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Review

The Role of Dynorphin and the Kappa Opioid Receptor in the Symptomatology of Schizophrenia: A Review of the Evidence

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ABSTRACT

Schizophrenia is a debilitating mental illness that affects approximately 1% of the world's population. Despite much research in its neurobiology to aid in developing new treatments, little progress has been made. One system that has not received adequate attention is the kappa opioid system and its potential role in the emergence of symptoms, as well as its therapeutic potential. Here we present an overview of the kappa system and review various lines of evidence derived from clinical studies for dynorphin and kappa opioid receptor involvement in the pathology of both the positive and negative symptoms of schizophrenia. This overview includes evidence for the psychotomimetic effects of kappa opioid receptor agonists in healthy volunteers and their reversal by the pan–opioid antagonists naloxone and naltrexone and evidence for a therapeutic benefit in schizophrenia for 4 pan–opioid antagonists. We describe the interactions between kappa opioid receptors and the dopaminergic pathways that are disrupted in schizophrenia and the histologic evidence suggesting abnormal kappa opioid receptor signaling in schizophrenia. We conclude by discussing future directions.

Keywords: Dynorphin, Kappa opioid, Naloxone, Naltrexone, Opioid antagonist, Schizophrenia

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Schizophrenia is a debilitating mental illness that affects approximately 1% of the world's population (1). It is characterized by a combination of positive symptoms (hallucinations, delusions, and disorganization), negative symptoms (flattened affect and social withdrawal), and cognitive symptoms (deficits in working memory, attention, and executive function) (2–4).

Kappa opioid receptors (KORs) play a critical role in modulating dopamine, serotonin, and glutamate release in the central nervous system. Dynorphin is a peptide neurotransmitter processed from its precursor prodynorphin and is the endogenous ligand of the KOR (5). Dysregulation of the dynorphin/KOR system has been implicated in several psychiatric diseases, including schizophrenia, depression, bipolar disorder, and drug addiction (1,6,7). At least 2 compounds that function as KOR antagonists have entered clinical trials for mood disorders and cocaine addiction (8–11). Presented here is a review of the evidence for possible dynorphin and/or KOR involvement in both the positive and the negative symptoms of schizophrenia.

KOR AGONISTS ARE PSYCHOTOMIMETICS, AND THEIR PSYCHOTOMIMETIC EFFECTS CAN BE BLOCKED WITH OPIOID RECEPTOR ANTAGONISTS NALOXONE AND NALTREXONE

In contrast to mu opioid receptor and delta opioid receptor agonists, KOR agonists are potent psychotomimetics in healthy people (Table 1). In the 1970s, as the need for analgesics with low potential for abuse grew, drug development focused on compounds that were selective agonists for the KOR rather than the mu opioid receptor. Rodent models showed that KOR agonists could produce strong analgesic effects without the potential for addiction. However, the use of the KOR agonist cyclazocine to treat opioid dependence resulted in psychotomimetic side effects (12,13). It was shown that cyclazocine and ketocyclazocine could induce paranoid delusions and hallucinations of monsters (14). Interestingly, cyclazocine is also a mu opioid receptor antagonist, and its psychotomimetic side effects were rapidly reversed by administration of the kappa, mu, and delta opioid receptor antagonist naloxone, indicating that although delta opioid receptors could not be fully excluded, these psychotomimetic side effects most likely occurred through the kappa, rather than the mu or delta, opioid receptor (15,16) (Table 2). Initial studies in the development of synthetic benzomorphan KOR agonist MR 2033/2034 as an analgesic resulted in the subjects experiencing psychotomimetic symptoms, including disturbances in the perception of space and time, visual hallucinations, racing thoughts, feelings of body distortion, and discomfort (17). Similar to the effects of cyclazocine, these effects could also be blocked with naloxone (Table 2). Later trials with the selective KOR agonists enadoline, niravoline, and bremazocine as analgesics, and spiradoline in Parkinson's disease, were discontinued when it was found that they caused psychotomimesis in healthy volunteers (18–23).

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Table 1. Kappa Opioid Receptor (KOR) Agonists Cause Psychotomimesis in Healthy Volunteers

Study	Drug	Mechanism	Effect in Healthy Volunteers
Resnick *et al.*, 1971 (12), Hanlon *et al.*, 1975 (13), Kumor *et al.*, 1986 (14)	Cyclazocine, ketocyclazocine	KOR agonist and mu receptor antagonist	Psychotomimesis
Pfeiffer *et al.*, 1986 (17)	MR 2033/2034	KOR agonist	Psychotomimesis
Giuffra *et al.*, 1993 (19)	Spiradoline	KOR agonist	Psychotomimesis
Reece *et al.*, 1994 (18)	Enadoline	KOR agonist	Psychotomimesis
Gadano *et al.*, 2000 (20)	Niravoline	KOR agonist	Psychotomimesis
Dortch-Carnes and Potter 2005 (23)	Bremazocine	KOR agonist	Psychotomimesis
MacLean *et al.*, 2013 (26), Maqueda *et al.*, 2016 (27)	Salvinorin A	KOR agonist	Psychotomimesis

More recently, salvinorin A, the active compound in the world's most potent hallucinogenic plant *Salvia divinorum*, was found to be a selective KOR agonist with greater than 5000 times selectivity for kappa over mu and delta receptors (24). Numerous studies of salvinorin A in healthy volunteers have documented its psychotomimetic effects (25–27). MacLean *et al.* (26) performed a double-blind placebo-controlled study examining dose-dependent responses of salvinorin A in 8 healthy adult volunteers. They found that all of the volunteers reported interacting and communicating with "entities or beings" and 5 volunteers experienced visual and auditory hallucinations (26). Finally, in a double-blind study of 24 healthy volunteers, Maqueda *et al.* (27) found that salvinorin A produced both visual and auditory changes that could be blocked by the kappa, mu, and delta receptor antagonist naltrexone (Table 2).

KOR ANTAGONISTS HAVE IMMEDIATE ANTIPSYCHOTIC EFFECTS IN PATIENTS WITH SCHIZOPHRENIA

There have been at least 32 trials investigating the therapeutic potential of 4 different pan–opioid receptor antagonists in patients with schizophrenia. We present a narrative review of 21 trials of naloxone, 8 trials of naltrexone, 1 trial of nalmefene, and 2 trials of buprenorphine. Naloxone, naltrexone, and nalmefene are all antagonists at the kappa, mu, and delta receptors, and buprenorphine is a dual KOR antagonist and mu receptor partial agonist (Table 3). While many of these studies have shown impressive and rapid efficacy in the treatment of both positive and negative symptoms, some of these studies have shown mixed results ranging from nonsignificant trends toward improvement to complete lack of efficacy. Here we postulate that the mixed results may have been due to differences in trial design, including the dose and method of administration of the antagonist and time point at which the patient was assessed for effects of the drug. We propose that the success of these trials depended on that ability of each of these drugs to antagonize the KOR at physiologically relevant concentrations. Additionally, inclusion of patients with different core symptoms may introduce more heterogeneity. As schizophrenia is a heterogeneous disorder, it is possible that dynorphin and KOR dysregulation might represent a subset of patients with schizophrenia and that KOR antagonists may be less effective in patients without KOR dysregulation.

Naloxone Trials

Naloxone is an extremely short-acting pan–opioid antagonist with a half-life of only 1 hour. In total, nearly all of these studies were designed to test for immediate effects on the positive symptoms of schizophrenia. Here we group them into 3 categories by dose: 1) 0.4 to 1.6 mg, 2) 4 to 10 mg, and 3) 20 mg to 2 mg/kg. Some of these categories can be further subdivided by method of administration. While some patients responded to the low dose range of 0.4 to 1.6 mg naloxone, most successful naloxone studies used at least 4 mg of naloxone delivered intravenously.

In the first group of very-low-dose naloxone, there were 7 trials and 2 case reports (28,29) in patients with schizophrenia without catatonia who were administered a dose of 0.4 to 1.6 mg of intravenous (IV) naloxone with improvement on the Brief Psychiatric Rating Scale (BPRS) as an end point. Two trials found significant improvement (30,31), while the others reported mixed results (32–36).

