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.

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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

of transporters and receptors, the flat, expansive, and adaptive topology of the protein–protein interface presents a sizeable challenge to the goal of identifying small molecules that result in a gain or loss of function of the protein complex. This is offset by the growing body of evidence to suggest that a few amino acids at the interface ('hot spot') contribute to the majority of the binding energy in protein–protein interactions suggesting that modulators with a high degree of specificity could be developed. Furthermore, recent advances in screening technologies and accessibility to an ever-increasing diversity of small molecules suggest that protein–protein interactions are a viable option for drug discovery (Simeonov *et al*, 2008; Wells and McClendon, 2007).

Much of the groundwork to suggest that targeting 'hot-spots' could result in either loss or gain of cellular function is found in the cancer field (Simeonov *et al*, 2008; Wells and McClendon, 2007). For example, the interaction between the C-terminal domain of the breast cancer gene 1 (early onset; BRCA1) protein and BRCA1-associated carboxyl terminal helicase (BACH1) protein is essential for DNA damage-induced checkpoint control. A competitive, high-throughput assay has allowed the identification of small molecule BRCA1-BACH1 inhibitors, which are currently being validated in cell-based assays and ultimately in preclinical studies to improve the efficacy of breast and ovarian cancer therapeutics (Simeonov *et al*, 2008).

Protein–protein interactions also hold promise as a target for medications development in neurology and psychiatry. Bertaso *et al* (2008) found that uncoupling of the metabotropic glutamate receptor 7a (mGluR7a) from protein interacting with kinase 1 (PICK1) is sufficient to induce absence seizures in rodents. A small molecule enhancer of this protein–protein interaction would be predicted to provide therapeutic potential for epilepsy. Therapeutic potential also may exist in the disruption of protein–protein interactions with the serotonin 5-HT_{2C} receptor (5-HT_{2C}R), an important protein in normal and abnormal psychiatric states (Bubar and Cunningham 2008). The 5-HT_{2C}R interacting protein multiple PDZ (MPDZ) domain protein encodes the first *bona fide* quantitative trait gene underlying physical dependence to abused drugs (Shirley *et al*, 2004). A small molecule inhibitor of the 5-HT_{2C}R-MPDZ interaction could alter downstream signaling associated with this receptor. Small peptide inhibitors of the 5-HT_{2C}R-MPDZ interaction have been developed (Sharma *et al*, 2007) but have yet to be tested for their ability to alter addiction-(or psychiatric-)relevant phenotypes. Thus, 5-HT_{2C}R protein–protein interactions represent a fruitful ground for the rational development of small molecular inhibitors to treat psychiatric illnesses.

A third example is the intracellular scaffolding protein Homer. Homer proteins form a network, which brings together key signaling molecules at the postsynaptic density (eg, mGluR5 and NMDA receptors) to regulate intracellular calcium cascades. Homer-2 expression critically regulates the responses to cocaine and alcohol (Szumlinski *et al*, 2008) probably through disruption of protein–protein interactions in which it participates. The design of small molecule inhibitors of Homer protein–protein interactions also holds promise for novel pharmacotherapies in psychiatry.

We are just beginning to appreciate the relationship between protein–protein interactions and neuronal function. Targeting protein–protein interactions has great therapeutic potential as noted in the above examples. Making these interactions 'druggable' is a critical challenge in the development of new treatments for psychiatric and neurological disorders. Thus, mining protein–protein interactions is opening the way for a paradigm shift in drug discovery efforts to identify new therapeutics for neurological and psychiatric disorders.

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Promise of mGluR2/3 activators in psychiatry

The group II metabotropic glutamate receptors (mGluRs), mGluR2 and mGluR3, have emerged as exciting and well-validated targets for novel therapeutic agents used for treating psychiatric disorders. A large number of preclinical and clinical studies provide strong evidence that mGluR2/3 agonists may provide a novel approach to treatment of anxiety disorders and