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# Neuropathic Pain Alters Reward and Affect via Kappa Opioid Receptor (KOR) Upregulation

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## Abstract

The kappa opioid receptor (KOR) is crucial for the regulation of mood and reward pathways in the brain. Activation of this receptor with endogenous ligand dynorphin or KOR agonists can lead to dysphoria in humans. It is hypothesized that chronic neuropathic pain leads to a decreased dopaminergic tone within the mesocorticolimbic pathway, which could induce depression, insomnia, anxiety, demotivation, and anhedonia. In this study, we aimed to determine the role of KOR signaling on the negative affective component of neuropathic pain.

We produced neuropathic pain (NP) in adult C57/BL6 male mice by implanting a polyethylene cuff around their left sciatic nerve. Using qRT-PCR analysis, we found that NP mice exhibited significant increases in dynorphin and KOR gene expression in the prefrontal cortex (PFC), nucleus accumbens (NAc), and amygdala when compared to sham counterparts. Furthermore, we observed increased KOR protein availability and activation in NP mice via phosphorylated KOR immunoblotting of brain tissue punches and agonist-stimulated [$^{35}$S]GTPγS autoradiography of coronal brain slices, suggesting a link between KOR and the resulting decrease in dopamine levels within these regions. To understand the functional consequences of the increase in KOR expression and activity, we tested the effects of KOR antagonist on pain induced affective like behaviors. NP mice also displayed negative affect symptoms such as increased anxiety in the light-dark test and increased depression in the forced swim test when compared to sham surgery mice. When NP mice were given the KOR-specific antagonist, JDTic, these symptoms were attenuated.

These results demonsrate that neuropathic pain increases the expression and activation of KOR, which subsequently leads to decreased dopamine release in brain regions important for reward and affect. This mechanism contributes to negative affect in chronic pain, and that inhibiting KOR activity can reduce the symptoms, thereby suggesting a novel therapeutic to treat chronic pain.

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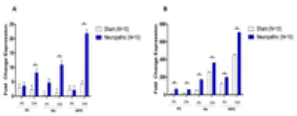

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Figure 1

Brains from sham and 8-week neuropathic mice (10 per group). The brains were snap-frozen and sectioned at 150 µm sections. Brain tissue

punches (1 mm diameter) were taken from ipsilateral (IPSI) and contralateral (CON) hemispheres of the prefrontal cortex (PFC), nucleus accumbens (NAc), and amygdala (AMYG). Total RNA was collected for qRT-PCR analysis on (A) dynorphin and (B) KOR gene expression. The results represent relative fold change expression levels compared to B-actin housekeeping gene controls. N= 10 per surgery group. Histogram values represent means ± SEM. The results were analyzed using two-way ANOVA with Bonferroni multiple comparisons. *P<0.05 comparing Sham vs. Neuropathic.

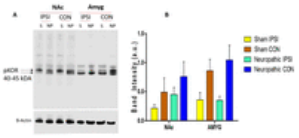

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Figure 2

Brain tissue punches (1 mm diameter) from ipsilateral (IPSI) and contralateral (CON) hemispheres of the nucleus accumbens (NAc) and amygdala (AMYG) were taken from adult male sham and neuropathic pain mice 14 days post-surgery. Total membrane protein was collected for western immunobloting on activated phosphorylated KOR (pKOR). (A) Representative western blot of pKOR with B-actin loading controls. (B) Quantitative analysis of all samples probed for pKOR. The resulting blot band intensities were normalized to B-Actin. N= 4 per surgery group. Histogram values represent means ± SEM.

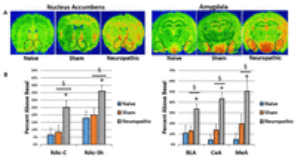

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Figure 3

Agonist-stimulated GTPγS autoradiography was conducted on brain slices collected from naïve, sham, and 2-week neuropathic adult male mice. The brains were snap-frozen, sliced at 20 µm sections, and processed via GTPγS assay on slides. The slides were exposed on film for 2 days, and subsequently analyzed using MCID software. The results depict KOR availability and activity. (A) Representative digital color-coded autoradiograms of brain sections containing nucleus accumbens and amygdala. (B) Quantitative comparison of naïve, sham, and neuropathic brains (N=8 per group) for nucleus accumbens core (NAc-C), shell (NAc-Sh), basolateral amygdala (BLA), central nucleus of the amygdala (CeA), and medial amygdala (MeA). Histogram values represent means ± SEM. Results were analyzed by 1-Way ANOVA within each brain region with Bonferroni Multiple Comparisons. *P<0.05 comparing Naïve vs. Neuropathic, §P<0.05 comparing Sham vs. Neuropathic.

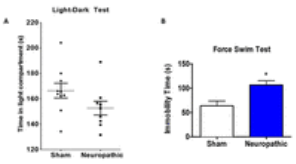


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Figure 4

Behavior tests were conducted on adult male sham and neuropathic pain mice 8 weeks post-surgery (N=10 per group). (A) Light-dark test was used to measure anxiety-like behaviors by quantifying total time in light compartment. (B) Force swim test was used to measure depressive-like behaviors by quantifying total immobility time. Statistical analysis was conducted with a Student's t-test between sham and neuropathic groups. Histogram values represent means ± SEM. *P<0.05.

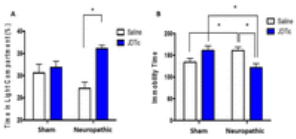


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Figure 5

Behavior tests were conducted on adult male sham and neuropathic pain mice 1 week post-surgery, in the presence or absence of highly KOR-specific antagonist JDTic (N=8 per group). (A) Light-dark test was used to measure anxiety-like behaviors by quantifying total time in light compartment. (B) Force swim test was used to measure depressive-like behaviors by quantifying total immobility time. Statistics analysis was conducted using 2-way ANOVA with Bonferroni multiple comparisons. Histogram values represent means ± SEM. *P<0.05.

## Footnotes

This abstract is from the Experimental Biology 2016 Meeting. There is no full text article associated with this abstract published in The FASEB Journal.