Successful follow-up studies of naloxone in patients with schizophrenia later recognized that a dose of 0.4 to 1.6 mg is too low to occupy the majority of opioid receptors in the brain or to produce an observable effect in most patients with schizophrenia (37). For reference, positron emission tomography imaging has recently shown that a 1-mg bolus of IV naloxone in an 80-kg person leads to a maximum of 50% opioid receptor occupancy (Table 4) (38). Each of the negative studies also had very small sample sizes ranging from 6 to 12 patients, and with the exception of the work of

Table 2. The Psychotomimetic Effects of Selective Kappa Opioid Receptor (KOR) Agonists Can Be Blocked by Pretreatment With Opioid Antagonists

Study	KOR Agonist	Antagonist	Effect in Healthy Volunteers
Pfeiffer *et al.*, 1986 (17)	MR 2033/2034	Naloxone	Reversal of kappa-induced psychotomimetic effects
Kumor *et al.*, 1986 (14)	Cyclazocine, ketocyclazocine	Naloxone	Reversal of kappa-induced psychotomimetic effects
Maqueda *et al.*, 2016 (27)	Salvinorin A	Naltrexone	Reversal of kappa-induced psychotomimetic effects

Table 3. Receptor Binding Affinity of Naloxone, Naltrexone, Buprenorphine, and Nalmefene at Cloned Human Receptors[a]

Drug	Kappa, nmol/L	Mu, nmol/L	Delta, nmol/L
Naloxone	2.5	1.4	67.5
Naltrexone	0.4	0.2	10.8
Buprenorphine	0.8	1.5 (partial agonist)	4.5
Nalmefene	0.3	0.3	7.3

[a]Data from Toll *et al*. (143).

Volavka *et al.* (32) evaluated the patients only 1 hour post injection, a time frame that was later recognized as generally too short to produce an observable effect in most patients with schizophrenia (39).

The second group of naloxone studies administered doses of 4 to 10 mg and also used BPRS as the end point. In this group, there are 5 studies that, in contrast to those that used lower doses, were generally much more rigorously designed, as reflected by longer duration and larger sample sizes. Of the 5 studies, 4 (15,37,40,41) found statistically significant improvement from IV administration of naloxone. The 1 study that did not find improvement used subcutaneous rather than IV injection for most of the doses (42). Subcutaneous and intramuscular administration of naloxone are considered to have similar pharmacokinetics, with only 36% bioavailability compared with that of IV administration (Table 4) (43).

The third group of naloxone studies consists of 7 studies that used doses above 10 mg, ranging from 20 mg to 2 mg/kg. Similar to results of studies in the second group, results of these studies showed that persons who received IV administration of naloxone tended to demonstrate significant improvement on BPRS (44–46), while those who received subcutaneous or intramuscular administration showed mixed results (47–50).

In one of the largest double-blind placebo-controlled crossover studies of naloxone in schizophrenia, Pickar *et al.* (51) recruited 32 patients with schizophrenia (19 medicated and 13 unmedicated) and 26 patients with mania from 6 international trial sites. Each patient received a single subcutaneous 0.3-mg/kg dose of either naloxone or saline followed by a washout. When combining both the medicated and unmedicated groups with schizophrenia, they found a significant improvement in only the BPRS Hallucinatory Behavior subscale. In the medication-treated patients, they also found a significant improvement in total BPRS as well as in the Paranoid-Suspicion and Anxiety-Depression subscales. The medicated group also showed a significant improvement in the self-rated Auditory Hallucination subscale. In contrast to the patients with schizophrenia, the patients with mania did not show any improvement in symptoms, leading the authors to conclude that while naloxone had efficacy in schizophrenia, it was without efficacy in mania.

In the final study of naloxone in patients with schizophrenia, Pickar *et al.* (52) conducted a World Health Organization phase 2 double-blind placebo-controlled crossover study in 43 patients with schizophrenia. They did not replicate their previous results because of a large placebo response.

Naltrexone Trials

In contrast to the naloxone trials, where patients were usually evaluated within hours after a single dose, the naltrexone trials administered daily dosages for weeks to months and could test efficacy on the negative symptoms. In addition, there were a number of trials testing the ability of naltrexone to help sustain abstinence in dual-diagnosed patients with schizophrenia and co-occurring alcohol abuse disorder, which we will not consider here. We will consider the naltrexone trials grouped into 2 daily dosage ranges: 1) 100 mg/day and 2) >100 mg/day. The results of these studies show that 100 mg of naltrexone was a generally successful oral dose for treating the positive and negative symptoms of schizophrenia. Positron emission tomography imaging has shown that this dosage produces an average of 87% KOR occupancy (Table 4) (53).

There were 3 studies with 100 mg/day naltrexone as the dosage. Of these, 2 were conducted by Marchesi *et al.* (54,55), and 100 mg/day naltrexone was administered for 2 weeks, with improvement in the Clinical Global Impression scale and BPRS over placebo as the end points. In the first study, in 12 patients, the drug group showed a statistically significant improvement in total BPRS and negative schizophrenia symptoms versus those at baseline, while the placebo group did not show a statistical improvement (54). In the second study, in 1995, Marchesi *et al.* found a statistically significant improvement in negative symptoms compared to those at baseline in 18 patients (55).

Finally, in the largest and most rigorous study of opioid receptor antagonists in patients with schizophrenia to date, Tatari *et al.* (56) randomized 60 patients who were all stabilized on risperidone to 100 mg/day naltrexone or placebo for 12 weeks. They found significant improvement of both positive and negative symptoms in the drug group versus that of the placebo group, as assessed by the Scale for the Assessment of Positive Symptoms and the Scale for the Assessment of Negative Symptoms.

Table 4. Bioavailability and PET–Measured and Estimated Receptor Occupancy of Different Doses of Naloxone, Naltrexone, Buprenorphine, and Nalmefene

Drug	Dose, mg	Route	Bioavailability, %	Opioid Receptor Occupancy via PET, %
Naloxone	1	IV	100	~50[a]
Naloxone	0.8	SC/IM	36[b]	Not reported
Naltrexone	100	Oral	5–60[c]	~87[d]
Buprenorphine	0.2	SL	49–63[e]	Not reported
Nalmefene	20	Oral	41[f]	87–100[g]

Data from [a]Melichar *et al*. (38), [b]Dowling *et al*. (43), [c]Gonzalez *et al*. (144), [d]Vijay *et al*. (53), [e]Elkader *et al*. (145), [f]Kyhl *et al*. (146), and [g]Ingman *et al*. (147).
IM, intramuscular; IV, intravenous; PET, positron emission tomography; SC, subcutaneous; SL, sublingual.

There were 5 studies of naltrexone with dosages greater than 100 mg/day with BPRS as the end point. These studies suffered from either very small sample sizes or very short durations, and most were without either placebo control or blinding, or both (57–60). Sernyak *et al.* (61) planned to test 200 mg/day naltrexone in 21 patients with schizophrenia stabilized on typical antipsychotics. This was initially designed as a double-blind placebo-controlled crossover trial, but halfway into the trial, the blind was broken and many of the patients were not crossed over to the comparator arm.

Trials With Other Opioid Antagonists

In addition to the previously discussed naloxone and naltrexone trials, there was one successful trial with nalmefene and two with buprenorphine.

In a double-blind placebo-controlled trial, Schmauss *et al.* (62) administered 0.2 mg of sublingual buprenorphine, a mu opioid receptor partial agonist and KOR antagonist, to 10 medication-free patients with schizophrenia with active positive symptoms. Buprenorphine exhibited an immediate antipsychotic effect on the Inpatient Multidimensional Psychiatric Scale in 7 of the patients but was ineffective in 3 patients previously diagnosed with residual schizophrenia. In an open study, Groves and Nutt (63) administered a single dose of 0.2 mg of sublingual buprenorphine to 7 patients with schizophrenia who were on antipsychotic medications. They found an immediate reduction in BPRS scores, particularly in the auditory hallucinations and mood scales.

In 1993, Rapaport *et al.* (64) tested nalmefene in a double-blind placebo-controlled crossover trial in 10 patients with schizophrenia who were on antipsychotics for an average of 36.7 days. They found a significant improvement over baseline in the BPRS thinking disturbance subscale and nurse-rated Bunney-Hamburg psychosis scale, and a trend toward significance in the physician-rated Bunney-Hamburg psychosis scale.

