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Kappa-opioid ligands in the study and treatment of mood disorders

William A. Carlezon Jr[1], **Cécile Béguin**[2], **Allison T. Knoll**[1], and **Bruce M. Cohen**[2]

[1]Behavioral Genetics Laboratory, Department of Psychiatry, Harvard Medical School, McLean Hospital, Belmont MA 02478

[2]Molecular Pharmacology Laboratory, Department of Psychiatry, Harvard Medical School, McLean Hospital, Belmont MA 02478

Abstract

The biological basis of mood is not understood. Most research on mood and affective states has focused on the roles of brain systems containing monoamines (e.g., dopamine, norepinephrine, serotonin). However, it is becoming clear that endogenous opioid systems in the brain may also be involved in regulation of mood. In this review, we focus on the potential utility of kappa-opioid receptor (KOR) ligands in the study and treatment of psychiatric disorders. Research from our group and others suggests that KOR antagonists might be useful for depression, KOR agonists might be useful for mania, and KOR partial agonists might be useful for mood stabilization. Currently available agents have some unfavorable properties that might be addressed through medicinal chemistry. The development of KOR-selective agents with improved drug-like characteristics would facilitate preclinical and clinical studies designed to evaluate the possibility that KORs are a feasible target for new medications.

Keywords

depression; antidepressant; dynorphin; kappa opioid; dopamine; model; rat; mouse

1. Introduction

The biological basis of mood is not understood. Most present day research on mood and affective states focuses on the roles of brain systems containing monoamines, such as dopamine (DA), norepinephrine (NE), and serotonin (5-hydroxytryptamine [5HT]). Drugs with mood-elevating effects have prominent interactions with these systems, in general by increasing extracellular concentrations of monoamines and prolonging their actions (Ritz et al., 1987; Di Chiara and Imperato, 1988; Koch et al., 2002). Increased DA is most often associated with

Corresponding author William A. Carlezon, Jr., Department of Psychiatry, McLean Hospital, MRC 217, 115 Mill Street, Belmont, MA 02478, bcarlezon@mclean.harvard.edu.

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rewarding (pleasurable) mood states: major drugs of abuse (including opiates, stimulants, nicotine, ethanol) have the common effect of increasing neurotransmission in midbrain DA systems (Wise and Bozarth, 1987; Di Chiara and Imperato, 1988). In contrast, antipsychotic drugs (which have prominent DA antagonist properties) tend to block reward, lower abnormally elevated mood, and produce anhedonia (Wise, 1982). Depression has often been associated with reduced NE, and one of the earliest classes of antidepressant drugs (tricyclic antidepressants [TCAs]) blocks synaptic reuptake of this transmitter (Frazer, 1997; Koch et al., 2002). The commercial success of selective serotonin reuptake inhibitors (SSRIs) as antidepressants—which appear to be safer, but possibly less clinically efficacious than TCAs (Fawcett and Barkin, 1997)—has led to discoveries of fundamental alterations in brain 5HT systems in mediating depression (e.g., the association of stress-induced depression with polymorphisms of the gene coding for the serotonin transporter may explain vulnerability to depressive disorders in some individuals) (Caspi et al., 2003; Vergne and Nemeroff, 2006). New generations of antidepressants target two or more of the monoamines. As such, studies of how brain monoamine systems regulate mood—and how they can be manipulated to control mood—have dominated the field for decades.

Endogenous opioid systems in the brain are also involved in regulation of mood, although they have received far less attention than monoamine systems. It is clear that such effects involve, at least in part, monoamines: indeed, some of the reward-related effects of opiates such as morphine appear to depend upon their ability to activate DA systems (Leone et al., 1991) via inhibition of neurons that normally inhibit the activity of midbrain DA neurons (Johnson and North, 1992). Considering that endogenous opioid systems are interwoven with monoamine systems in the brain (see Snyder and Pasternak, 2003), it should not be surprising that some effects of opioid receptor stimulation involve monoamine neurotransmitters. However, there is also evidence that rewarding effects of opiates are DA-independent (Olds, 1982). Relevant findings suggest that the major consequence of activation of endogenous opioid receptors—stimulation of inhibitory G-proteins (see Snyder and Pasternak, 2003)—could be sufficient to alter mood states. The fact that both endogenous and exogenous opioids can affect mood raises the possibility that drugs that target endogenous opioid systems could be utilized in the treatment of debilitating psychiatric conditions.

We have become particularly interested in how kappa-opioid receptors (KORs)—so-named for the prototype KOR agonist ketocyclazocine (Martin et al., 1976)—contribute to regulation of mood. Our interest in KORs has evolved from what began as disparate lines of research. The idea that KOR antagonists might be useful for the treatment of depression can be traced back to studies of the neurobiological consequences of long-term exposure to addictive drugs such as cocaine (Carlezon et al., 1998). The idea that KOR agonists might be useful for the treatment of bipolar disorder or mania can be traced back to studies of the molecular mechanisms of action of antipsychotic drugs (Ma et al., 2003), which are often used to manage the symptoms of these conditions. Studies of the antidepressant-like effects of KOR antagonists led directly to studies of the prodepressant-like effects of KOR agonists (Mague et al., 2003; Carlezon et al., 2006). In this review, we present evidence for a role of KORs in the regulation of mood, describe issues that currently hinder research in this area, and provide suggestions for how the field might be advanced.

2. KOR Antagonists

History

Until recently, the prospects for clinical applications of KOR antagonists seemed limited. One consequence of the discovery of endogenous opioid receptors (see Snyder and Pasternak, 2003) and their agonists—including dynorphin, an endogenous agonist at brain KORs (Chavkin et al., 1982)—was an interest in developing analgesic agents with reduced abuse

liability. Dynorphin (Han and Xie, 1982; Han et al., 1984) and synthetic KOR agonists (e.g., bremazocine; Pazos et al., 1983) have antinociceptive effects in rats, and KOR antagonists were primarily developed and utilized initially to block and characterize these actions (Portoghese et al., 1987). There were scattered reports suggesting potential clinical uses for KOR antagonists, such as minimizing the effects of traumatic injury to the CNS (Faden et al., 1987; Vink et al., 1991) or manipulating feeding behavior (Carr et al., 1989). In general, however, these agents seemed envisioned primarily as "molecular probes" (Portoghese et al., 1987) for studies of interactions between agonists and KORs and the functional significance of KORs for behavior.

