A major goal in the field of drug abuse has been to identify neuroadaptive mechanisms that lead from recreational use to addiction. Such research has determined that repeated intake of abused drugs induces specific changes in cellular signal transduction, leading to changes in synaptic strength (long-term potentiation or depression) and neuronal structure (altered dendritic branching or cell soma size) within the brain's reward circuitry. These modifications are mediated in part by changes in gene expression, achieved by drug regulation of transcription factors (e.g., CREB [cAMP response element-binding protein] and ΔFosB [a Fos family protein]) and their target genes. Such alterations in gene expression are associated with lasting alterations in epigenetic modifications, including histone acetylation and methylation and DNA methylation. These adaptations provide opportunities for developing treatments targeted to drug-addicted individuals. The fact that the spectrum of these adaptations partly differs depending on the particular addictive substance used creates opportunities for treatments that are specific for different classes of addictive drugs and that may, therefore, be less likely to disturb basic mechanisms that govern normal motivation and reward.

Increasingly, causal relationships are being established between individual molecular and cellular adaptations and specific behavioral abnormalities that characterize the addicted state. For example, acute activation of μ-opioid receptors by morphine or other opiates activates $G_{i/o}$ proteins, leading to inhibition of adenylyl cyclase, resulting in reduced cyclic AMP (cAMP) production, protein kinase A (PKA) activation, and activation of the transcription factor CREB. Repeated administration of these drugs **(Fig. 465e-1)** evokes a homeostatic response involving upregulation of adenylyl cyclases and PKA and increased activation of CREB. Such upregulation of cAMP-CREB signaling has been identified in the locus coeruleus, periaqueductal gray, ventral tegmental area (VTA), nucleus accumbens, and several other CNS regions, and contributes to opiate craving and signs of opiate withdrawal. The fact that endogenous opioid peptides do not produce tolerance and dependence, while morphine and heroin do, may relate to the observation that, unlike endogenous opioids, morphine and heroin are weak inducers of μ-opioid receptor desensitization and endocytosis. Therefore, these drugs cause prolonged receptor activation and inhibition of adenylyl cyclases, which provides a powerful stimulus for the upregulation of cAMP-CREB signaling that characterizes the opiate-dependent state.

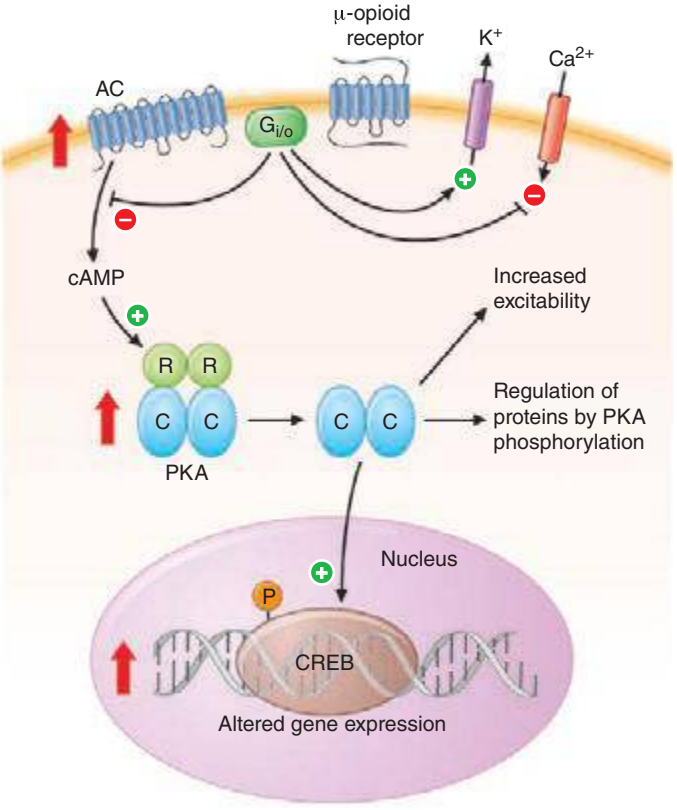

FIGURE 465e-1 Opiate action in the locus coeruleus (LC). Binding of opiate agonists to μ-opioid receptors catalyzes nucleotide exchange on G_i and G_o proteins, leading to inhibition of adenylyl cyclase, neuronal hyperpolarization via activation of K^+ channels, and inhibition of neurotransmitter release via inhibition of Ca^{2+} channels. Inhibition of adenylyl cyclase (AC) reduces protein kinase A (PKA) activity and phosphorylation of several PKA substrate proteins, thereby altering their function. For example, opiates reduce phosphorylation of the cAMP response element-binding protein (CREB), which appears to initiate longer term changes in neuronal function. Chronic administration of opiates increases levels of AC isoforms, PKA catalytic (C) and regulatory (R) subunits, and the phosphorylation of several proteins, including CREB (indicated by *red arrows*). These changes contribute to the altered phenotype of the drug-addicted state. For example, the excitability of LC neurons is increased by enhanced cAMP signaling, although the ionic basis of this effect remains unknown. Activation of CREB causes upregulation of AC isoforms and tyrosine hydroxylase, the rate-limiting enzyme in catecholamine biosynthesis.

SYSTEMS NEUROSCIENCE

The study of interconnected brain circuits that drive behavior has been greatly advanced through newer methods in brain imagining that have documented abnormalities in neural function and connectivity in psychiatric disorders. The past decade has also witnessed the development of revolutionary new techniques—optogenetics and designer receptors and ligands—that provide unprecedented temporal and spatial control of neural circuits and permit detection of neural activity in real time in awake, behaving animals.

Positron emission tomography (PET), diffusion tensor imaging (DTI), and functional magnetic resonance imaging (fMRI) have identified neural circuits that contribute to psychiatric disorders, for example, defining the neural circuitry of mood within the brain's limbic system **(Fig. 465e-2)**. Integral to this system are the nucleus accumbens (important also for brain reward—see below), amygdala, hippocampus, and regions of prefrontal cortex. Recent optogenetic research in animals, where the activity of specific types of neurons in defined circuits can be controlled with light, has confirmed the importance of this limbic circuitry in controlling depression-related behavioral abnormalities. Given that many symptoms of depression (so-called neurovegetative symptoms) involve physiologic functions, a key role for the hypothalamus is also presumed. A subset of depressed individuals shows a small reduction in hippocampal size, as noted above. In addition, brain imaging investigations have revealed increased activation of the amygdala by negative stimuli and reduced activation of the nucleus accumbens by rewarding stimuli. There is also evidence for altered activity in prefrontal cortex, such as hyperactivity of subgenual area 25 in anterior cingulate cortex. Such findings have led to trials of deep brain stimulation (DBS) of either the nucleus accumbens or subgenual area 25, which appears to be therapeutic in some severely depressed individuals.

In schizophrenia, structural and functional imaging studies have identified a 3% loss of brain volume, most of which is in gray matter. This loss is progressive, and cortical gray matter appears to be particularly affected over time. The temporal lobes, particularly the left superior temporal gyrus, Heschl gyrus, and planum temporale, are often the most severely affected. The rate of loss in these regions as well as in frontal and parietal lobes appears to be greatest early in the course of the disease. Functional imaging studies provide evidence of reduced metabolic (presumably neural) activity in the dorsolateral prefrontal cortex at rest and when performing tests of executive function, including working memory. There is also evidence for impaired structural and task-related functional connectivity, mainly in frontal and temporal lobes.

These neuroimaging findings in schizophrenia have been confirmed in pathologic studies that show enlargement of the ventricular