Conclusions

In summary, pan–opioid antagonists may have a therapeutic effect on both the positive and negative symptoms of schizophrenia. When viewed in light of the psychotomimetic effects of selective KOR agonists, these trials support the hypothesis that the therapeutic effect of pan–opioid antagonists may be mediated through the KOR.

KORs MODULATE THE DOPAMINE PATHWAYS DISRUPTED IN SCHIZOPHRENIA

While the role of dopamine in schizophrenia was first hypothesized in the 1960s, the theory that endogenous opioid peptides and their receptors may play a role in the symptoms of schizophrenia was developed more than 10 years later, in the 1970s. Upon the realization that the endogenous opioid system plays a major role in dopamine regulation, researchers hypothesized a potential link between the two theories. They postulated that the dopamine imbalance in schizophrenia may be a downstream consequence of a disrupted opioid system (65,66).

Imaging studies in patients with schizophrenia using positron emission tomography and single-photon emission computed tomography have shown an excess of presynaptic striatal dopamine and a deficiency of cortical dopamine (67,68). The cortical dopamine deficiency observed in the mesocortical pathway has been hypothesized to play a role in the negative and cognitive symptoms of schizophrenia (69,70). The increased presynaptic release of dopamine observed in the striatum of patients with schizophrenia has long been thought to play a critical role in the positive symptoms of schizophrenia. While both the ventral and dorsal striatum have shown increased dopamine release, the magnitude of the increase is much greater in the nigrostriatal pathway to the dorsal striatum, and particularly in the rostral caudate (67).

A POSSIBLE ROLE FOR KORs IN THE POSITIVE SYMPTOMS OF SCHIZOPHRENIA

KORs are present on presynaptic axons of the mesolimbic and nigrostriatal dopamine pathways throughout the striatum (6,71–74) (Figure 1A), where they negatively regulate dopamine release (75) and represent an important mechanism for maintaining dopamine homeostasis and synaptic plasticity (76,77). Consistent with this mechanism, rodent studies in vivo have shown that systemic administration of a short-term dose of selective KOR agonists reduces dopamine levels in mesolimbic and nigrostriatal pathways by acting on presynaptic KORs on dopaminergic neurons. This result was shown with the following selective KOR agonists: U50,488 in the ventral striatum (75,78–81) and dorsal striatum (75,78), U69,593 in the ventral striatum (82,83), spiradoline and enadoline in the dorsal striatum (84), and salvinorin A in the ventral striatum (85) and dorsal striatum (86,87) (Figure 1B).

It may seem counterintuitive that increased KOR signaling could play a role in the increased striatal dopamine levels seen in schizophrenia, as the direct mechanism of KORs is to lower striatal dopamine levels. However, long-term KOR stimulation has been shown to play a role in increasing the amount of presynaptic dopamine released in both the mesolimbic and nigrostriatal paths in response to stimulus or systemic administration of dopaminergic drugs. Long-term administration of U69,593 increases stimulus- and drug-evoked dopamine levels in both the mesolimbic (88–91) and nigrostriatal (91) paths (Figure 1C). Similarly, long-term administration of salvinorin A leads to increased drug-evoked dopamine levels in the nigrostriatal pathway (87). Immediately following long-term administration, basal dopamine levels are unaltered and the ability of a single systemic dose of U69,593 to reduce dopamine levels is preserved, indicating that stimulated increases in dopamine may not be due to KOR desensitization (73,88).

In both the dorsal and ventral striatum, KORs form a complex with the dopamine active transporter (92) and with both presynaptic D_2 autoreceptors on dopamine terminals of the nigrostriatal and mesolimbic paths, and postsynaptic D_2 receptors on medium spiny neurons (MSNs) (73). The increase in stimulus- and drug-evoked dopamine release from both the mesolimbic and nigrostriatal paths following long-term exposure to KOR agonists has been attributed to reduced presynaptic D_2 autoreceptor function (88).

Interestingly, KORs have also been shown to interact with postsynaptic D_2 receptors on MSNs in ways that may have relevance for schizophrenia. When rodents are exposed to long-term doses of the D_2/D_3 agonist quinpirole or to drugs that increase dopamine levels, such as amphetamines, they

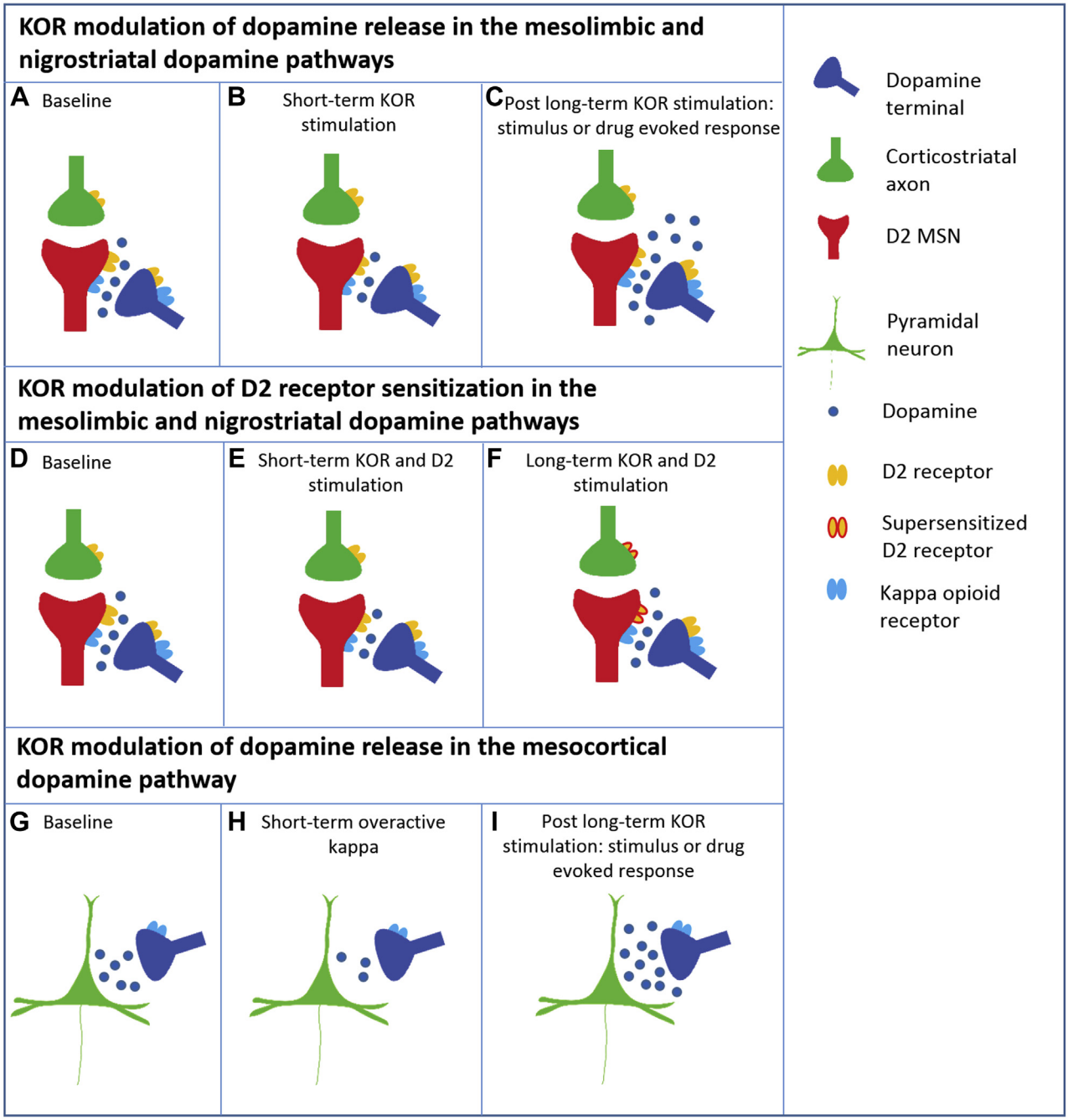

Figure 1. Kappa opioid receptor (KOR) modulation of dopamine in the cortex and striatum. **(A)** Normal levels of dopamine at baseline in the ventral and dorsal striatum. **(B)** Short-term KOR activation lowers dopamine release in the nigrostriatal path. **(C)** Long-term KOR activation results in higher levels of evoked dopamine release in the mesolimbic and nigrostriatal paths. **(D)** Normal levels of D_2 receptors in the ventral and dorsal striatum. **(E)** Short-term KOR activation with a D_2 agonist lowers dopamine release in the mesolimbic and nigrostriatal paths. **(F)** Long-term KOR activation with D_2 agonists results in acceleration of sensitization of postsynaptic D_2 receptors. **(G)** Normal levels of dopamine at baseline in the cortex. **(H)** Short-term KOR activation lowers dopamine release in the mesocortical path. **(I)** Long-term KOR activation results in higher levels of evoked dopamine release in the mesocortical path. MSN, medium spiny neuron.