Our interest in KOR antagonists evolved from research on the ability of drugs of abuse to induce neuroadaptations within brain reward circuits, including the nucleus accumbens (NAc). Some of our early work focused on the effects of stimulant drugs on cAMP response element binding protein (CREB) (see Carlezon et al., 2005). CREB is located in the nucleus of all cells in the brain and belongs to a family of proteins called transcription factors. Transcription factors play a crucial role in translating events that occur on the cell membrane into alterations in gene and protein expression. They regulate sets of genes called "transcriptomes"; the CREB transcriptome includes genes that encode other transcription factors (e.g., Fos), enzymes (e.g., tyrosine hydroxylase), receptor subunits (e.g., GluRs), growth factors (e.g., brain-derived neurotrophic factor), stress factors (e.g., corticotropin releasing factor), and opioid peptides (e.g., dynorphin) (Carlezon et al., 2005). Alterations in the expression of these genes can "re-program" cells, leading to modification of the activity of neural circuits. In turn, these changes in activity encode behavior and, presumably, mood. Repeated administration of stimulants such as amphetamine increases the function of the transcription factor CREB within the NAc (Turgeon et al., 1997). At the time, the biological significance (if any) of this change was unclear; conceivably, it could contribute to drug tolerance or drug sensitization (reverse tolerance), two processes thought to play significant roles in the development and maintenance of addictive behaviors. In an attempt to establish causal relationships between drug-induced alterations in CREB function in the NAc and complex behaviors, we engineered viral vectors that would enable us to elevate CREB expression (thereby modeling one consequence of drug exposure) or block CREB function, specifically within this region. In tests of sensitivity to the rewarding effects of cocaine, elevated expression of CREB in the NAc caused complex alterations in behavior: it made low doses of the drug aversive, and higher doses less rewarding than normal (Carlezon et al., 1998). Only through the use of additional models did it become apparent that elevation of CREB function in the NAc was eliciting the rodent equivalent of signs of major depression: dysphoria (a state of aversion), anhedonia (a state of reduced sensitivity to pleasure), and despair (a state of hopelessness) (Pliakas et al., 2001). In addition, it became clear that stress, a common trigger for both depressive and addictive disorders (Kendler et al., 1999), also activates CREB in the NAc (Pliakas et al., 2001). Disruption of CREB function in the NAc caused opposite effects to those induced by elevated CREB, and had antidepressant-like effects that were indistinguishable from those of standard antidepressants. These findings led to the working hypothesis that activation of CREB in the NAc is a molecular trigger or mediator for aversive or depressive-like symptoms (Carlezon et al., 1998; Pliakas et al., 2001; Carlezon et al., 2005).

Because CREB is a transcription factor that regulates expression of a variety of genes, it seemed likely that the aversive effects of elevated CREB function in the NAc were mediated by CREB-regulated target genes. Evidence already in the literature implicated dynorphin: both *in vitro* and *in vivo* studies indicated that CREB regulates expression of the gene encoding the peptide precursor of the endogenous KOR agonist dynorphin (prodynorphin) (Daunais et al., 1993; Douglass et al., 1994; Cole et al., 1995). Recent work confirms that the same types of stress that activate CREB in the NAc also increase prodynorphin expression (Chartoff et al., 2009). In addition, it was already known that KOR agonists cause aversive and depressive signs

(including dysphoria) in humans (Pfeiffer et al., 1986) and rodents (Bals-Kubik et al., 1989). We found that viral vector-mediated elevations in CREB function within the NAc increased prodynorphin expression, whereas disruption of CREB function reduced it (Carlezon et al., 1998). This work suggested that the ability of CREB activation in the NAc to trigger aversive states could be related to increased dynorphin and subsequent elevations in KOR activation in this brain region. This hypothesis was supported by a series of experiments demonstrating that intracerebroventricular (ICV) administration of the KOR antagonist nor-binaltorphimine (norBNI) blocked the aversive-like effects of elevated CREB on cocaine reward (Carlezon et al., 1998) as well as depressive-like behavior in the Forced Swim Test (FST) (Pliakas et al., 2001). Importantly, the effects of KOR antagonists were not limited to conditions in which CREB function had been artificially boosted using viral vectors: norBNI and related derivatives (GNTI, ANTI) had antidepressant-like effects of their own in the FST (Mague et al., 2003), a procedure that identifies in rats treatments with antidepressant efficacy in humans (Willner, 1984). The antidepressant-like effects of KOR antagonists have since been confirmed by other researchers, who have extended these finding to other protocols (Newton et al., 2002; McLaughlin et al., 2003) and structurally dissimilar drugs (Beardsley et al., 2005). More recent work has demonstrated that KOR antagonists also have acute anxiolytic-like actions (Knoll et al., 2007). Interestingly, standard antidepressant drugs often have anxiogenic effects upon acute administration (Artaiz et al., 1998; Bagdy et al., 2001; Drapier et al., 2007). Thus the behavioral profile of KOR antagonists—acute antidepressant and anxiolytic effects—is somewhat unique and suggests that this class of drugs might be particularly effective for the treatment of comorbid depressive and anxiety disorders.

Mechanisms

The mechanisms by which KOR antagonists produce antidepressant-like effects are not fully understood. There is compelling evidence that alterations in DA function within the NAc are involved; on the basis of a broad and multidisciplinary literature (see Carlezon and Thomas, 2009), we have developed a highly simplified model that enables us to test our working hypotheses (Figure 1). A key difference between KORs and both mu-opioid receptors (MORs) and delta-opioid receptors (DORs) is their anatomical localization within the NAc: KORs are located primarily on the terminals of inputs from the mesolimbic system (Svingos et al., 1999, 2002), whereas MORs and DORs are on the cell bodies of GABAergic medium spiny neurons or interneurons (Mansour et al., 1995). Thus despite common (inhibitory) effects on signal transduction, stimulation of KORs often causes effects opposite to those caused by stimulation of MORs or DORs. For example, whereas MOR and DOR agonists increase extracellular concentrations of DA in the NAc (Leone et al., 1991; Devine et al., 1993), KOR agonists decrease them (Devine et al., 1993; Carlezon et al., 2006). These effects appear to be mediated, at least in part, within the NAc: microinfusions of KOR agonists into this region decrease local DA concentrations (Donzanti et al., 1992; Spanagel et al., 1992), most likely by stimulating presynaptic KORs that inhibit DA release from ventral tegmental area (VTA) neurons (Svingos et al., 1999). Thus CREB-mediated increases in dynorphin expression within the NAc could result in local decreases in DA release, which triggers signs of depression (particularly, given the specific role of the NAc, those reflecting altered motivation). Although these effects might occur predominately in the NAc, KOR ligands could also have effects within other parts of the reward circuitry where KORs are expressed, such as the VTA and prefrontal cortex (PFC) (Svingos et al., 2002; Margolis et al., 2003). According to our model (Figure 1), KOR antagonists have antidepressant effects because they block the consequences of CREB-mediated upregulation of dynorphin function in the NAc by blocking KORs in the NAc (or other regions), leading to restored function of the mesolimbic DA system. Another possibility—which is not mutually exclusive—is that KOR antagonists reduce activation of CREB in the NAc, which normally contributes to elevated dynorphin function. There is evidence that antidepressants may, in fact, interfere with CREB function under some

circumstances. A variety of antidepressants induce decreased CREB phosphorylation and CREB-mediated gene transcription in certain *in vitro* preparations (Schwaninger et al., 1995; Chartoff et al., 2009). In addition, chronic antidepressant treatment can lead to increased expression of cAMP phosphodiesterases (PDEs)—which metabolize cAMP—in the NAc (Takahashi et al., 1998). These findings raise the possibility that molecular processes involving CREB and KORs in the NAc play an underappreciated role in the therapeutic actions of many types of antidepressants. Yet another possibility is that KOR antagonists work through yet-to-be described interactions with 5HT or NE systems, which appear to be critically involved in the therapeutic effects of SSRIs and TCAs, the most widely prescribed classes of antidepressant drugs.

