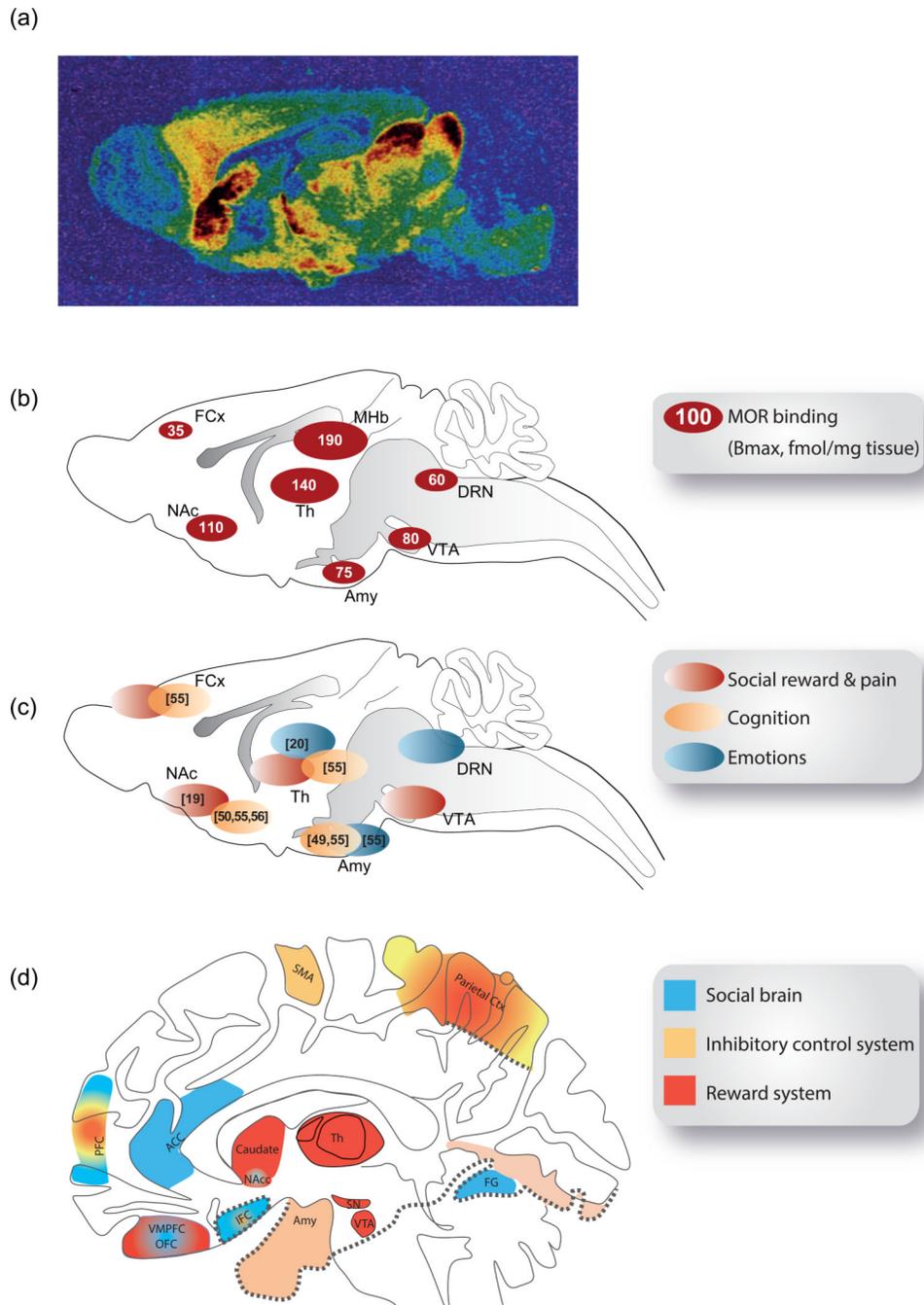


Figure 2. The mu opioid receptor (MOR) controls a number of addiction-related neuronal processes throughout the brain

In rodents, the MOR is enriched in brain regions mediating: social reward and pain, cognition (impulsive behaviors and decision-making) and emotional responses. (a) Autoradiogram of a sagittal mouse brain section showing [^3H]-DAMGO MOR binding (Courtesy of Pr Ian Kitchen [60–62]), where highest densities are represented in dark red. (b) Corresponding absolute values of [^3H]-DAMGO MOR binding in selected brain regions. (c) Addiction-related brain structures and neuronal functions for which a role of MOR is demonstrated (references between brackets, see also the main text) or suggested. MOR pools in the ventral tegmental area (VTA) and the frontal cortex (FCx) tightly control drug reward,

and likely also regulate social reward. MORs in the dorsal raphe nucleus (DRN) and thalamus (Th) may modulate emotions and the affective dimension of social painful experiences, respectively. The potential relevance for addiction of MOR located in the medial habenula (MHb) – the highest MOR expression site in the brain – remains currently unknown. **(d)** Although rodent and human brain functions cannot be matched exactly, studies of human addiction similarly focus on social reward and dysfunction, the disruption of executive functions and the development of emotional comorbidities (courtesy of Pr Gunter Schuman [63]). Abbreviations: ACC, anterior cingulate cortex; Amy, amygdala; BLA, basolateral amygdala; IFC, infralimbic cortex; NAc, nucleus accumbens; OFC, orbitofrontal cortex; PFC, prefrontal cortex; SN, substantia nigra; VMPFC, ventromedial prefrontal cortex.