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Orexin/hypocretin in psychiatric disorders: present state of knowledge and future potential

The orexins (or hypocretins) are hypothalamic neuropeptides involved in the regulation of a variety of complex behaviors, ranging from feeding to sleep and arousal (Adamantidis and de Lecea, 2009). Recent evidence has shown that these peptides can modulate the mesocorticolimbic dopamine circuit, and thus they have also been implicated in the pathology of numerous psychiatric disorders, including schizophrenia, depression, and addiction. Orexin-containing neurons constitute a small population of lateral and perifornical hypothalamic neurons, but project widely throughout the brain, including a substantial projection to the ventral tegmental area (VTA), a region involved in motivation and reinforcement processes. Hence, orexin can modulate dopaminergic firing, enhance synaptic transmission, and increase dopamine release in target areas of VTA neurons, such as the nucleus accumbens and the prefrontal cortex.

The potential links between orexin and schizophrenia or depression have only recently been explored. Preclinical data suggest that certain neuroleptic drugs associated with weight gain can activate orexin neurons (Deutch and Busber, 2007), suggesting a secondary target for the drugs' actions. Furthermore, in patients suffering from schizophrenia, cerebrospinal fluid levels of orexin A are lower in those treated with neuroleptic drugs. Thus, the orexin system may be a potential target for the side effects of neuroleptic drugs and a promising candidate for pharmacological treatment in schizophrenia. Depression is associated with sleep disturbances and circadian abnormalities. Dampened diurnal variations in orexin have been observed in depressed subjects (Salomon *et al*, 2003). Although diminished orexin signaling does not recapitulate the full spectrum of symptoms observed in depression, orexin signaling appears to be involved in the antidepressant-like effect of calorie restriction (Lutter *et al*, 2008). This raises the interesting possibility that orexin receptor agonists, which are currently in development for narcolepsy treatment, may also have antidepressant-like activity.

Evidence supporting the central role of orexin in drug reward and addiction is abundant (reviewed in Bonci and Borgland, 2009). In preclinical studies, blockade of orexin signaling has been shown to sufficiently inhibit two main behaviors defining addiction: motivated drug seeking and relapse. Orexin neurons are activated by preference to a context associated with drug intake. Furthermore, orexin receptor 1 antagonists block stress- or cue-induced reinstatement of extinguished cocaine or ethanol seeking, as well as high-fat food, ethanol, and nicotine self-administration. However, the antagonists do not block self-administration of cocaine, water, or food, suggesting that the effects of orexin signaling on self-administration of natural or drug rewards may be specific to the qualities of the reinforcer (Bonci and Borgland, 2009). Some of the behavioral actions of orexins may be due to their neuroplastic effects at glutamatergic synapses in the VTA. Interestingly, the involvement of the VTA in the neuronal and behavioral changes caused by cocaine requires input from orexin neurons (Borgland *et al*, 2006). It will be interesting to determine whether orexin-mediated neuroplasticity in the VTA underlies the effects of other drugs of abuse, such as morphine. Orexin receptor antagonists, in particular those to the orexin 1 receptor, may be clinically useful in the treatment of craving or the prevention of relapse.

In summary, orexin activation of the mesolimbic dopamine system may underlie some of its actions in schizophrenia, depression, or addiction. New therapeutic strategies to either activate (in depression) or inactivate (in schizophrenia or addiction) the orexin system may prove to be effective approaches in the treatment of such disorders.

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New vaccine development for chronic brain disease

The discovery of prophylactic vaccines to protect children from life-threatening infectious diseases was an extremely successful accomplishment of the twentieth century, resulting in 31 vaccines in use today. At the dawn of the twenty-first century, vaccines effective for treatment of established chronic diseases are now under investigation, building on the basic science that has identified molecules that participate in the disease process. Excitingly, progress is being made in exploiting antibody-based therapies against chronic brain disorders that represent a major public health burden.

Both passive and active immunization strategies show promise in the treatment of two classes of chronic brain disease, Alzheimer's disease, and addiction. Active immunization is the traditional approach to systemically administer a drug or molecule of interest to generate an intended antibody response in patients. Passive immunization involves the administration of an antibody generated in a host or model system, which is maximized for efficacy before administration to a patient. Active immunization with Aβ or passive immunization with anti-Aβ antibodies, for example, dramatically reduced amyloid burden and ameliorated behavioral deficits in a transgenic mouse model of Alzheimer's disease (β-amyloid mice) (Kayed and Jackson, 2009). Similarly, active and passive approaches to vaccinate against cocaine, nicotine, morphine, and methamphetamine indicate reductions in their behavioral and neurochemical effects in animal models (Orson *et al*, 2008). Despite adverse events such as encephalitis observed in clinical trials of amyloid vaccines, as well as variable antibody levels and short duration of action for these vaccines, the preclinical data continue to spur efforts to overcome remaining challenges and develop human vaccines for chronic brain diseases.

The molecule targeted for antibody development, the delivery system and formulation, and the maintenance of antibody response are some of the key variables in the pursuit of safe and effective immunotherapy for chronic brain disease. To date, the primary molecules of interest in Alzheimer's disease have been the pathological hallmarks of the disease Aβ and τ (self-antigens), aggregation of which is widely believed to be downstream of Aβ deposition (Kayed and Jackson, 2009), although the drug molecules (foreign antigens) are of interest for addiction (Orson *et al*, 2008). These small molecules or peptides are generally poor immunogens and must be tethered to a carrier protein with the goal to stimulate antibodies with high specificity, but to minimize tolerance and adaptive immunity (for example, virus-like particles; Chackerian *et al*, 2006). Adjuvants are also used to enhance the immune response. Few adjuvants are currently approved for use in humans, but new adjuvants in advanced development may help boost the immune response, particularly induction of antibodies, and therefore their efficacy in Alzheimer's, addiction, and other chronic brain diseases (Reed *et al*, 2009).

The maintenance of an adequate antibody response in vaccines is a critical hurdle. Multiple doses of the vaccines have been used to maintain sufficient (normally high) antibody levels in blood to overcome short-term activity; however, the issue of immune tolerance lingers and may explain, in part, the highly variable antibody responses seen in vaccinees. An interesting question that remains to be adequately addressed is the biological activity of the antibodies. Studies of immune responses against infectious diseases have shown that that the biological activity, rather than the antibody level, is more relevant to ultimate vaccine-induced immunity (see Gromowski and Barrett (2007), for an example). It remains to be seen whether the same is true for immunity induced by vaccines developed for Alzheimer's disease, addictions, and other chronic brain disorders.

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