Studies in mutant mice provide genetic validation of the role of the KORs in stress-induced depressive and anxiety-like behaviors. KOR −/− mice show a complete loss of KOR transcript and receptor binding and a significant reduction in stress-induced behaviors. A series of studies by McLaughlin and colleagues (2006a) in which these mice were used has demonstrated that repeated exposure to forced swimming induces several stress-induced behaviors in wild-type mice including analgesia, increased immobility in the FST (a prodepressive-like effect), and potentiation of cocaine conditioned place preference (CPP). These stress-induced behavioral effects were completely absent in KOR −/− mice or in wild-type mice that had been treated with the KOR antagonist norBNI; that is, KOR ablation and KOR antagonists produced identical effects on these behaviors. Moreover, pretreatment of wild-type mice with the KOR agonist U50,488 mimicked the potentiation of cocaine CPP produced by forced swimming, suggesting that KOR activation is necessary and sufficient to produce this stress-induced behavior. It is important to note that initial characterizations of a separate line of KOR −/− mice under minimally stressful testing conditions did not detect differences in depression or anxiety-like behavior . Rather than reflecting an absence of a role of the KOR system in anxiety and depressive behavior, numerous lines of evidence suggest that these results reflect low levels of basal KOR signaling under non-stressful conditions. For example, studies demonstrating a reduction in depressive behavior in KOR −/− mice similarly do not see behavioral phenotypes in initial tests, but marked decreases in stress-induced behavior occur upon repeated testing . These data highlight the importance of tone in the KOR system in mediating stress-induced behaviors.

PDyn −/− mice also show reduced immobility in the FST (an antidepressant-like effect), decreased induction of stress-induced analgesia, decreased social defeat and blockade of stress-induced potentiation of cocaine CPP . A separate line of PDyn −/− mice show an anxiolytic phenotype in the elevated plus maze and open field paradigms as well as a significant decrease in serum corticosterone and corticotrophin releasing factor mRNA in the amygdala and paraventricular nucleus of the hypothalamus, brain regions involved in anxiety and depressive behaviors . In these studies, treatment of wild-type littermates with KOR antagonist mimics the anxiolytic phenotype whereas pretreatment of PDyn −/− mice with KOR agonist eliminates the anxiolytic behavioral phenotype . Taken together, the marked reduction of stress-induced behaviors in KOR −/− and PDyn −/− mice, highlights the importance of the KOR system in mediating depressive and anxiety-like behaviors.

Complexities

The possibility that the antidepressant-like effects of KOR antagonists are related to an ability to boost the function of brain DA systems adds an additional level of complexity to the development of these drugs for mood disorders. Virtually all addictive drugs facilitate brain DA function (Wise and Bozarth, 1987; Di Chiara et al., 1988), an effect often associated with their abuse liability. Standard antidepressant drugs have no abuse liability, so KOR antagonists would not represent an improved therapeutic approach if they posed a risk for misuse. To

address the possibility that KOR antagonists have properties that might lead to abuse, we examined their effects in the intracranial self-stimulation (ICSS) test, which identifies drugs with reward-altering actions (Carlezon and Chartoff, 2007). We observed that the selective KOR antagonist ANTI does not alter ICSS behavior at doses 8 times higher than those with antidepressant effects in the FST (Todtenkopf et al., 2004), and we have since extended this finding to doses 32 times higher (W. A. Carlezon Jr., unpublished observations). These data suggest that although KOR antagonists may be able to reverse reductions in DA caused by increased KOR tone, they have a limited ability to enhance DA function to the degree that would make the drugs rewarding. In addition, these results suggest that KOR antagonists would not be likely to produce mania-like states, a problem seen with stimulants and, sometimes, with standard antidepressants. Indeed, the effects of KOR antagonists on DA appear to be modest: direct administration of KOR antagonists into the NAc increases local concentrations of DA to ~175% of baseline (Maisonneuve et al., 1994), whereas psychostimulants such as cocaine and amphetamine can cause increases ranging from 500–1000% of baseline (Di Chiara et al., 1988; Maisonneuve et al., 1994). Modest increases in DA concentrations within the NAc may be sufficient to cause antidepressant-like effects in the FST without producing rewarding effects. As such, it appears unlikely that KOR antagonists would have abuse liability, at least on their own. Notably, cocaine induced place preferences were not altered in KOR −/− or PDyn −/− mice or in wild-type mice treated with KOR antagonists, although these manipulations were sufficient to block stress-induced potentiation of cocaine CPP (McLaughlin et al., 2003, 2006a,b), further suggesting minimal role of KORs in establishing basal DA tone. Studies with JDTic provide no evidence of interactions between KOR antagonists and the incentive-motivational effects of cocaine (Beardsley et al., 2005).

Another factor that complicates studies of known KOR antagonists in these species is the long-time course of these agents: a single injection of these drugs can block the effects of KOR agonists for as long as 56 days (Spanagel and Shippenberg, 1993). The reasons for this extraordinarily long time course are not understood; this issue is addressed in more detail within the next section. Regardless, such a long time course can make many types of preclinical studies —particularly those designed to assess abuse liability (e.g., intravenous drug self-administration, place conditioning)—difficult because of persistent drug actions. It is also less than optimal for studies in humans, at least at the early stages of drug development, when a short duration of action or the ability to reverse unanticipated side effects would be preferable until drug safety is established.

Chemistry

In this brief section, we cannot provide a comprehensive review of the medicinal chemistry of KOR antagonists, which is available elsewhere (Beguin and Cohen, 2008). Instead, we list most brain-permeable non-peptidic selective antagonists (or inverse agonists) available for preclinical studies. We have not included selective KOR partial agonists, since, in most cases, partial agonism was detected *in vitro* and it is not known whether such compounds would be partial agonists *in vivo*.