exhibit locomotor sensitization (93), a phenomenon that involves the sensitization of postsynaptic D_2 receptors on MSNs (73,94,95). Since it was shown that the activity of antipsychotics correlates with their ability to block the D_2 receptor (96,97), increased dopamine signaling through postsynaptic striatal D_2 receptors that have become sensitized has been hypothesized to play a critical role in the positive symptoms of schizophrenia (98–102). Importantly, while endogenous levels

of KOR signaling do not have an effect on locomotor sensitization (73), administration of KOR agonists resulting in supraphysiological levels of KOR signaling during the sensitization period both accelerate and potentiate this process (73,94,95,103,104).

Both the acceleration and potentiation of sensitization are relevant to schizophrenia for two reasons. First, the acceleration of locomotor sensitization has been attributed to the ability of presynaptic KORs to directly increase presynaptic D_2 autoreceptor function on dopaminergic terminals where they colocalize, resulting in faster inhibitory responses in presynaptic D_2 receptors as measured by fast-scan cyclic voltammetry (73). This change reduces phasic dopamine release, resulting in accelerated sensitization of postsynaptic D_2 receptors on MSNs (73) (Figure 1D–F). Second, the potentiation of locomotor sensitization has been attributed to both presynaptic KORs colocalized with D_2 autoreceptors and postsynaptic KORs colocalized with D_2 receptors on MSNs. In both of these locations, it is hypothesized that KORs increase the efficacy of the D_2 receptor signaling (73,94). Escobar *et al.* hypothesized that this increase in efficacy may occur through stabilizing the pre- and postsynaptic D_2 receptor or increasing second messenger coupling (73).

Finally, it has been proposed that the timing of KOR activation and the neural context of elevated dopamine levels play critical roles in the outcome of long-term KOR activation on sensitization (94), as it has been shown that KOR activation has the opposite effect on sensitization if KOR agonists are administered sequentially with dopamine agonists rather than simultaneously (105–108). The importance of neural context is further supported by short-term studies of KOR on dopamine release, showing that the effects of U50,488 and salvinorin A on drug- and stimulus-evoked dopamine response shift from inhibition to potentiation depending on the timing of KOR agonist administration relative to that of stimulus (109,110).

In conclusion, we have shown there are several ways in which KORs may contribute to the positive symptoms of schizophrenia. First, long-term overactivation of KORs in the context of the dysregulated dopamine system in schizophrenia may contribute to the increased presynaptic striatal dopamine release by interacting with presynaptic D_2 autoreceptors to modulate the response of the dopamine system to various stimuli. Second, although KOR activation has not been shown to result in greater total levels of sensitized postsynaptic D_2 receptors (73), the fact that presynaptic KORs accelerate sensitization of postsynaptic D_2 receptors and that postsynaptic KORs increase signaling through sensitized postsynaptic D_2 receptors has potential relevance to the positive symptoms of schizophrenia. While the mechanisms underlying the therapeutic effects of blocking the D_2 receptor and the mechanism of the striatal dopamine excess that are observed in schizophrenia yet unknown, the KOR is uniquely positioned to play a possible role in this pathology.

A POSSIBLE ROLE FOR KORs IN THE NEGATIVE AND COGNITIVE SYMPTOMS OF SCHIZOPHRENIA

Presynaptic activation of KORs on mesocortical projection neurons has been shown to decrease dopamine levels in the medial prefrontal cortex of the rodent, an effect that can be blocked by KOR antagonist nor-binaltorphimine both in vitro (111) and in vivo (112). It has also been shown that KOR activation in the medial prefrontal cortex produces conditioned place aversion (113). Additionally, KOR activation on the soma of mesocortical dopamine projection neurons in in the ventral tegmental area inhibits dopamine release in the medial prefrontal cortex (114). By decreasing mesocortical dopamine release, a hypothetical overactivation of KORs could play a role in the cortical dopamine deficit observed in patients with schizophrenia. However, the relationship is likely more complex, as long-term treatment with U69,593 increases potassium-stimulated dopamine levels (115) (Figure 1F, G).

Excessive KOR activation could also play a possible role in the cognitive symptoms. Behavioral studies in rodents show that KOR agonists can cause cognitive deficits. The selective KOR agonist U-50488H induces a dose-dependent reduction of prepulse inhibition, which can be restored by the KOR antagonist nor-binaltorphimine and atypical antipsychotic clozapine but not by the typical antipsychotic haloperidol (116). In contrast, a study using U50,488, U69,593, and salvinorin A did not find any effect on prepulse inhibition (117). The KOR agonists U689593, U50488, and GR89,696 all produce impairment of attention as measured by the 5-choice serial reaction-time task, and this disruption can be reversed by naltrexone (118). Salvinorin A also causes impairment on the 5-choice serial reaction-time task, an effect that can be blocked by pretreatment with the selective KOR antagonist JDTic (119). Additionally, salvinorin A has been shown to cause cognitive dysfunction and disruption of learning and memory (120). Most recently, it was shown that U-50488H induced cognitive disruption as measured by the differential reinforcement of low response-rate task, and cognitive deficits could be blocked by the selective KOR antagonist nor-binaltorphimine (121). Finally, selective KOR agonist enadoline (CI-977) (122) was shown to induce cognitive impairment in rhesus monkeys on the continuous performance task (123). It is important to note that this result may depend on the state of the system, as both enadoline and U50488 have been shown to have short-term neuroprotective effects in animals if administered immediately prior to the onset of ischemic brain damage (124–128).

Ultimately, the complete mechanism underlying the positive and negative symptoms of schizophrenia may likely involve contributions from other brain regions and neurotransmitter systems. KORs also modulate glutamate neurotransmission in the ventral tegmental area (129) and are present throughout diverse brain regions that have been implicated in the pathology of schizophrenia, including the hippocampus, locus coeruleus, hypothalamus, and amygdala. For a comprehensive review of KORs in other brain regions, see previous reports (130–132).

HISTOLOGICAL STUDIES IN PATIENTS WITH SCHIZOPHRENIA HAVE SHOWN ABNORMALITIES IN THE DYNORPHIN/KOR SYSTEM

The evidence for elevated levels of dynorphin or other endorphins is mixed. Heikkilä *et al.* (133) found that elevated levels of dynorphin in the cerebrospinal fluid of patients with schizophrenia compared with that in healthy controls correlated with worsening BPRS scores. In another, larger study of 120

hospitalized patients with schizophrenia, Lindström *et al.* (134) found that elevated dynorphin levels were predicative of worse disease outcomes. Another study of 35 patients with schizophrenia found lower levels of dynorphin in the cerebrospinal fluid; however, the comparison group was patients with various neurologic diseases, including tumors, rather than healthy control subjects (135). In addition to dynorphin studies, there have been other studies showing increased beta-endorphin levels (136–138). In contrast, another study did not replicate these findings (139).

In a limited postmortem study of 4 patients and 4 controls, Royston *et al.* (140) found that the KOR distribution in the parahippocampal gyrus of patients with schizophrenia was significantly different from that in control participants, although the significance of this finding is unclear. In a postmortem study of both patients with schizophrenia and patients with bipolar disorder, Peckys and Hurd (141) did not find any significant difference in the expression of prodynorphin and KOR messenger RNA in the frontal cortex.

