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Kappa opioid receptor signaling in the brain: Circuitry and implications for treatment

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ABSTRACT

Kappa opioid receptors (KORs) in the central nervous system have been known to be important regulators of a variety of psychiatry illnesses, including anxiety and addiction, but their precise involvement in these behaviors is complex and has yet to be fully elucidated. Here, we briefly review the pharmacology of KORs in the brain, including KOR's involvement in anxiety, depression, and alcohol addiction. We also review the known neuronal circuitry impacted by KOR signaling, and interactions with corticotrophin-releasing factor (CRF), another key peptide in anxiety-related illnesses, as well as the role of glucocorticoids. We suggest that KORs are a promising therapeutic target for a host of neuropsychiatric conditions.

1. Introduction: KORs in the central nervous system

Kappa opioid receptors (KORs) and their endogenous ligand, the peptide dynorphin (Chavkin and Goldstein, 1981a,1981b; Chavkin et al., 1982) are at the forefront of potential therapeutic targets for a range of health issues, including anxiety, depression, and drug addiction (Bruchas et al., 2010). Here, we outline current neurobiological research of KORs, focusing on the discrete circuit elements that are regulated by KOR signaling and their role in behavior.

2. Pharmacology

Kappa opioid receptors are seven transmembrane g-protein coupled receptors, coupled to Gαi/o, and are known to utilize a variety of signaling cascades (reviewed in detail, Bruchas and Chavkin, 2010). KORs signal through both Gα and Gβγ subunits, and then activate a host of downstream signaling molecules, thereby activating g-protein gated inwardly rectifying potassium channels (GIRKs), reducing calcium currents, and decreasing cyclic AMP. KORs have been shown to activate both MEK/ERK (Belcheva et al., 2005; Hahn et al., 2010; Kivell et al., 2014a; Li et al., 2012; McLennan et al., 2008; Potter et al., 2011; Yoshizawa et al., 2011) (although some groups do not see significant MEK/ERK activation following KOR activation, see Asensio et al., 2006) and MAPK signaling cascades, and in particular, p38 (Bruchas et al., 2006, 2011; Hahn et al., 2010; Yoshizawa et al., 2011). This KOR interaction with p38 is thought to be mediated by arrestin signaling; co-expression with the dominant-mutant of β-arrestin prevents human KOR internalization in CHO cells (Li et al., 1999). The interaction between p38 and arrestin may mediate the dysorphia-like side effects of KOR agonists (Bruchas et al., 2007), possibly through a reduction in biogenic amine levels (Chefer et al., 2005; Spanagel et al., 1994) such as serotonin, as shown in Bruchas et al. The ability of KORs to signal through different GPCR signaling cascades may prove useful in creating biased agonists at the KOR, allowing for therapeutic treatments for pain or neuropsychiatric illnesses without the unwanted side effects, such as dysphoria and psychomemetic effects observed in humans (Pfeiffer et al., 1986). Interestingly, KORs can utilize different signaling cascades in a single brain region (Hjelmstad and Fields, 2003). Notably, Hjelmstad & Fields demonstrated that while KOR activation inhibits GABA release via a calcium dependent mechanism, it's inhibition of glutamate is calcium-independent. Other groups have similarly demonstrated KOR-mediated inhibition of GABA (Li et al., 2012), but more in-depth assessments of biased KOR signaling in a single brain region have not been conducted. Potent long acting inhibitors of KOR include norBNI (Endoh et al., 1992) and JDTic (Bruchas and Chavkin, 2010). More recently, short acting antagonists such as LY2456302, and the tracer 11C-LY2795050 developed by Eli Lilly and Company have recently emerged (Lowe et al., 2014; Zheng et al., 2013). As KORs may utilize different signaling cascades, understanding this divergent pharmacological mechanisms will not only lead to greater understanding of the role KORs play in an assortment of behaviors and conditions, it will also allow for greater tailoring of pharmacological treatments.