The first selective KOR antagonist (norBNI, Figure 2) was developed as a bivalent derivative of the non-selective opioid antagonist naltrexone (Portoghese et al., 1987), itself a derivative of morphine. It has been the agent of choice for many preclinical studies. However, in a few *in vivo* behavioral assays norBNI induced rapid and brief MOR antagonist effects in addition to its long-lasting KOR antagonist properties (Endoh et al., 1992; Broadbear et al., 1992; Spanagel et al., 1993). Structurally-simplified second-generation analogues (e.g., GNTI and ANTI; Jones et al., 1998;Stevens et al., 2000) (Figure 2) may be more selective as KOR antagonists. It is not clear if these agents act as neutral antagonists or inverse agonists (Wang et al., 2007). More recently, JDTic (Figure 2) has been developed as a potent and selective

KOR antagonist (Thomas et al., 2001). JDTic is a *trans*-3,4-dimethyl(3-hydroxyphenyl) piperidine analogue, a class of compounds initially derived from meperidine (Zimmerman et al., 1978), a non-selective opioid agonist. Despite few similarities in structure, both the morphine analogues (norBNI, GNTI) and JDTic have a slow onset of maximal KOR antagonist action (24–48 h) and extraordinarily long-lasting effects (several weeks) *in vivo* (Endoh et al., 1992;Spanagel et al., 1993;Beardsley et al., 2005;Metcalf and Koop, 2005). The reasons for the long duration of action are not understood; it does not seem to be an inevitable consequence of KOR blockade, since non-selective opioid antagonists do not share this property (Bruchas et al., 2007). One potential explanation would be the so-called "depot effect": the lipophilic properties of some molecules cause them to deposit and persist within brain membranes. However, since the KOR antagonists tested in vivo possess varying degrees of lipophilicity (logD values at pH 7 predicted using ACD/Labs: norBNI: -4.2; GNTI: -2.0; ANTI: -1.0; JDTic: 0.4), it seems unlikely that they would all deposit within brain membranes for extended periods of time. Interestingly, recent work suggests these KOR antagonists induce long-lasting changes in the function of c-Jun N-terminal kinase (JNK) (Bruchas et al., 2007), a property that might be responsible for persistent effects in vivo. These researchers also showed that pretreatment with a short-acting nonselective opioid receptor antagonist (naloxone) prevented the long-lasting effects of a single injection of norBNI, providing evidence against a depot effect. A current challenge is to determine if it is possible to design shorter-lasting potent and selective KOR antagonists, which might help to determine if the long-lasting effects of the prototypical KOR antagonists is essential for their therapeutic-like effects in animal models.

One strategy might involve designing selective KOR antagonists from other classes of compounds. For example, some of the biaryl compounds (Figure 2, compounds **5** and **6**) described in two recent patent applications (Magnus-Aryitey et al., 2008;Magnus-Aryitey and Ruggeri, 2008) are moderately selective KOR antagonists. If these compounds have relatively short-lasting effects, then further chemical modifications may enhance KOR selectivity. Another strategy is to base the structures on peptides, which are rapidly metabolized. Early attempts with this strategy appear to have promise (Bennett et al., 2002). Finally, there has been a growing interest in designing G-protein coupled receptors allosteric modulators (Conn et al., 2009). Negative allosteric modulation of the KOR may be an alternative way of inducing short-lasting receptor blockade. Regardless, there is a pressing need for selective KOR antagonists with improved pharmacokinetic and pharmacodynamic properties.

Potential for Clinical Use

As yet, the antidepressant-like effects of KOR antagonists have not been examined thoroughly in non-human primates or humans. Studies in non-human primates are complicated by the fact that there are no widely-accepted models of depression or antidepressant efficacy in these species. Instead, KOR antagonists have been examined in drug self-administration studies in monkeys, and mainly in the context of their ability to block the effects of KOR agonists (Negus et al., 2002; Negus, 2004). Selective KOR antagonists have not been examined in humans, although mixed agents with some ability to disrupt KOR function have been tested. One example is buprenorphine, which reportedly has antidepressant effects in certain individuals (Bodkin et al., 1995). Buprenorphine is often described as a mixed MOR agonist/KOR antagonist, although there is compelling evidence that it is actually a KOR partial-agonist: it causes low efficacy stimulation of [^{35}S]GTP-γS in cells engineered to express human KORs, whereas true antagonists (e.g., norBNI) are without effect in this assay (Zhu et al., 1997). Thus although reports that buprenorphine can have antidepressant effects in humans are encouraging, it is difficult at this time to attribute them to antagonism of KOR receptors, considering the complex pharmacologic profile of this drug. Similarly, the mixed MOR/KOR antagonists naltrexone and nalmephene have been used in clinical trials of substance use and impulse disorders, which have a high degree of comorbid depression. At human opioid

receptors, naltrexone and nalmephene have roughly equal binding affinity for MORs and KORs (Toll et al., 1997; Bart et al., 2005); nalmephene may be a weak partial agonist at KORs (Remmers et al., 1999). Naltrexone is FDA approved for use in alcohol dependence and nalmephene appears to have some efficacy for pathological gambling (Grant et al., 2006), but neither has been explicitly tested for depression, and the interpretation of their effects on depression is made difficult by their dual actions at two opioid receptors. At the present time, we are not aware of any published studies describing clinical trials of selective KOR antagonists.

Summary

The idea that KOR antagonists might be useful for the treatment of depression has emerged from basic research demonstrating that stress or repeated exposure to drugs of abuse—two stimuli that can trigger depressive conditions in humans—can activate endogenous dynorphin function. Considering that many treatments for mood disorders were discovered serendipitously over a half century ago (Nestler and Carlezon, 2006), the development of KOR antagonists for depressive conditions would represent a rare example of rational drug design in psychiatry. In rodent models, KOR antagonists block signs of anhedonia, dysphoria, and despair. The mechanisms that mediate these effects are not clear, but they may depend largely upon secondary alterations in the function of brain DA systems. Despite actions on brain DA systems, currently available evidence suggests that KOR antagonists do not cause behavioral effects that normally accompany drugs with abuse potential. A great deal of additional work is required to further characterize these agents, with particular emphasis on how chronic KOR blockade would ultimately affect behavior. Studies in rodents, non-human primates, and humans are complicated by the fact that all currently available selective KOR antagonists appear to have exceptionally long durations of action, for reasons that are not understood. The development of new classes of selective KOR antagonists with shorter durations of action is needed; such ligands would facilitate the design and performance of studies to address all of the issues described above.