CONCLUSIONS

In conclusion, while there are several generations of antipsychotic drugs that are effective for treating the positive symptoms of schizophrenia, not all patients fully respond to the antipsychotics with safer clinical profiles. Clozapine, the most effective antipsychotic and drug of last resort for many nonresponders, is often not prescribed because of fear of side effects. Additionally, there are currently no effective treatments for the negative or cognitive symptoms (142). There is a need to examine novel targets to find effective treatments for the negative and cognitive symptoms, as well as to find safer and more effective treatments for the positive symptoms for nonresponders. This review shows that the KOR may be a reasonable new therapeutic target to investigate further, and we hope that our review will provide support for additional studies targeting this mechanism for the treatment of positive and negative symptoms in schizophrenia.

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REFERENCES

1. Karam CS, Ballon JS, Bivens NM, Freyberg Z, Girgis RR, Lizardi-Ortiz JE, *et al.* (2010): Signaling pathways in schizophrenia: emerging targets and therapeutic strategies. Trends Pharmacol Sci 31:381–390.
2. Goldman-Rakic PS (1994): Working memory dysfunction in schizophrenia. J Neuropsychiatry Clin Neurosci 6:348–357.
3. Green MF (1996): What are the functional consequences of neurocognitive deficits in schizophrenia? Am J Psychiatry 153:321–330.
4. Keefe RS, Eesley CE, Poe MP (2005): Defining a cognitive function decrement in schizophrenia. Biol Psychiatry 57:688–691.
5. Chavkin C, James IF, Goldstein A (1982): Dynorphin is a specific endogenous ligand of the kappa opioid receptor. Science 215:413–415.
6. Schwarzer C (2009): 30 years of dynorphins—New insights on their functions in neuropsychiatric diseases. Pharmacol Ther 123:353–370.
7. Darcq E, Kieffer BL (2018): Opioid receptors: Drivers to addiction? Nat Rev Neurosci 19:499–514.
8. Ragguett R-M, Rong C, Rosenblat JD, Ho RC, McIntyre RS (2018): Pharmacodynamic and pharmacokinetic evaluation of buprenorphine + samidorphan for the treatment of major depressive disorder. Expert Opin Drug Metab Toxicol 14:475–482.
9. Li W, Sun H, Chen H, Yang X, Xiao L, Liu R, *et al.* (2016): Major depressive disorder and kappa opioid receptor antagonists. Transl Perioper Pain Med 1:4–16.
10. Carlezon WA Jr, Krystal AD (2016): Kappa-opioid antagonists for psychiatric disorders: From bench to clinical trials. Depress Anxiety 33:895–906.
11. Reed B, Butelman ER, Fry RS, Kimani R, Kreek MJ (2018): Repeated administration of opra kappa (LY2456302), a novel, short-acting, selective KOP-r antagonist, in persons with and without cocaine dependence. Neuropsychopharmacology 43:739.
12. Resnick RB, Fink M, Freedman AM (1971): Cyclazocine treatment of opiate dependence: A progress report. Compr Psychiatry 12:491–502.
13. Hanlon TE, McCabe OL, Savage C, Kurland AA (1975): A controlled comparison of cyclazocine and naloxone treatment of the paroled narcotic addict. Int Pharmacopsychiatry 10:240–250.
14. Kumor KM, Haertzen CA, Johnson RE, Kocher T, Jasinski D (1986): Human psychopharmacology of ketocyclazocine as compared with cyclazocine, morphine and placebo. J Pharmacol Exp Ther 238:960–968.
15. Watson SJ, Berger PA, Akil H, Mills MJ, Barchas JD (1978): Effects of naloxone on schizophrenia: Reduction in hallucinations in a subpopulation of subjects. Science 201:73–76.
16. Jasinski DR, Martin WR, Sapira JD (1968): Antagonism of the subjective, behavioral, pupillary, and respiratory depressant effects of cyclazocine by naloxone. Clin Pharmacol Ther 9:215–222.
17. Pfeiffer A, Brantl V, Herz A, Emrich HM (1986): Psychotomimesis mediated by k opiate receptors. Science 233:774–776.
18. Reece PA, Sedman AJ, Rose S, Wright DS, Dawkins R, Rajagopalan R (1994): Diuretic effects, pharmacokinetics, and safety of a new centrally acting kappa-opioid agonist (CI-977) in humans. J Clin Pharmacol 34:1126–1132.
19. Giuffra M, Mouradian M, Davis T, Ownby J, Chase T (1993): Dynorphin agonist therapy of Parkinson's disease. Clin Neuropharmacol 16:444–447.
20. Gadano A, Moreau R, Pessione F, Trombino C, Giuily N, Sinnassamy P, *et al.* (2000): Aquaretic effects of niravoline, a κ-opioid agonist, in patients with cirrhosis. J Hepatol 32:38–42.
21. Walsh SL, Strain EC, Abreu ME, Bigelow GE (2001): Enadoline, a selective kappa opioid agonist: Comparison with butorphanol and hydromorphone in humans. Psychopharmacology (Berl) 157:151–162.
22. Wadenberg ML (2003): A review of the properties of spiradoline: A potent and selective k-opioid receptor agonist. CNS Drug Rev 9:187–198.
23. Dortch-Carnes J, Potter DE (2005): Bremazocine: A κ-opioid agonist with potent analgesic and other pharmacologic properties. CNS Drug Rev 11:195–212.
24. Roth BL, Baner K, Westkaemper R, Siebert D, Rice KC, Steinberg S, *et al.* (2002): Salvinorin A: A potent naturally occurring nonnitrogenous κ opioid selective agonist. Proc Natl Acad Sci U S A 99:11934–11939.
25. Addy PH (2012): Acute and post-acute behavioral and psychological effects of salvinorin A in humans. Psychopharmacology (Berl) 220:195–204.
26. MacLean KA, Johnson MW, Reissig CJ, Prisinzano TE, Griffiths RR (2013): Dose-related effects of salvinorin A in humans: dissociative,

