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The Brain Dynorphins/Kappa Opioid Receptor (DYN/KOPR) System Plays a Role in Anxiety Regulation

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Our current understanding of the biological basis of anxiety is limited. Research on affective states including anxiety has focused on the roles of the brain gama-aminobutyric acid (GABA) and monoamine (e.g., serotonin, dopamine, norepinephrine) systems. The brain opioid systems have been implicated in the regulation of emotion. In this review, we will focus on the role of dynorphins / kappa opioid receptor (DYN/KOPR) system in anxiety regulation. Recent preclinical research suggests that KOPR antagonists have anxiolytic effects. Together with the roles of this brain system in depression and drug addiction, KOPR is a potential target for new medications.

Key words: dynorphin, kappa opioid receptor, anxiety, anxiolytic, anxiogenic, fear

Abbreviations: BLA (basolateral amygdala), CRF (corticotropin-releasing factor), EPM (elevated plus-maze) DYN (dynorphins), FAAH (fatty acid amide hydrolase), FPS (fear-potentiated startle), GABA(gama-aminobutyric acid), JDTic ((3R)-7-Hydroxy-N-[(1S)-1-[[(3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethyl-1-pipe ridinyl]methyl]-2-methylpropyl]-1-,2,3,4-tetrahydro-3-isoquinoline-carboxamide), KOPR (kappa opioid receptor), norBNI (nor-binaltorphimine), OF (open field), PAG (periaqueductal gray), U50,488H ((trans)-3,4-Dichloro-N-methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]benzeneacetamide)

INTRODUCTION

DYN bind to all three (mu, delta and kappa) opioid receptors but show a preference for KOPR.[1-3] DYN and KOPR are expressed throughout limbic brain areas implicated in stress and emotional responses, including basolateral amygdala (BLA), central amygdala and bed nucleus of the stria terminalis.[4-6] DYN/KOPR system has long been hypothesized to mediate negative emotional states. For example, KOPR agonists were reported to produce dysphoric and psychotomimetic effects in humans by Pfeiffer et al.[7] and conditioned place aversion in animals.[8] The roles of DYN/KOPR system in depression,[9] stress responses[10] and drug addiction[11] have been reviewed. Although a KOPR agonist was shown to increase anxiety in humans more than twenty years ago,[7] the role of DYN/KOPR system in anxiety has been largely unknown until recently. These recent findings summarized below were based on rat or mouse models of anxiety, among which the elevated plus-maze (EPM) test (see[12,13] for reviews) is the most commonly used.

The effects of KOPR antagonists

Several groups have demonstrated that KOPR antagonists reduced anxiety-like behaviors in rat and mouse models. Knoll et al.[14] were the first to report that KOPR antagonists affected anxiety/fear-like behaviors. The animal models they used were unlearned fear (anxiety) in the elevated plus maze (EPM) and open field (OF) paradigms and learned fear in the fear-potentiated startle (FPS) paradigm. Rats received an i.p. injection of the selective KOPR antagonist norBNI (3.0-30 mg/kg) or JDTic (1.0-10 mg/kg), both of which are known to have very long durations of action. One day later, they were tested in the OF; two days later, EPM testing was performed; 5 and 7 days later, they were trained and tested in the FPS paradigm. Both KOPR antagonists dose-dependently increased open arm exploration in the EPM without affecting the OF behavior. They also decreased conditioned fear in the FPS paradigm. The anxiolytic-like effects of KOPR antagonists were qualitatively similar to those of the benzodiazepine chlordiazepoxide in the EPM. Based

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on their previous data on depression, Knoll et al.[14] suggested that KOPR antagonists produce a unique combination of antidepressant- and anxiolytic-like effects and that this class of drugs may be particularly effective for the treatment of comorbid depressive and anxiety disorders. Wittmann et al.[15] reported that the KOPR antagonists GNTI or norBNI showed anxiolytic effects in mice. The KOPR antagonists was not effective at 1 h, but was fully effective at 48 h after injection. Bruchas et al.[16] reported that central corticotropin-releasing factor (CRF) administration significantly reduced the percent open-arm time in mice in the EPM via the CRF1 receptor and this effect was blocked by pretreatment with the KOPR antagonist norBNI. Local injection of norBNI into BLA blocked stress- or CRF-induced increase in anxiety-like behavior, whereas norBNI injection in a nearby thalamic nucleus did not.[16] The results indicate that stimulation of the DYN/KOPR system in the BLA of the mouse brain downstream of CRF1-receptor activation mediates anxiety-like behavior. Methylphenidate exposure increased anxiety-like behaviors in rats in the EPM, and these behavioral effects were normalized by norBNI treatment.[17] Central administration of norBNI induced a decrease of the fear-like responses evoked by electrical stimulation of the inferior colliculus in rats.[18] The cannabinoid agonist CP 55,940-induced anxiogenic-like effect was antagonized by norBNI.[19] In addition, in the EPM, the anxiety-like effects of morphine microinjected into the dorsal PAG were significantly reduced by systemic administration of norBNI.[20]

The DYN/KOPR system has been proposed to be a target for the treatment of drug addiction (see[11,21,22] for reviews). The role of this system has also been investigated recently using the KOPR antagonists in the opiate and nicotine abstinence-induced anxiety-like responses,[23,24] a common affective component of withdrawal from various drugs of abuse.[22] In rats withdrawn from chronic morphine treatment, norBNI promoted anti-fear effects when injecting in the dorsal periaqueductal gray (PAG) and inferior colliculus.[23] JDTic and norBNI attenuated the expression of both the physical (somatic signs and hyperalgesia) and affective (anxiety-related behavior and conditioned place aversion) signs of nicotine withdrawal in the mouse.[24]

Thus, all the findings summarized above demonstrated anxiolytic effects of KOPR antagonists. However, there is one report showing that the anxiolytic effect of diazepam in mice was significantly abolished by pretreatment with norBNI.[25]

The effects of KOPR agonists

The benzomorphan KOPR agonist MR 2033 was shown to increase anxiety in humans more than twenty years ago.[7] However, the effect of KOPR agonists on anxiety-like behaviors in animals has been a matter of debate.