3. Behavior

3.1. Depression

The forced swim test (FST) is a classic screen for depressive phenotypes, and has been used since the 1970s as a way to screen for novel antidepressive drugs (Porsolt et al., 1977). Porsolt et al. first described

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the FST as a measurement of behavioral despair, wherein immobility indicates that the animal is no longer attempting to escape the experimental condition; antidepressants typically reverse this behavior (Castagné et al., 2001) (however, it should be noted that though the FST is effective as a screen for anti-depressants, it was not originally intended as a measurement of an actual depressive phenotype in the rodent). KOR antagonists produce antidepressant like effects in the FST, as measured by a decrease in immobile behavior (Reindl et al., 2008). A variety of studies have shown that administration of the KOR antagonist norBNI leads to decreased immobility in the FST (Carr et al., 2009; Mague et al., 2003). norBNI-induced decreases in immobility and increases in swimming are observed in Wistar Kyoto rats, but not in Sprague Dawleys, highlighting important strain differences (Carr et al., 2010). This effect was also seen when Carr et al. administered norBNI directly into the piriform cortex. The KOR antagonist DIPPA prevented the adenosine-mediated decrease in immobility time in the FST, highlighting how KORs' effect on depressive-like behaviors may involve the moderation of other neurotransmitter systems (Kaster et al., 2007). Therefore, as the KOR system seems to produce a robust phenotype in the FST, this behavioral test may function as a useful screen for future KOR antagonist compound development.

In addition to it's effects on the FST model of depression, KORs are also involved in depressive like states following drug withdrawal. Work from Chartoff et al. has demonstrated that though norBNI alone had no effect on latency to immobility in the FST, norBNI was able to block the cocaine-withdrawal induced decrease in time to immobility (Chartoff et al., 2012). Like norBNI, JDTic has been shown to decrease immobility in the FST, and JDTic also decreased stress-induced reinstatement of cocaine responding (Beardsley et al., 2005). In other behavioral assays related to depression, site specific infusion of the KOR antagonist norBNI in to either the hippocampus and nucleus accumbens was able to prevent the depressive phenotype seen in a learned helplessness paradigm (Shirayama et al., 2004). Consistent with these results, KOR agonists also increase intracranial self-stimulation (ICSS) thresholds, indicating a potential depressive-like phenotype (Todtenkopf et al., 2004).

3.2. Anxiety

Much of the animal literature has focused on KOR-modulation of anxiety related behaviors. A common test for rodent anxiety, the elevated plus maze (EPM), involves letting the rodent explore an apparatus with both closed arms and open exposed arms, with more time spent exploring the open arms being indicative of an anxiolytic phenotype (Pellow and File, 1986). Knoll et al. showed that administration of the KOR antagonist norBNI resulted in an anxiolytic phenotype in the EPM (Knoll et al., 2011). KOR antagonists can also reverse the anxiogenic effects of stress in the EPM (Peters et al., 2011), and similarly, KOR antagonists can reverse the anxiogenic effects of a KOR agonist (Valdez and Harshberger, 2012). These experiments would point to an anxiogenic effect of KOR agonists, and an anxiolytic effect of KOR antagonists. However, some contradictory literature has emerged: administration of the KOR agonist Salvinorin-A increases both open arm time and entries into the open arm of the EPM (Braida et al., 2009). In addition, the KOR agonist U50,4888 can produce anxiolytic effects in the EPM at low doses (10–100 μg/kg) (Privette and Terrian, 1995). These discrepancies may be driven by two important points: first, in the Braida et al., study, Salvinorin-A was used. Salvinorin-A has been shown to utilize the ERK1/2 signaling cascade (Kivell et al., 2014b), and this biased ligand may produce differential behavioral effects as compared to those of other KOR agonists (this hypothesis of differential effects by some KOR agonists is supported by work demonstrating that ICV administration of low, but not high, doses of Salvinorin produces a robust conditioned place preference (Braida et al., 2008)). Similarly, the global anxiogenic effect of KOR agonists may be dose dependent; the conditioned place preference seen by Braida et al., as well as the anxiolytic effect in the EPM seen by Privette & Terrian, were seen at lower doses of KOR agonists that were typically used. This may indicate that KOR agonists do have the potential to be used for therapeutic purposes, but much more research is needed.