hallucinogenic, and memory effects. Psychopharmacology (Berl) 226:381–392.
27. Maqueda AE, Valle M, Addy PH, Antonijoan RM, Puntes M, Coimbra J, *et al.* (2016): Naltrexone but not ketanserin antagonizes the subjective, cardiovascular, and neuroendocrine effects of salvinorin-A in humans. Int J Neuropsychopharmacol 19:pyw016.
28. Orr M, Oppenheimer C (1978): Effects of naloxone on auditory hallucinations. Br Med J 1:481.
29. Jørgensen HA, Cappelen C (1982): Naloxone-induced reduction of schizophrenic symptoms: A case report. Acta Psychiatr Scand 65:370–374.
30. Gunne L-M, Lindström L, Terenius L (1977): Naloxone-induced reversal of schizophrenic hallucinations. J Neural Transm (Vienna) 40:13–19.
31. Davis GC, Bunney WE, DeFraites EG, Kleinman JE, van Kammen DP, Post RM, Wyatt RJ (1977): Intravenous naloxone administration in schizophrenia and affective illness. Science 197:74–77.
32. Volavka J, Mallya A, Baig S, Perez-Cruet J (1977): Naloxone in chronic schizophrenia. Science 196:1227–1228.
33. Janowsky DS, Segal DS, Bloom F, Abrams A, Guillemin R (1977): Lack of effect on naloxone on schizophrenic symptoms. Am J Psychiatry 134:926–927.
34. Kurland AA, McCabe OL, Hanlon TE, Sullivan D (1977): The treatment of perceptual disturbances in schizophrenia with naloxone hydrochloride. Am J Psychiatry 134:1408–1410.
35. Lipinski J, Meyer R, Kornetsky C, Cohen B (1979): Naloxone in schizophrenia: Negative result. Lancet 313:1292–1293.
36. Freeman C, Fairburn C (1981): Lack of effect of naloxone and schizophrenic auditory hallucinations. Psychol Med 11:405–407.
37. Emrich H, Cording C, Piree S, Kölling A, Zerssen D, Herz A (1977): Indication of an antipsychotic action of the opiate antagonist naloxone. Pharmakopsychiatr Neuropsychopharmakol 10:265–270.
38. Melichar JK, Nutt DJ, Malizia AL (2003): Naloxone displacement at opioid receptor sites measured in vivo in the human brain. Eur J Pharmacol 459:217–219.
39. Mueser KT, Dysken MW (1983): Narcotic antagonists in schizophrenia: A methodological review. Schizophr Bull 9:213–225.
40. Lehmann HE, Cooper TH, Nair NPV, Kline NS (1979): Beta-endorphins and naloxone in psychiatric patients: Clinical and biological effects. In: Saletu B, Berner P, Hollister L, editors. Neuro-Psychopharmacology: Proceedings of the 11th Congress of the Collegium Internationale Neuro-Psychopharmacologicum, Vienna, July 9–14, 1978. Elmsford, New York: Pergamon Press, 535–539.
41. Berger P, Watson S, Akil H, Barchas J (1981): The effects of naloxone in chronic schizophrenia. Am J Psychiatry 138:913–918.
42. Naber D, Münch U, Wissmann J, Grosse R, Ritt R, Welter D (1983): Naloxone treatment for five days ineffective in schizophrenia. Acta Psychiatr Scand 67:265–271.
43. Dowling J, Isbister GK, Kirkpatrick CM, Naidoo D, Graudins A (2008): Population pharmacokinetics of intravenous, intramuscular, and intranasal naloxone in human volunteers. Ther Drug Monit 30:490–496.
44. Emrich H, Höllt V, Laspe H, Fischler M, Heinemann H, Kissling W, *et al.* (1979): Studies on a possible pathological significance of endorphins in psychiatric disorders. Neuropsychopharmacology 527–534.
45. Kleinman JE, Weinberger DR, Rogol A, Shiling DJ, Mendelson WB, Davis GC, *et al.* (1982): Naloxone in chronic schizophrenic patients: neuroendocrine and behavioral effects. Psychiatry Res 7:1–7.
46. Cohen MR, Pickar D, Cohen RM (1985): High-dose naloxone administration in chronic schizophrenia. Biol Psychiatry 20:573–575.
47. Emrich H, Bergmann M, Kissling W, Schmid W, Zerssen D, Costa AHE, Trabucchi M (1980): Neural Peptides and Neuronal Communication. New York: Raven Press.
48. Sethi BB Prakash R (1981): A study of naloxone with schizophrenic and manic patients. Br J Psychiatry 138:501–503.
49. Naber D, Leibl K (1983): Repeated high dosage naloxone treatment without therapeutic efficacy in schizophrenic patients. Pharmacopsychiatria 16:43–45.
50. Verhoeven WM, Van Praag HM, Van Ree JM (1984): Repeated naloxone administration in schizophrenia. Psychiatry Res 12:297–312.
51. Pickar D, Vartanian F, Bunney WE, Maier HP, Gastpar MT, Prakash R, *et al.* (1982): Short-term naloxone administration in schizophrenic and manic patients: A World Health Organization collaborative study. Arch Gen Psychiatry 39:313–319.
52. Pickar D, Bunney W, Douillet P, Sethi B, Sharma M, Vartanian M, *et al.* (1989): Repeated naloxone administration in schizophrenia: a phase II World Health Organization study. Biol Psychiatry 25:440–448.
53. Vijay A, Morris E, Goldberg A, Petrulli J, Liu H, Huang Y, Krishnan-Sarin S (2017): Naltrexone occupancy at kappa opioid receptors investigated in alcoholics by PET occupancy at kappa opioid receptors investigated in alcoholics by PET. J Nucl Med 58(suppl 1): 1297–1297.
54. Marchesi G, Santone G, Cotani P, Giordano A, Chelli F (1992): Naltrexone in chronic negative schizophrenia. Clin Neuropharmacol 15(part A):56A–57A.
55. Marchesi GF, Santone G, Cotani P, Giordano A, Chelli F (1995): The therapeutic role of naltrexone in negative symptom schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 19:1239–1249.
56. Tatari F, Shakeri J, Farnia V, Hashemian A, Rezaei M, Abdoli N (2014): Naltrexone augmentation of risperidone in treatment of schizophrenia symptoms: A randomized placebo-controlled study. Ann Psychiatry Ment Health 2:1016.
57. Mielke DH, Gallant DM (1977): An oral opiate antagonist in chronic schizophrenia: A pilot study. Am J Psychiatry 134:1430–1431.
58. Simpson G, Branchey M, Lee J (1977): Trial of naltrexone in chronic-schizophrenia. Curr Ther Res Clin Exp 22:909–913.
59. Ragheb M, Berney S, Ban T (1980): Naltrexone in chronic schizophrenia. International pharmacopsychiatry 15:1–5.
60. Gitlin MJ, Gerner RH, Rosenblatt M (1981): Assessment of naltrexone in the treatment of schizophrenia. Psychopharmacology (Berl) 74:51–53.
61. Sernyak MJ, Glazer WM, Heninger GR, Charney DS, Woods SW, Petrakis IL, *et al.* (1998): Naltrexone augmentation of neuroleptics in schizophrenia. Journal of clinical psychopharmacology 18:248–251.
62. Schmauss C, Yassouridis A, Emrich HM (1987): Antipsychotic effect of buprenorphine in schizophrenia. Am J Psychiatry 144:1340–1342.
63. Groves S, Nutt NJ (1991): Buprenorphine and schizophrenia. Hum Psychopharmacol 6:71–72.
64. Rapaport MH, Wolkowitz O, Kelsoe JR, Pato C, Konicki PE, Pickar D (1993): Beneficial effects of nalmefene augmentation in neuroleptic-stabilized schizophrenic patients. Neuropsychopharmacology 9:111–115.
65. Volavka J, Davis LG, Ehrlich YH (1979): Endorphins, dopamine, and schizophrenia. Schizophr Bull 5:227–239.
66. Schmauss C, Emrich HM (1985): Dopamine and the action of opiates: A reevaluation of the dopamine hypothesis of schizophrenia with special consideration of the role of endogenous opioids in the pathogenesis of schizophrenia. Biol Psychiatry 20:1211–1231.
67. Weinstein JJ, Chohan MO, Slifstein M, Kegeles LS, Moore H, Abi-Dargham A (2017): Pathway-specific dopamine abnormalities in schizophrenia. Biol Psychiatry 81:31–42.
68. Slifstein M, van de Giessen E, Van Snellenberg J, Thompson JL, Narendran R, Gil R, *et al.* (2015): Deficits in prefrontal cortical and extrastriatal dopamine release in schizophrenia: A positron emission tomographic functional magnetic resonance imaging study. JAMA Psychiatry 72:316–324.
69. Weinberger DR, Berman KF (1988): Speculation on the meaning of cerebral metabolic hypofrontality in schizophrenia. Schizophr Bull 14:157–168.
70. Weinberger DR, Berman KF, Illowsky BP (1988): Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia: III. A new cohort and evidence for a monoaminergic mechanism. Arch Gen Psychiatry 45:609–615.
71. Steiner H, Gerfen CR (1996): Dynorphin regulates D1 dopamine receptor-mediated responses in the striatum: Relative contributions of

