Previous work indicated that hypothalamic BDNF participates in homeostatic processes that preserve energy levels essential for survival. Recently, we demonstrated an intimate involvement of BDNF in the regulation of hedonic feeding via the positive modulation of the mesolimbic dopamine pathway (Cordeira *et al*, 2010). This neural circuit mediates motivated and reward-seeking behaviors, including consumption of palatable food, and has well-established roles in drug addiction. Mice with selective deletion of *Bdnf* in the ventral tegmental area (VTA), a principal source of mesolimbic BDNF, consumed significantly more palatable high-fat food than control mice, while exhibiting normal intake of standard chow. Furthermore, evoked release of dopamine by mesolimbic fibers in the nucleus accumbens was diminished in mice lacking central BDNF, suggesting decreased VTA dopamine neuron activity and concomitant reductions in neurotransmitter release. It was proposed previously that hypoactivity of the mesolimbic system might result in reward deficiency syndrome and, behaviorally, in compensatory overeating to enhance a deficient dopaminergic system. In support of this model, hyperphagic leptin-deficient mice were also reported to have reduced evoked dopamine release in the nucleus accumbens (Fulton *et al*, 2006). Moreover, we found that administration of a dopamine-1 receptor agonist abrogated overeating in BDNF mutant mice. The results argue strongly that BDNF is a natural modulator of hedonic food intake and that dysregulation of BDNF signaling in the reward circuitry increases the drive to eat in the absence of a homeostatic requirement.

BDNF facilitates synaptic sensitization of VTA dopamine neurons following cocaine withdrawal, which might represent a mechanism mediating cue-associated drug craving and relapse (Pu *et al*, 2006). Many questions remain regarding the effects of BDNF on excitability within the VTA during food reward-related processes. For example, does BDNF facilitate forms of synaptic plasticity in the VTA necessary for food reward learning? Does deficient BDNF signal affect the firing rate of dopamine neurons and impede transitions to burst firing and subsequent dopamine release during food reward-related processes? A better understanding of the cellular and molecular mechanisms underlying the anorexigenic effects of this pleiotropic neurotrophin will facilitate the development of novel therapies for appetitive disorders.

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DISCLOSURE

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The Therapeutic Potential of κ-Opioids for Treatment of Pain and Addiction

When the κ-subtype of opioid receptor was first distinguished, there was tremendous interest in developing analgesics that would provide pain-relief without activating the reward pathways stimulated by morphine-like μ-opioids. A nonaddictive opioid has been a holy grail of medicinal chemistry ever since Friedrich Serturner isolated morphine from opium in 1804. Selective κ-agonists were developed, but quickly found to produce different problems including dysphoria, diuresis, and constipation. In addition, their maximal analgesic effects were weaker than μ-opioids in rodents. But interest in κ-opioids as therapeutic tools did not completely die; Shippenberg and colleagues found that κ-agonists reduced the rewarding effects of co-administered addictive drugs; κ-opioid analgesia using pentazocine was seen as an alternative for pain control in people with a risk of drug abuse; and κ-agonists entered clinical trials for the treatment of pain and itch (see Millan, 1990).

Although enthusiasm for agonists waned, interest in κ-antagonists as therapeutic tools got a boost when Carlezon and colleagues showed their activity in the forced swim assay, predictive of antidepressant activity (Mague *et al*, 2003). Following on that study, we reported that κ-antagonism blocked stress-induced potentiation of cocaine reinforcement (McLaughlin *et al*, 2003). Numerous studies have replicated and extended those findings showing the utility of κ-antagonists to block stress-induced reinstatement of extinguished cocaine- and ethanol-seeking, block μ-opioid and cannabinoid withdrawal signs, and block the aversive effects of nicotine. All these effects of κ-antagonists can be attributed to block of the actions of endogenous dynorphins, which are κ-selective opioid peptides released during the stress response (Land *et al*,

