The dynorphin/kappa opioid receptor system: a new target for the treatment of addiction and affective disorders?

Over twenty years ago, kappa-opioid receptor (KOPr) agonists were reported to produce dysphoric and psychotomimetic effects (Pfeiffer *et al*, 1986). In contrast to μ-opiate receptor (MOPr) agonists, KOPr agonists function as negative reinforcers, producing conditioned aversive effects. These findings and the demonstration of antidepressant effects of buprenorphine, a MOPr/KOPr antagonist (Emrich *et al*, 1982) prompted Herz and colleagues to hypothesize that opposing endogenous opioid systems regulate emotional and perceptual experience (Pfeiffer *et al*, 1986). Until recently, studies addressing this issue have been lacking. However, in the last decade, it has become apparent that functionally opposing KOPr and MOPr systems regulate the activity of dopamine (DA) neurons within the brain's motive circuit. Furthermore, studies in experimental animals suggest that manipulations that decrease the activity of KOPr systems may be effective in the treatment of depression and drug addiction.

The KOPr and the endogenous KOPr ligand dynorphin are enriched in the ventral tegmental area, nucleus accumbens (Acb), and prefrontal cortex; brain regions that regulate mood and motivation. Neurochemical and electrophysiological data have shown that KOPr activation in these regions decreases DA transmission. KOPr deletion or blockade of KOPr in the Acb increases basal DA release indicating the existence of a tonically active KOPr system that inhibits basal mesoaccumbal neurotransmission (review: Shippenberg *et al*, 2007).

Decreased mesoaccumbal DA transmission is implicated in certain symptoms of depression and several medications with proven antidepressant efficacy in humans are selective DA uptake inhibitors. Withdrawal from repeated cocaine use is associated with dysphoria and anhedonia. These consequences of drug use are thought to contribute to the compulsive drug seeking and taking that characterizes addiction. Prodynorphin gene expression and dynorphin tissue levels are elevated in individuals with a history of psychostimulant abuse (Hurd and Herkenham, 1993). Given the dysphoric and inhibitory effects of KOPr agonists on DA transmission, these findings suggest that upregulation of KOPr/DYN systems may not only lead to certain forms of depression but to the 'cocaine crash' that characterizes withdrawal. Consistent with this idea, Nestler and Carlezon (2006) showed that KOPr agonists and CREB-mediated induction of Acb dynorphin produce pro-depressant-like effects in rodents whereas KOPr antagonists produce antidepressant-like effects. Rodent studies have shown that KOPr antagonists attenuate stress-induced reinstatement of cocaine-seeking (Beardsley *et al*, 2005) and stress-induced potentiation of the conditioned rewarding of cocaine (McLaughlin *et al*, 2003). These findings are noteworthy and have prompted the phase I testing of KOPr antagonists for the treatment of addiction (DIH/DIDA Division of Pharmacotherapies and Medical Consequences of Drug Abuse). However, many questions remain unanswered. KOPr antagonists attenuate stress-induced reinstatement of cocaine seeking. Yet, they do not alter cocaine seeking produced by other stimuli (eg environmental cues; drug reexposure) that precipitate relapse in humans. As drug abstinence produces time-related alterations in brain chemistry, evaluation of the effects of KOPr antagonists at various stages of the addiction cycle is needed. If as has been suggested, KOPr systems serve an essential role in opposing the rewarding effects of cocaine, then administration of KOPr antagonists to individuals not yet abstinent from cocaine could exacerbate drug taking. Advances in our understanding of KOPr system plasticity will provide important insights regarding the role of opioid peptides systems in normal brain function and various psychiatric disorders.

Toni S Shippenberg[1]

[1]Integrative Neuroscience Section, NIH/NIDA Intramural Research Program, Baltimore, MD, USA
E-mail: tshippen@intra.nida.nih.gov

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Protein–protein interactions as therapeutic targets in neuropsychopharmacology

Protein–protein interactions between membrane-localized receptors and intracellular signaling molecules control neuronal function and theoretically provide a rich source of vastly overlooked targets for drug discovery in neuropsychopharmacology. But, unlike the well-defined binding pocket