Taken together, the literature on KORs and both depression and anxiety provides a mixed and muddled picture at best. Future experiments will need to address the nuances of behavioral effects (such as comparing multiple KOR agonists, and importantly, detailed dose response curves) in order to thoroughly understand the relationship between the dynoprhin/KOR signaling system and depression and anxiety. In addition, circuit and site-specific manipulations, discussed below, provide some clarity as to the convoluted effect seen with systemic administration of KOR agonists. This provides key important information as to how KOR modulation can be used to shift anxiety-related behaviors: both low doses of KOR agonists, as well as KOR antagonists, may prove to be effective.

3.3. Addiction

KORs have been shown to be involved in the consumption, withdrawal, and escalation of a variety of drugs of abuse, such as alcohol (Zhou et al., 2013) heroin (Schlosburg et al., 2013; Sedki et al., 2014) and cocaine (Al-Hasani et al., 2013; Trifilieff and Martinez, 2013b). Despite of an abundance of literature showing KORs to be a promising therapeutic target for the treatment of drug addiction (Hasebe et al., 2004; Wee and Koob, 2010) few drugs impacting the KOR system have been taken to the level of human clinical trials. The KOR antagonist JDTic did reach stage 1 clinical trials for the treatment of cocaine dependence, but the research was terminated due to adverse effects (RTI-International, 2012, May 9). The antagonist LY2456302 has upcoming phase 1 and phase 2 clinical trials for treatment resistant depression, anxiety disorders, and has completed phase 1 clinical trials for alcohol dependence (Massachusetts General Hospital July 30, 2013). The existing animal literature on KORs and addiction, discussed below, should encourage further clinical investigations.

Work on the KOR system and cocaine has shown that activation of KORs can reduce cocaine self-administration (Glick et al., 1995), and the utility of mixed mu/kappa opioid receptor agonists have been shown for the treatment of cocaine dependence (Bidlack, 2014). Administration of both a KOR agonist and cocaine blocks sensitization to the conditioned rewarding properties of cocaine using a conditioned place preference model (Shippenberg et al., 1996). Freeman and colleagues used experimental manipulations in non-human primates to support the hypothesis that this suppression of self-administration and rewarding properties of cocaine may be due to the ability of KOR agonists to punish responding for cocaine (Freeman et al., 2014). In these experiments, monkeys decreased operant responding for either cocaine or remifentanil when paired with the KOR agonist Salvinorin A, highlighting the potential role of the KOR system to curtail drug self-administration. The hypothesized mechanism for KOR-induced changes in cocaine administration and dependence is fairly well established, as KORs are present on dopaminergic terminals and can inhibit dopamine release (Trifilieff and Martinez, 2013a). However, Ehrich, Phillips, and Chavkin (2014) found that KOR activation can potentiate cocaine-induced increases in evoked dopamine release, depending on the timing of KOR activation and cocaine administration (Ehrich and Phillips, 2014). This study emphasizes that while KORs may be a promising target for drug addiction, for cocaine in particular and likely for other drugs as well, timing of the intervention may be crucial. If KOR activation can both increase and decrease drug self-administration based on timing, it is unlikely to be useful for treating addiction (to those particular drugs) in the real world.

KORs have also been implicated in morphine abuse, by interacting with morphine's ability to potentiate dopamine release in the nucleus accumbens via its actions at the mu opioid receptor (MOR) in the ventral tegmental area (Vander Weele et al., 2014). Supporting this

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