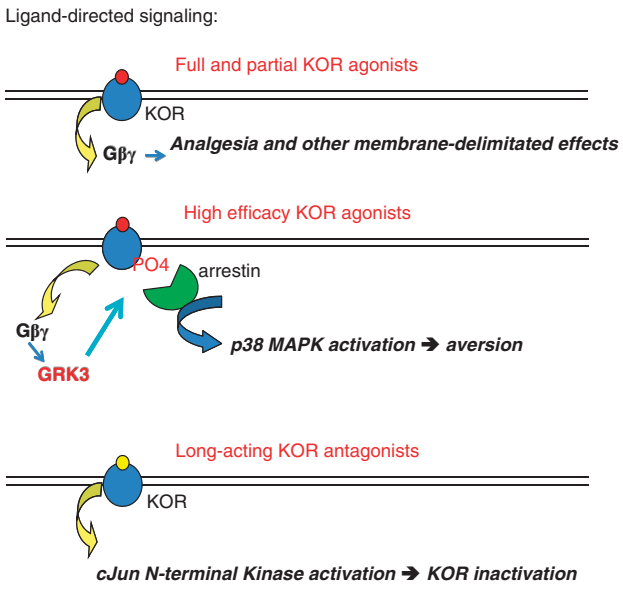

Figure 1. Three possible forms of ligand-directed signaling are illustrated.

2008). Consistent with the dysphoric effects of κ-agonist drugs and natural κ-opioids isolated from the plant *Salvia divinorum*, endogenous dynorphins encode a component of the anxiogenic and dysphoric responses to stressful experience.

Thus, κ-opioid antagonists show promise as therapeutic tools to promote stress resilience that may be effective in treating certain forms of anxiety, depression, and addiction disorders, as stress-hypersensitivity exacerbates each of these syndromes. However, selective κ-opioid antagonists have been known since their initial development by Portoghese and Takemori more than 20 years ago to have remarkably long durations of action. Although this property might be considered a therapeutic advantage (as infrequent dosing may be sufficient and missed doses would be less concerning), the lack of understanding of its basis has slowed drug development. We recently reported (Bruchas *et al*, 2007; Melief *et al*, 2010) that the long action was not a result of κ-receptor downregulation or drug persistence, but rather that these ligands were not truly competitive antagonists; instead their effects were caused by the activation of c-Jun N-terminal kinase (JNK) following κ-receptor binding (Figure 1). We think that JNK activation phosphorylates a component of the κ-receptor signaling complex, thus preventing G-protein activation and causing long-lasting receptor inactivation. This mechanism predicts that low-efficacy ligands that bind to κ-receptors without activating JNK may be short-acting antagonists. Conventional, competitive κ-antagonists may more easily gain approval.

The therapeutic promise of κ-agonists has also been recently revived by studies showing that their dysphoric effects require activation of G-protein receptor kinase, arrestin recruitment and subsequent p38 MAPK activation, whereas their analgesic effects do not (Bruchas and Chavkin, 2010). As evident from ligands initiating μ-opioid signaling, some analgesic opioids including fentanyl effectively recruit arrestin, whereas morphine is an excellent analgesic, but does not recruit arrestin. The realization that different agonists binding to the same receptor can produce different actions has been variously called 'biased agonism', 'functional selectivity', and 'ligand directed signaling' (see Melief *et al*, 2010). On the basis of this concept, an analgesic κ-opioid that did not recruit arrestin might not produce dysphoria (Figure 1). A formulation of such a ligand, combined with a peripherally restricted κ-antagonist to block the constipating and diuretic effects, might result in the long-sought non-addictive opioid analgesic. These are exciting times in the κ-world.

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New Treatments in Amyotrophic Lateral Sclerosis

Identification of New ALS Relevant Genes and Animal Model Development

For the past 15 years, the field of amyotrophic lateral sclerosis (ALS) pathophysiology and drug development has largely been dominated by