3. KOR Agonists

History

Initially it was believed that KOR agonists could be utilized as non-addictive analgesics, since these drugs have antinociceptive properties but lower abuse potential than MOR agonists (Fraser and Rosenberg, 1964). Pentazocine, which is a relatively specific KOR partial agonist/MOR antagonist (Toll et al., 1999), is still used for obstetrical pain because it has a low propensity to produce respiratory depression. Administration of more selective KOR agonists (e.g., MR2033) elicit unwanted side effects in humans including dysphoria, derealization, and depersonalization (Pfeiffer et al., 1986). These observations precluded further development of these agents for clinical use. Trials of KOR agonists for psychiatric conditions have been limited and have shown only mixed success: the KOR agonist spiradoline produces sedation and decreases the frequency of tics in individuals with Tourette's Syndrome at low doses but produces increased dysphoria and altered perception at high doses (Chappell et al., 1993). In clinical studies of substance abusers, the KOR agonist enadoline reduces some of the effects of cocaine, but also caused sedation, depersonalization, visual distortions, confusion, and (at high doses) paranoia (Walsh et al., 2001a, 2001b). Perhaps the most interesting evidence on the effects of KOR agonists in humans comes from experience with salvinorin A, the active component of the plant *Salvia divinorum*, used by the Mazatec peoples of Oaxaca, Mexico, in spiritual and healing rituals. Salvinorin A is currently the most selective and potent KOR agonist known (Roth et al., 2002). Its effects are highly situation dependent (Valdes, 1994), but it often induces perceptual distortions, depersonalization, and feelings of spatiotemporal dislocation (Siebert, 1994; Yan and Roth, 2004). Other reports describe derealization

accompanied by brief euphoria (Gonzalez et al., 2006). Although salvinorin A is used recreationally, there is currently no evidence that it is addictive (i.e., used compulsively); notably, humans will take other substances that are aversive in other species, such as lysergic acid diethylamide (LSD). Nonetheless, despite evidence in humans and laboratory animals that KOR agonists should lower mood, there are occasional reports of salvinorin A leading to improved mood and even having antidepressant effects (Hanes, 2003). These seemingly paradoxical effects are not understood, although they may reflect individual differences in brain chemistry, effects of salvinorin A different from those of other selective KOR agonists, or homeostatic-like responses to KOR stimulation (Potter et al., 2008). Until recently there has been little consideration of the potential KOR agonists might have for the treatment of mood disorders.

The idea that KOR agonists could play an important role in the study and treatment of mood disorders is derived from two sets of preclinical studies. Antipsychotic drugs are all potent antimanic agents and all induce activation of similar populations of cells in the NAc (Cohen et al., 1998), regions that may be responsible for mediating many of the symptoms of bipolar disorder. While these studies were performed in rats, similar regional effects of antipsychotic drugs may occur in human subjects (Cohen and Yurgelun-Todd, 2001). Double-label immunohistochemistry identified the cells responding to antimanic/antipsychotic drugs as dynorphinergic/GABAergic neurons (Ma et al., 2003), implying that antipsychotic drugs may increase dynorphin release, leading to an antimanic or mood-lowering effect. The mechanism of this activation of dynorphinergic cells is likely inhibition of multiple monoamine receptors at which antipsychotic drugs are potent antagonists (Ma et al., 2006).

In parallel, the effects of KOR agonists were studied as comparison drugs in experiments designed to evaluate the antidepressant-like effects of KOR antagonists in rats. These studies demonstrated that U69,593 (a selective KOR agonist) increases immobility behavior in the FST (Mague et al., 2003). This effect is identical to that caused by elevation of CREB in the NAc (Pliakas et al., 2001), drug withdrawal (Cryan et al., 2002), or administration of antimanic agents (Tomasiewicz et al., 2006), and opposite of that caused by standard antidepressant drugs. As such, elevated immobility behavior in the FST is a putative indicator of “prodepressive” or mood-lowering effects. U69,593 also elevated ICSS thresholds (Todtenkopf et al., 2004), a prodepressive-like effect similar to that caused by drug withdrawal and antimanic agents (Markou et al., 1992; Tomasiewicz et al., 2006; Carlezon and Chartoff, 2007), and thus is a putative indicator of motivational deficits that often accompany affective disorders. An identical pattern of effects was caused by salvinorin A (Carlezon et al., 2006). When considered together, these molecular and behavior studies are consistent with the conclusion that stimulation of brain KORs causes behavioral signs that closely resemble those that characterize depressive disorders.

Mechanisms

KORs are located throughout the brain (Mansour et al., 1995), including areas such as the mesocorticolimbic system, PFC, amygdala, and septum. All of these areas have been associated with motivation and emotion, and it is easy to imagine that each plays a role in the regulation of mood and affective states (see Nestler and Carlezon, 2006). As described above, our work has tended to focus on the mesolimbic DA system, because of our strong interest in motivated behavior. KORs are expressed throughout the mesolimbic DA system and are located both on dopaminergic neurons within the VTA and on their efferent terminals in the NAc (Svingos et al., 1999; Margolis et al., 2003) (Figure 1). Stimulation of KORs in either region decreases DA function. For example, administration of KOR agonists into the NAc decreases local DA concentrations (Donzanti et al., 1992; Spanagel et al., 1992), most likely by stimulating presynaptic KORs that inhibit DA release from VTA neurons (Svingos et al., 1999). KOR

agonists also have VTA-dependent inhibitory effects on the mesolimbic DA neurons, and both direct and indirect circuits may be involved (Margolis et al., 2003; Margolis et al., 2005; Margolis et al., 2006). Future studies involving brain region-specific microinfusions of KOR selective ligands will determine if stimulation of KORs in these other brain areas synergize with—or counteract—the general prodepressive consequences of systemic administration of KOR agonists (Mague et al., 2003; Todtenkopf et al., 2004; Carlezon et al., 2006).

Complexities

The effects of KOR agonists are not limited to the mesolimbic DA system. They affect other neurotransmitter systems that may be important in regulating mood. Indeed, NE release is reduced by KOR agonists, as studied in rat synaptosomes (Adamson et al., 1989) and rabbit hippocampal slices (Allgaier et al., 1989). In addition, the effects of KOR agonists on monoamine turnover may differ by brain region (Ford et al., 2006).

Although a decrease in DA neurotransmission is the immediate response to KOR agonists, less is known about the consequences of repeated or long-term drug administration. In monkeys, single doses of KOR agonists reduce cocaine intake, but this effect wanes over time (Mello and Negus, 1998). Similarly, acute administration of salvinorin A reduces the locomotor-stimulating effects of cocaine in rats, although these same effects are increased after salvinorin A is given repeatedly and then withdrawn, suggesting the development of tolerance (Chartoff et al., 2008). It is important to note that few KOR agonists are entirely selective and full agonists at KORs. Agents such as U50,488 and U69,593 are not as selective nor do they cause as full an activation of KORs as salvinorin A (Chavkin et al., 2004). Also, both U50,488 and U69,593 cause more KOR internalization than salvinorin A (Wang et al., 2005) or its derivatives (e.g., herkinorin; Groer et al., 2006). Therefore, each of these drugs may activate different intracellular signaling pathways and have different effects with repeated or long-term administration.