Dynorphin A caused a significant anxiogenic effect in mice following i.c.v injection and in rats after microinjection into the BLA.[26] Wittmann et al.[15] reported that prodynorphin knockout mice showed lower levels of anxiety-like behaviors than the wildtype animals (see section 5) and a two-day treatment with the selective KOPR agonist U50,488H [(2.5 mg/kg) at 48 h and then 24 h before testing] fully reversed the anxiolytic phenotype of the knockout mice. However, a single injection of 2.5 mg/kg U50,488H 30 min (a time point most commonly used in other studies cited in this section) before testing did not affect the difference between the genotypes.[15] Methylphenidate exposure increased anxiety-like behaviors in the EPM in rats, and these behavioral effects were intensified by U50,488H at 5 mg/kg.[17] In addition, U50,488H administered into dorsal PAG induced anxiety-like behaviors in the EPM, which were antagonized by i.p. norBNI.[27]

In contrast, the KOPR agonists U50,488H and U69,593 at low doses (10-1000 g/kg, i.p.) have been reported to reduce anxiety-like behaviors in the EPM in rats.[28] In addition, U50,488H at 2.5 mg/kg produced an anxiolytic effect in mice pre-injected with normal saline, but had no effect in animals chronically injected with cocaine.[29] Another study in mice showed that in losers with repeated experience of social defeats, U50,488H at 0.6, 1.25, and 2.5 mg/kg reduced anxiety-like effects in the EPM and partition tests in a dose dependent manner, whereas winners with repeated experience of victories hardly responded to U50,488H.[30] It should be noted that in both tests the losers had higher basal anxiety levels than the controls and winners.[30] Salvinorin A, a KOPR agonist with hallucinogenic and psychedelic/dissociative effects, given s.c. (0.001-1000 g/kg), exhibited both anxiolytic- and antidepressant-like effects that were prevented by norBNI in mice and/or rats.[31] Salvinorin A induced a significant inhibition of fatty acid amide hydrolase (FAAH) activity in the amygdala, which may significantly elevate the level of anandamide, an endogenous cannabinoid in brain, and thereby account for the anxiolytic effects of salvinorin A. How salvinorin A alters FAAH activity is unclear as is the connection between decreased FAAH activity and KOPR-mediated responses.[31]

Thus, how KOPR agonists affect anxiety-like behav-

iors may depend on (1) the treatment period and the dose of the KOPR agonist, (2) the basal level of anxiety of the animal, which may be affected by repeated saline injections or other handling (winner/looser) paradigms prior to the behavioral test, and (3) the agonist-specific effects, e.g. salvinorin A, which has KOPR-mediated and/or non-KOPR-mediated actions.

The effects of prodynorphin or KOPR gene disruption

Prodynorphin knockout mice were reported to have a reduction in anxiety-like behaviors.[15,16] Wittmann et al.[15] showed that mice lacking prodynorphin had 2-4-fold decreases in anxiety parameters of exploratory behavior in the OF, the EPM and the light-dark tests. These knockout mice were backcrossed onto the C57BL/6N background over 8-10 generations.[15] These behavioral manifestations were accompanied by an approximately 30% reduction in CRF mRNA expression in the hypothalamic paraventricular nucleus and central amygdala and a concomitant 30-40% decrease in serum corticosterone levels in prodynorphin knockout mice. Bruchas et al.[16] reported that central CRF administration significantly reduced the percent open-arm time in the EPM, indicative of anxiogenic effect, in the wildtype mice, but not in mice lacking prodynorphin. The mice were backcrossed onto the C57BL/6 background over 10 generations.[16]

In contrast, prodynorphin knockout mice, crossed more than 10 generations to C57BL/6J mice, were reported to have an increase or no change in anxiety-like behaviors.32 Moreover, KOPR null mice with a hybrid 129 SV/C57BL/6 (50%/50%) genetic background exhibited no change in anxiety-like behaviors.[33,34]

The discrepancy in the phenotypes of knockout mice may be due to (1) the expression of functional redundancy (i.e., compensation) of effects of the missing protein, which is the most commonly cited disadvantage of using gene knockout models for the study of physiological processes, (2) variations in the genetic background of the generated mouse population, which is one of the most influential factors on the phenotype of a gene knockout model.

SUMMARY

The vast majority of studies have demonstrated that KOPR antagonists have anxiolytic effects in the mouse and rat models of anxiety. This supports the hypothesis that the DYN/KOPR system in the brain plays an important role in the anxiety-like responses to stress. However, studies on KOPR agonists and on prodynorphin or KOPR knockout mice did not always corroborate the statement. The discrepancy suggests that (1) there may be agonist dosing regimen-dependent, animal basal anxiety-related and other agonist-specific differences in the behavioral responses to KOPR activation, (2) the gene disruption-associated compensatory changes during development may mask the role of the gene in the adult state, and (3) the prodynorphin or KOPR knockout mice with varying strain backgrounds may yield different anxiety-related phenotypes.

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