pre-and postsynaptic mechanisms in dorsal and ventral striatum demonstrated by altered immediate-early gene induction. J Comp Neurol 376:530–541.
72. Svingos AL, Chavkin C, Colago EE, Pickel VM (2001): Major coexpression of κ-opioid receptors and the dopamine transporter in nucleus accumbens axonal profiles. Synapse 42:185–192.
73. Escobar AP, González MP, Meza RC, Noches V, Henny P, Gysling K, *et al.* (2017): Mechanisms of kappa opioid receptor potentiation of dopamine D2 receptor function in quinpirole-induced locomotor sensitization in ratsKOR potentiation of D2R-induced behavior. Int J Neuropsychopharmacol 20:660–669.
74. Bruijnzeel AW (2009): kappa-Opioid receptor signaling and brain reward function. Brain Res Rev 62:127–146.
75. Di Chiara G, Imperato A (1988): Opposite effects of mu and kappa opiate agonists on dopamine release in the nucleus accumbens and in the dorsal caudate of freely moving rats. J Pharmacol Exp Ther 244:1067–1080.
76. Hawes SL, Salinas AG, Lovinger DM, Blackwell KT (2017): Long-term plasticity of corticostriatal synapses is modulated by pathway-specific co-release of opioids through κ-opioid receptors. J Physiol 595:5637–5652.
77. Tejeda HA, Wu J, Kornspun AR, Pignatelli M, Kashtelyan V, Krashes MJ, *et al.* (2017): Pathway-and cell-specific kappa-opioid receptor modulation of excitation-inhibition balance differentially gates D1 and D2 accumbens neuron activity. Neuron 93:147–163.
78. Manzanares J, Lookingland KJ, Moore KE (1991): Kappa opioid receptor-mediated regulation of dopaminergic neurons in the rat brain. J Pharmacol Exp Ther 256:500–505.
79. Devine DP, Leone P, Pocock D, Wise R (1993): Differential involvement of ventral tegmental mu, delta and kappa opioid receptors in modulation of basal mesolimbic dopamine release: In vivo microdialysis studies. J Pharmacol Exp Ther 266:1236–1246.
80. Maisonneuve I, Archer S, Glick S (1994): U50, 488, a κ opioid receptor agonist, attenuates cocaine-induced increases in extracellular dopamine in the nucleus accumbens of rats. Neurosci Lett 181:57–60.
81. Xi Z-X, Fuller SA, Stein EA (1998): Dopamine release in the nucleus accumbens during heroin self-administration is modulated by kappa opioid receptors: An in vivo fast-cyclic voltammetry study. J Pharmacol Exp Ther 284:151–161.
82. Gray AM, Rawls SM, Shippenberg TS, McGinty JF (1999): The K-opioid agonist, U-69593, decreases acute amphetamine-evoked behaviors and calcium-dependent dialysate levels of dopamine and glutamate in the ventral striatum. J Neurochem 73:1066–1074.
83. Chefer VI, Bäckman CM, Gigante ED, Shippenberg TS (2013): Kappa opioid receptors on dopaminergic neurons are necessary for kappa-mediated place aversion. Neuropsychopharmacology 38:2623.
84. Zaratin P, Clarke GD (1994): Comparative effects of selective κ-opioid receptor agonists on dopamine levels in the dorsal caudate of freely moving rats. Eur J Pharmacol 264:151–156.
85. Carlezon WA, Béguin C, DiNieri JA, Baumann MH, Richards MR, Todtenkopf MS, *et al.* (2006): Depressive-like effects of the κ-opioid receptor agonist salvinorin A on behavior and neurochemistry in rats. J Pharmacol Exp Ther 316:440–447.
86. Zhang Y, Butelman ER, Schlussman SD, Ho A, Kreek MJ (2005): Effects of the plant-derived hallucinogen salvinorin A on basal dopamine levels in the caudate putamen and in a conditioned place aversion assay in mice: Agonist actions at kappa opioid receptors. Psychopharmacology (Berl) 179:551–558.
87. Gehrke BJ, Chefer VI, Shippenberg TS (2008): Effects of acute and repeated administration of salvinorin A on dopamine function in the rat dorsal striatum. Psychopharmacology (Berl) 197:509–517.
88. Fuentealba JA, Gysling K, Magendzo K, Andrés ME (2006): Repeated administration of the selective kappa-opioid receptor agonist U-69593 increases stimulated dopamine extracellular levels in the rat nucleus accumbens. J Neurosci Res 84:450–459.
89. Fuentealba JA, Gysling K, Andrés ME (2007): Increased locomotor response to amphetamine induced by the repeated administration of the selective kappa-opioid receptor agonist U-69593. Synapse 61:771–777.
90. Escobar Adel P, Cornejo FA, Andrés ME, Fuentealba JA (2012): Repeated treatment with the kappa opioid receptor agonist U69593 reverses enhanced K (+) induced dopamine release in the nucleus accumbens, but not the expression of locomotor sensitization in amphetamine-sensitized rats. Neurochem Int 60:344–349.
91. Heidbreder CA, Schenk S, Partridge B, Shippenberg TS (1998): Increased responsiveness of mesolimbic and mesostriatal dopamine neurons to cocaine following repeated administration of a selective κ-opioid receptor agonist. Synapse 30:255–262.
92. Kivell B, Uzelac Z, Sundaramurthy S, Rajamanickam J, Ewald A, Chefer V, *et al.* (2014): Salvinorin A regulates dopamine transporter function via a kappa opioid receptor and ERK1/2-dependent mechanism. Neuropharmacology 86:228–240.
93. Szechtman H, Talangbayan H, Eilam D (1993): Environmental and behavioral components of sensitization induced by the dopamine agonist quinpirole. Behav Pharmacol 4:405–410.
94. Perreault ML, Graham D, Bisnaire L, Simms J, Hayton S, Szechtman H (2006): Kappa-opioid agonist U69593 potentiates locomotor sensitization to the D2/D3 agonist quinpirole: Pre-and postsynaptic mechanisms. Neuropsychopharmacology 31:1967–1981.
95. Perreault ML, Graham D, Scattolon S, Wang Y, Szechtman H, Foster JA (2007): Cotreatment with the kappa opioid agonist U69593 enhances locomotor sensitization to the D2/D3 dopamine agonist quinpirole and alters dopamine D2 receptor and prodynorphin mRNA expression in rats. Psychopharmacology (Berl) 194:485–496.
96. Seeman P, Chau-Wong M, Tedesco J, Wong K (1975): Brain receptors for antipsychotic drugs and dopamine: Direct binding assays. Proc Natl Acad Sci U S A 72:4376–4380.
97. Seeman P, Lee T (1975): Antipsychotic drugs: Direct correlation between clinical potency and presynaptic action on dopamine neurons. Science 188:1217–1219.
98. Kapur S, Mamos D (2003): Half a century of antipsychotics and still a central role for dopamine D2 receptors. Prog Neuropsychopharmacol Biol Psychiatry 27:1081–1090.
99. Kessler RM, Ansari MS, Riccardi P, Li R, Jayathilake K, Dawant B, Meltzer HY (2006): Occupancy of striatal and extrastriatal dopamine D 2 receptors by clozapine and quetiapine. Neuropsychopharmacology 31:1991.
100. Seeman P (2011): All roads to schizophrenia lead to dopamine supersensitivity and elevated dopamine $D2^{High}$ receptors. CNS Neurosci Ther 17:118–132.
101. Seeman P (2013): Are dopamine D2 receptors out of control in psychosis? Prog Neuropsychopharmacol Biol Psychiatry 46:146–152.
102. Seeman MV, Seeman P (2014): Is schizophrenia a dopamine supersensitivity psychotic reaction? Prog Neuropsychopharmacol Biol Psychiatry 48:155–160.
103. Perreault ML, Seeman P, Szechtman H (2007): Kappa-opioid receptor stimulation quickens pathogenesis of compulsive checking in the quinpirole sensitization model of obsessive-compulsive disorder (OCD). Behav Neurosci 121:976–991.
104. Beerepoot P, Lam V, Luu A, Tsoi B, Siebert D, Szechtman H (2008): Effects of salvinorin A on locomotor sensitization to D2/D3 dopamine agonist quinpirole. Neurosci Lett 446:101–104.
105. Acri JB, Thompson AC, Shippenberg T (2001): Modulation of pre-and postsynaptic dopamine D2 receptor function by the selective kappa-opioid receptor agonist U69593. Synapse 39:343–350.
106. Collins SL, D'Addario C, Izenwasser S (2001): Effects of κ-opioid receptor agonists on long-term cocaine use and dopamine neurotransmission. Eur J Pharmacol 426:25–34.
107. Collins S, Gerdes R, D'Addario C, Izenwasser S (2001): Kappa opioid agonists alter dopamine markers and cocaine-stimulated locomotor activity. Behav Pharmacol 12:237–245.
108. Shippenberg T, Chefer V, Zapata A, Heidbreder CA (2001): Modulation of the behavioral and neurochemical effects of psychostimulants by κ-opioid receptor systems. Ann N Y Acad Sci 937:50–73.