Sex, strain, and age differences in response to KOR agonists have also been described in rats (Barrett et al., 2002; Smith and French, 2002), and species differences have been observed with regard to receptor densities (Mansour et al., 1988) turnover of DA in response to KOR agonists (Barber and Gottschlich, 1997; Fantegrossi et al., 2005) and phosphorylation and desensitization of KORs (Li et al., 2002). Lastly, KORs may also exist as components of homomeric and heterodimeric receptor complexes , which may contribute to region-, sex-, and species-specific effects of KOR agonists (see Devi, 2001). Thus caution should to be applied in generalizing between results in rodents, monkeys, and humans.

Chemistry

In the 1980s and 90s, several research programs focused on designing selective KOR agonists as potential treatments for pain. As noted above, such agents were predicted to possess analgesic properties and be free of the side-effects associated with MOR agonists: physical dependence and respiratory depression. Intensive medicinal chemistry efforts at Upjohn led to the identification of arylacetamide analogues as potent KOR agonists. Later, this class of compounds was studied in several other research centers. Examples include U50,488 (Szmuszkovicz and Von Voigtlander, 1982), U62,066 (spiradoline) (Wadenberg, 2003), U69,593 (Lahti et al., 1985), CI-977 (enadoline) (Wadenberg, 2003), and ICI-199441 (Costello et al., 1991) (Figure 3). These compounds are still being used in preclinical studies and a few (e.g., enadoline and spiradoline) entered clinical trials for the treatment of pain or addiction. However, the tendency of KOR agonists to produce dysphoria and other aversive effects prevented their clinical use. Structure-activity relationships have been studied in great detail for the arylacetamides, and KOR antagonist properties have never been reported for any compound belonging to this class of agents.

As is the case with KOR antagonists, many KOR agonists have been derived from morphine. Only a few of these analogues display some degree of selectivity for the KOR. One of them, the 4,5-epoxymorphinan TRK-820 (nalfurafine, Figure 3), is being developed as an antipruritic agent (Kawai et al., 2008).

The neoclerodane diterpenoid salvinorin A (Figure 3) is the main psychotropic component of the ethnobotanical *Salvia divinorum* (Roth et al., 2002;Chavkin et al., 2004). Since its identification as a potent and selective KOR agonist, salvinorin A has been characterized in multiple preclinical studies and it is being modified chemically in several laboratories (e.g., Prisinzano and Rothman, 2008) to alter its pharmacokinetic and pharmacodynamic properties. Salvinorin A is structurally unusual in the sense that it does not possess any protonated sites, a characteristic previously believed to be necessary for interaction with the KOR.

It is important to note that the crystal structure of the KOR has not been determined, making it difficult to model agonist/antagonist interactions with active sites on the receptor. However, structurally distinct full agonists appear to have different effects on secondary signaling pathways, probably due to their interaction with different conformational states of the KOR (Wang et al., 2005).

Potential for Clinical Use

Under some circumstances, the ability of KOR-agonists to decrease DA function in the basal forebrain might have clinical utility, particularly in the treatment of conditions characterized by increased motivation (e.g., drug abuse or mania). Antipsychotic drugs—which are frequently used to treat mania—activate dynorphinergic neurons (Ma et al., 2003). Also, although salvinorin A and other KOR agonists can produce psychotomimetic effects under some conditions (especially at high doses) (Pfeiffer et al., 1986; Bucheler et al., 2005), it is conceivable that administration of a derivative or related compound under more carefully controlled conditions might have useful effects. In this regard, it is notable that the effects of KOR agonists on DA turnover in the mesolimbic system are state-dependent, with reduction of release greatest when DA cells are most active (Manzanares et al., 1991), as they may be in mania or mood elevation.

With these caveats in mind, we examined the possibility that KOR agonists might have mood-normalizing effects for patients in manic episodes of bipolar disorder. The relatively KOR specific agents spiradoline and enadoline were not available for clinical studies, and salvinorin A was not initially chosen for study because it is very short acting and difficult to administer: it is often used by means that achieve absorption from the buccal or nasal mucosa, and is not reliably absorbed following ingestion. Rather, we performed our first studies with commercially available pentazocine, which has been safely given to patients and is approved for pain relief. Pentazocine is nearly a full agonist at KORs, with lower affinity for MORs, at which it is predominantly an antagonist. In an initial open-label study in ten patients with mania, two sequential doses of pentazocine (50 mg, as often used for pain) given two hours apart, reduced manic symptoms transiently but substantially and significantly in each subject without causing notable sedation or affecting concomitant psychotic symptoms (Cohen and Murphy, 2008). While preliminary, these results are consistent with the implications of studies in rats, which suggest that KOR agonists may decrease mood, especially when mood is abnormally elevated. Preclinical studies that model hallmark signs of mania provide complementary evidence that KOR agonists might be useful for treating conditions characterized by increased motivation and hyperfunction of brain reward systems (Tomasiewicz et al., 2008).

Summary

The development of KOR agonists as possible antimanic agents was suggested by the results of parallel studies in rats, one of which observed that clinically used antimanic agents increase the activity of dynorphinergic neurons (Ma et al., 2003), while the other directly documented mood lowering effects of KOR agonists (Carlezon et al., 2006; Tomasiewicz et al., 2008). Further support for this research direction comes from evidence in human subjects that both naturally occurring and synthetic KOR agonists can lower mood with acute dosing (Bucheler et al., 2005; Cohen and Murphy, 2008). Against this background, the finding that pentazocine may reduce manic symptoms is promising. However, these results should not be taken to imply that pentazocine or other KOR agonists will be useful therapeutic agents for the treatment of mania. More work is needed, including controlled blinded trials with repeated dosing to gauge the tolerability and longer term efficacy of this or similar agents.

While most synthetic chemistry has been devoted to developing KOR-specific agonists and antagonists, some agents are or will turn out to be partial agonists or mixed agonist/antagonists. These agents may also be clinically useful, especially in the treatment of bipolar disorder, as they may produce a relatively constant signal through KORs, thereby helping to restrict to a limited range the activity of DA and other monoamine neurons thought to be responsible for regulation of mood. Thus, it is possible that partial agonists will have mood-stabilizing, rather than simply antidepressant or antimanic, effects in patients with bipolar disorder.

4. Conclusions

Psychiatry needs drugs that are safer, act faster, and have fewer side effects. Virtually all existing medications for psychiatric disorders are based on serendipitous discoveries made decades ago (Ressler and Nemeroff, 2000; Manji et al., 2001; Nestler et al., 2002; Nestler and Carlezon, 2006). Despite great effort and expense, the field has not succeeded in developing fundamentally new treatments—with distinct mechanisms of action—for mood disorders. Much current research is “drug-centric” (focusing on the mechanisms by which currently available psychotropic drugs act) rather than “brain-centric” (focusing on the abnormal states that are treated by these drugs). In turn, much of what is believed about the molecular basis of mood disorders is based upon our understanding of the most prominent and immediate effects of standard medications (Nestler and Carlezon, 2006). Regardless of whether KOR ligands are ever utilized in the treatment of mood disorders, the study of endogenous KOR systems has increased our understanding of some of molecular events in the brain that cause dysregulation of mood states. Our findings have contributed to the development of a simple “brain-centric” hypothesis that treatments that reduce the excitability of the NAc elevate mood, whereas treatments that increase its excitability depress mood (Figure 1) (Carlezon and Thomas, 2009). Rigorous tests of this hypothesis will have important implications for our understanding of the biological basis of motivation, which is abnormal in mood disorders. As has been the case with other disease states, understanding how the organs of the body function normally can be the first step toward designing innovative treatments that prevent or reverse the pathophysiology underlying debilitating disorders.

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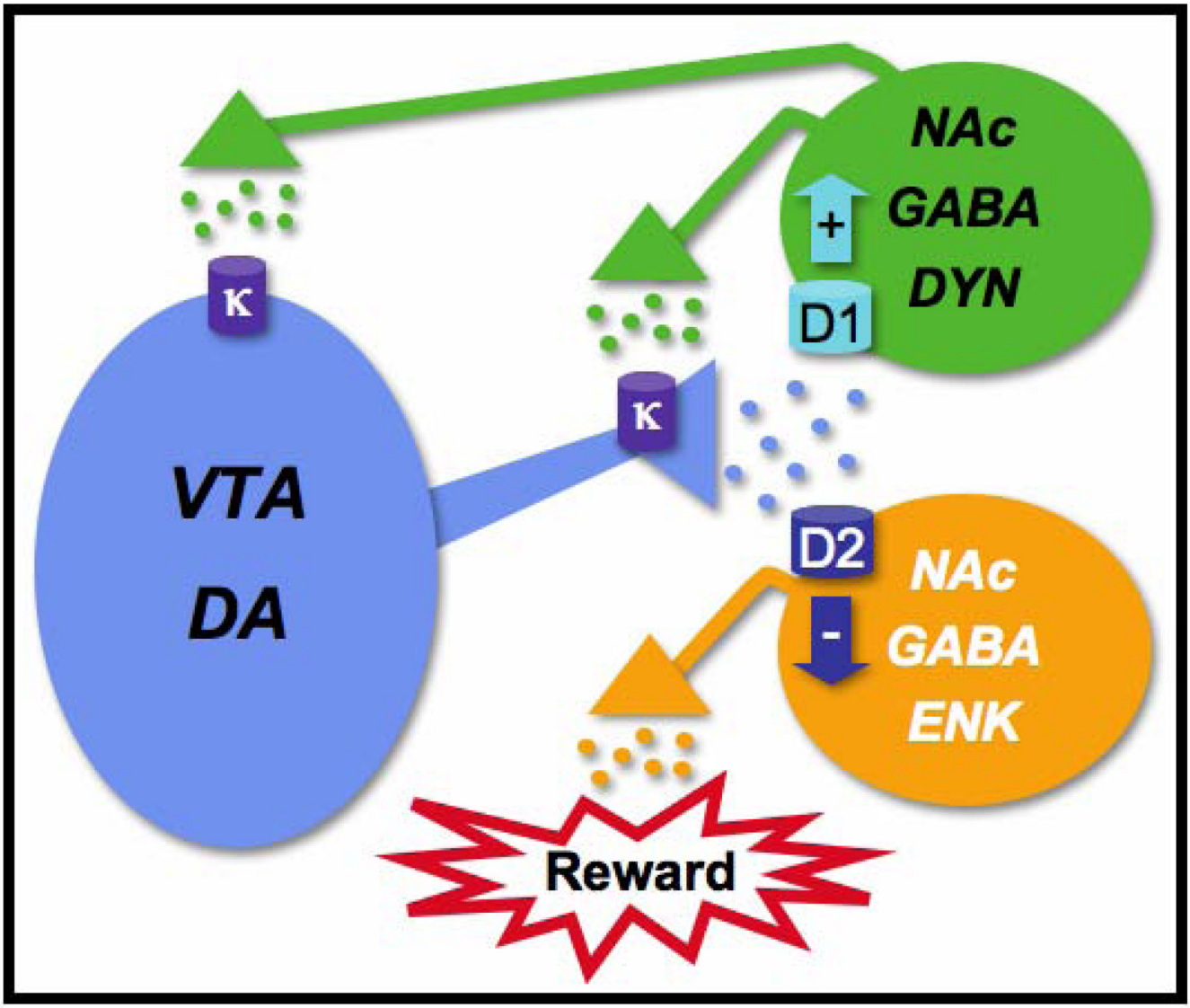

Fig.1.

A highly simplified hypothetical scheme by which kappa-opioid receptors (KORs) in the mesolimbic system might regulate mood. Dopamine (DA) neurons (blue) originating in the ventral tegmental area (VTA) project to the nucleus accumbens (NAc). Within the NAc, DA acts upon two populations of medium spiny (GABAergic) neurons. One type of neuron expresses dopamine D2 receptors and enkephalin (ENK). These neurons (orange) normally inhibit reward; DA binding at D2 receptors activates inhibitory G-proteins (G_i) and decreases the activity of these neurons, which enables reward via processes that might involve outputs to other regions (e.g., ventral pallidum). The other type of neuron expresses dopamine D1 receptors and dynorphin (DYN). These neurons (green) provide feedback regulation of the VTA; DA binding at D1 receptors activates stimulatory G-proteins (G_s) and increases the activity of these neurons. Subsequent increases in DYN-induced stimulation of G_i-coupled KORs would tend to decrease the activity of VTA DA neurons. One consequence of this effect would be reduced D2 receptor function and increased inhibition of reward, causing hallmark signs of depression (e.g., anhedonia, dysphoria). According to this scheme, administration of KOR agonists would produce signs of depression by causing acute reductions in the activity

of VTA neurons, whereas exposure to stress and drugs of abuse lead to CREB-regulated increases in DYN expression and more persistent behavioral effects. KOR antagonists might normalize the function of VTA neurons by preventing overstimulation of KORs, thereby producing antidepressant effects. For additional detail, see Carlezon and Thomas (2009).