109. Ehrich JM, Phillips PE, Chavkin C (2014): Kappa opioid receptor activation potentiates the cocaine-induced increase in evoked dopamine release recorded in vivo in the mouse nucleus accumbens. Neuropsychopharmacology 39:3036–3048.
110. Chartoff EH, Ebner SR, Sparrow A, Potter D, Baker PM, Ragozzino ME, Roitman MF (2016): Relative timing between kappa opioid receptor activation and cocaine determines the impact on reward and dopamine release. Neuropsychopharmacology 41:989–1002.
111. Werling L, Frattali A, Portoghese P, Takemori A, Cox B (1988): Kappa receptor regulation of dopamine release from striatum and cortex of rats and guinea pigs. J Pharmacol Exp Ther 246:282–286.
112. Tejeda HA, Counotte DS, Oh E, Ramamoorthy S, Schultz-Kuszak KN, Bäckman CM, *et al.* (2013): Prefrontal cortical kappa-opioid receptor modulation of local neurotransmission and conditioned place aversion. Neuropsychopharmacology 38:1770–1779.
113. Bals-Kubik R, Ableitner A, Herz A, Shippenberg TS (1993): Neuroanatomical sites mediating the motivational effects of opioids as mapped by the conditioned place preference paradigm in rats. J Pharmacol Exp Ther 264:489–495.
114. Margolis EB, Lock H, Chefer VI, Shippenberg TS, Hjelmstad GO, Fields HL (2006): κ opioids selectively control dopaminergic neurons projecting to the prefrontal cortex. Proc Natl Acad Sci U S A 103:2938–2942.
115. Fuentealba JA, Gysling K, Andrés ME (2010): Repeated treatment with the κ-opioid agonist U-69593 increases K+-stimulated dopamine release in the rat medial prefrontal cortex. Synapse 64:898–904.
116. Bortolato M, Aru GN, Frau R, Orrù M, Fà M, Manunta M, *et al.* (2005): Kappa opioid receptor activation disrupts prepulse inhibition of the acoustic startle in rats. Biol Psychiatry 57:1550–1558.
117. Tejeda HA, Chefer VI, Zapata A, Shippenberg TS (2010): The effects of kappa-opioid receptor ligands on prepulse inhibition and CRF-induced prepulse inhibition deficits in the rat. Psychopharmacology (Berl) 210:231–240.
118. Shannon HE, Eberle EL, Mitch CH, McKinzie DL, Statnick MA (2007): Effects of kappa opioid receptor agonists on attention as assessed by a 5-choice serial reaction time task in rats. Neuropharmacology 53:930–941.
119. Nemeth CL, Paine TA, Rittiner JE, Béguin C, Carroll FI, Roth BL, *et al.* (2010): Role of kappa-opioid receptors in the effects of salvinorin A and ketamine on attention in rats. Psychopharmacology (Berl) 210:263–274.
120. Braida D, Donzelli A, Martucci R, Capurro V, Sala M (2011): Learning and memory impairment induced by salvinorin A, the principal ingredient of Salvia divinorum, in wistar rats. Int J Toxicol 30:650–661.
121. Abraham AD, Fontaine HM, Song AJ, Andrews MM, Baird MA, Kieffer BL, *et al.* (2018): κ-Opioid receptor activation in dopamine neurons disrupts behavioral inhibition. Neuropsychopharmacology 43:362–372.
122. Hunter J, Leighton G, Meecham K, Boyle S, Horwell D, Rees D, Hughes J (1990): CI-977, a novel and selective agonist for the κ-opioid receptor. Br J Pharmacol 101:183–189.
123. Davis RE, Callahan MJ, Dickerson M, Downs DA (1992): Pharmacologic activity of CI-977, a selective kappa opioid agonist, in rhesus monkeys. J Pharmacol Exp Ther 261:1044–1049.
124. Kusumoto K, Mackay KB, McCulloch J (1992): The effect of the kappa-opioid receptor agonist CI-977 in a rat model of focal cerebral ischaemia. Brain Res 576:147–151.
125. Mackay KB, Kusumoto K, Graham DI, McCulloch J (1993): Effect of the kappa-1 opioid agonist CI-977 on ischemic brain damage and cerebral blood flow after middle cerebral artery occlusion in the rat. Brain Res 629:10–18.
126. Hayward NJ, McKnight AT, Woodruff GN (1993): Neuroprotective effect of the χ-agonist enadoline (CI-977) in rat models of focal cerebral ischaemia. Eur J Neurosci 5:961–967.
127. Mackay KB, Kusumoto K, Graham DI, McCulloch J (1993): Focal cerebral ischemia in the cat: Pretreatment with a kappa-1 opioid receptor agonist, CI-977. Brain Res 618:213–219.
128. Hiramatsu M, Hyodo T, Kameyama T (1996): U-50488H, a selective κ-opioid receptor agonist, improves carbon monoxide-induced delayed amnesia in mice. Eur J Pharmacol 315:119–125.
129. Margolis EB, Hjelmstad GO, Bonci A, Fields HL (2005): Both kappa and mu opioid agonists inhibit glutamatergic input to ventral tegmental area neurons. J Neurophysiol 93:3086–3093.
130. Tejeda HA, Bonci A (2019): Dynorphin/kappa-opioid receptor control of dopamine dynamics: Implications for negative affective states and psychiatric disorders. Brain Res 1713:91–101.
131. Crowley NA, Kash TL (2015): Kappa opioid receptor signaling in the brain: Circuitry and implications for treatment. Prog Neuropsychopharmacol Biol Psychiatry 62:51–60.
132. Tejeda H, Shippenberg T, Henriksson R (2012): The dynorphin/κ-opioid receptor system and its role in psychiatric disorders. Cell Mol Life Sci 69:857–896.
133. Heikkilä L, Rimón R, Ternius L (1990): Dynorphin A and substance P in the cerebrospinal fluid of schizophrenic patients. Psychiatry Res 34:229–236.
134. Lindström LH (1996): Clinical and biological markers for outcome in schizophrenia: A review of a longitudinal follow-up study in Uppsala schizophrenia research project. Neuropsychopharmacology 14(suppl):23S–26S.
135. Zhang A, Zhou G, Xi G, Gu N, Xia Z, Yao J, *et al.* (1985): Lower CSF level of dynorphin (1–8) immunoreactivity in schizophrenic patients. Neuropeptides 5:553–556.
136. Lindtröm L, Winderlöv E, Gunne LM, Wahlström A, Terenius L (1978): Endorphins in human cerebrospinal fluid: clinical correlations to some psychotic states. Acta Psychiatr Scand 57:153–164.
137. Domschke W, Dickschas A, Mitznegg P (1979): CSF β-endorphin in schizophrenia. Lancet 313:1024.
138. Lindström LH, Besev G, Gunne LM, Terenius L (1986): CSF levels of receptor-active endorphins in schizophrenic patients: Correlations with symptomalogy and monoamine metabolites. Psychiatry Res 19:93–100.
139. Ross M, Berger PA, Goldstein A (1979): Plasma beta-endorphin immunoreactivity in schizophrenia. Science 205:1163–1164.
140. Royston M, Slater P, Simpson M, Deakin J (1991): Analysis of laminar distribution of kappa opiate receptor in human cortex: comparison between schizophrenia and normal. J Neurosci Methods 36:145–153.
141. Peckys D, Hurd Y (2001): Prodynorphin and κ opioid receptor mRNA expression in the cingulate and prefrontal cortices of subjects diagnosed with schizophrenia or affective disorders. Brain Res Bull 55:619–624.
142. Sarkar S, Hillner K, Velligan DI (2015): Conceptualization and treatment of negative symptoms in schizophrenia. World J Psychiatry 5:352–361.
143. Toll L, Berzetei-Gurske IP, Polgar WE, Brandt SR, Adapa ID, Rodriguez L, *et al.* (1998): Standard binding and functional assays related to medications development division testing for potential cocaine and opiate narcotic treatment medications. NIDA Res Mongr 178:440–446.
144. Gonzalez JP, Brogden RN (1988): Naltrexone. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in the management of opioid dependence. Drugs 35:192–213.
145. Elkader A, Sproule B (2005): Buprenorphine: Clinical pharmacokinetics in the treatment of opioid dependence. Clin Pharmacokinet 44:661–680.
146. Kyhl LE, Li S, Faerch KU, Soegaard B, Larsen F, Areberg J (2016): Population pharmacokinetics of nalmefene in healthy subjects and its relation to μ-opioid receptor occupancy. Br J Clin Pharmacol 81:290–300.
147. Ingman K, Hagelberg N, Aalto S, Någren K, Juhakoski A, Karhuvaara S, *et al.* (2005): Prolonged central mu-opioid receptor occupancy after single and repeated nalmefene dosing. Neuropsychopharmacology 30:2245–2253.