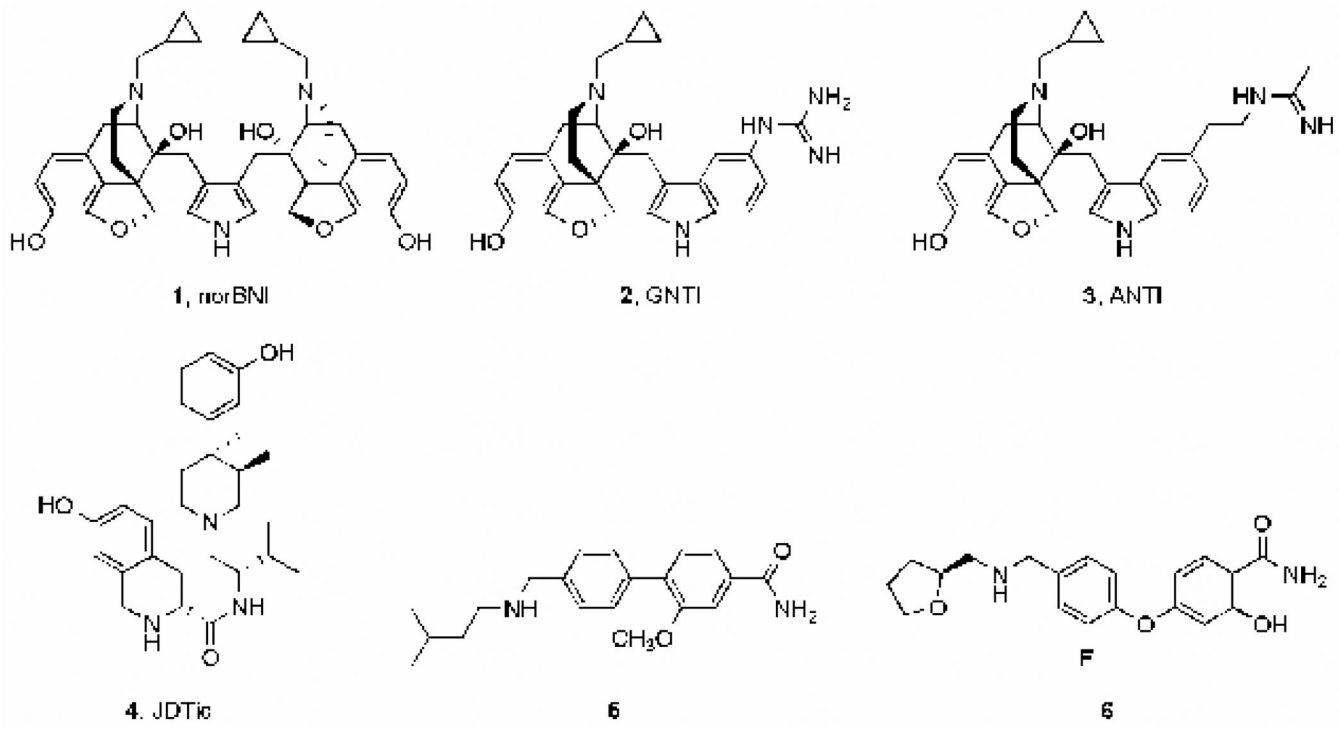

Fig.2.
Selective kappa-opioid receptor (KOR) antagonists.

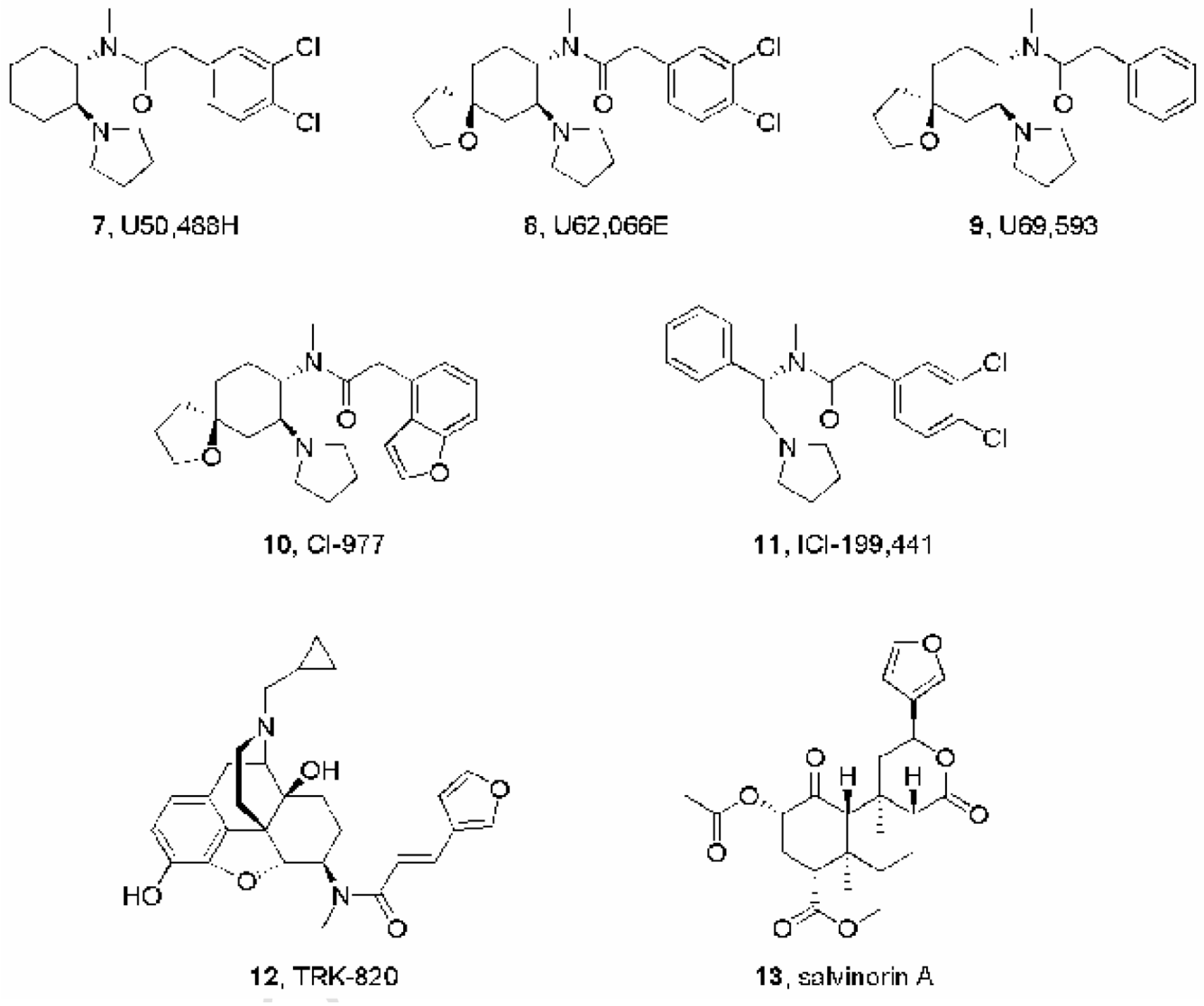

Fig.3.
Selective kappa-opioid receptor (KOR) agonists.