The Mesolimbic Dopamine Reward Circuit in Depression

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The neural circuitry that mediates mood under normal and abnormal conditions remains incompletely understood. Most attention in the field has focused on hippocampal and frontal cortical regions for their role in depression and antidepressant action. While these regions no doubt play important roles in these phenomena, there is compelling evidence that other brain regions are also involved. Here we focus on the potential role of the nucleus accumbens (NAc; ventral striatum) and its dopaminergic input from the ventral tegmental area (VTA), which form the mesolimbic dopamine system, in depression. The mesolimbic dopamine system is most often associated with the rewarding effects of food, sex, and drugs of abuse. Given the prominence of anhedonia, reduced motivation, and decreased energy level in most individuals with depression, we propose that the NAc and VTA contribute importantly to the pathophysiology and symptomatology of depression and may even be involved in its etiology. We review recent studies showing that manipulations of key proteins (e.g. CREB, dynorphin, BDNF, MCH, or Clock) within the VTA-NAc circuit of rodents produce unique behavioral phenotypes, some of which are directly relevant to depression. Studies of these and other proteins in the mesolimbic dopamine system have established novel approaches to modeling key symptoms of depression in animals, and could enable the development of antidepressant medications with fundamentally new mechanisms of action.

D epression and related mood disorders are among the world's greatest public health problems. While there are many effective treatments of depression, roughly half of affected individuals are inadequately treated by available medications and psychotherapeutic approaches (see Depression Guideline Panel 1993). In addition, virtually all of the existing antidepressant medications, which act on the brain's serotonergic or noradrenergic systems, are based on serendipitous discoveries made more than a half-century ago (see Ressler and Nemeroff 2000; Manji et al 2001; Nestler et al 2002; Morilak and Frazer 2004). Despite tremendous effort, the field has not yet succeeded in developing fundamentally new antidepressants with distinct mechanisms of action. One reason for this lack of progress is that a great deal of research in the field has focused on studies of available antidepressant drugs per se rather than on depressive-like states. Indeed, much of what we know about depression is based upon our understanding of prominent, and often rapid, actions of standard antidepressants. We also still lack a clear understanding of the neural substrates that are abnormal in depression and related syndromes. A stark reminder of this fact is that if we had an opportunity to biopsy the brains of patients with depression, it is not at all clear which brain regions should be biopsied. In a similar vein, we still have incomplete knowledge of the neural circuitry in the brain that is responsible for the regulation of mood under normal conditions. The likelihood that depression comprises numerous, distinct disease states also raises the possibility that different subtypes of depression may be mediated by pathology localized to different brain areas, which might be responsive to very different types of treatments.

The hippocampus and frontal regions of cerebral cortex have received the most attention in animal research on depression and antidepressant medications (Dranovsky and Hen 2006). This impressive body of work is reviewed elsewhere in this volume (Duman and Monteggia 2006; Müller and Holsboer 2006; Turner et al 2006). This focus makes some sense, given the likely involvement of these regions in depression and its treatment. Several groups have documented small reductions in hippocampal volumes in patients with depression or post-traumatic stress disorder (see Manji et al 2001). A decline in hippocampal function, which exerts inhibitory control over the hypothalamic-pituitary-adrenal (HPA) axis, could contribute to the hypercortisolemia found in a subset of depressed individuals (Ressler and Nemeroff 2000; Müller and Holsboer 2006). Brain imaging studies have documented abnormalities in blood flow and related measures in hippocampus and frontal cortex in depression (see Mayberg 2003). In fact, deep brain stimulation of a particular subregion of anterior cingulate cortex has recently been shown to be effective in the treatment of severe depression (Mayberg et al 2005).

However, while the hippocampus and frontal cortex are undoubtedly involved in aspects of depression and its treatment, it is unlikely that these regions account for all symptoms of the disorder (Nestler et al 2002). The hippocampus is best understood for its role in declarative memory and spatial learning, while frontal regions of cortex are implicated in working memory, attention, impulse control and other aspects of executive function. Abnormalities in these cognitive domains are certainly seen in depression and related disorders, but in many patients such symptoms do not represent the overwhelming presentation of the illness. These regions likely function more broadly in regulating emotional behavior; nevertheless, we believe that other neural circuits in the brain, more closely linked with emotions, require study for their role in depression as well. Indeed, human brain imaging studies and examination of human postmortem brain tissue document abnormalities in many regions beyond hippocampus and frontal cortex, including thalamus, amygdala, striatum, hypothalamus, and brainstem, among others (e.g., Brody et al 2001; Drevets 2001; Drevets et al 2001;

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Klimek et al 2002; Mayberg 2003; Rajkowska 2003; Karolewicz et al 2004; Tremblay et al 2005). These findings cannot be viewed as definitive, since many imaging and autopsy studies have yielded contradictory findings. Still, this work has underscored the need to investigate mechanisms of mood regulation and dysregulation in regions well beyond the hippocampus and frontal cortex.

In recent years, we and other groups have been interested in a role for the brain's reward regions in depression and antidepressant treatment. Studies from the drug addiction field have identified the nucleus accumbens (NAc; also called ventral striatum) and its dopaminergic inputs from the ventral tegmental area (VTA) of the midbrain, as the one of the most important anatomical substrates for drug reward as well as for natural rewards, such as food, sex, and social interactions (Wise 1998; Koob and Le Moal 2001). The amygdala, traditionally viewed as being critical for learned associations between negative emotional stimuli and environmental cues, serves a similar function for rewarding stimuli (Davis and Whalen 2001; LeDoux 2000; Koob and Le Moal 2001; Everitt et al 2003). Several neuropeptide systems in the hypothalamus, known to be important mediators of feeding behavior, also influence rewarding responses to drugs of abuse (e.g., Fulton et al 2000; Shalev et al 2001; Kelley and Berridge 2002; Kiefer and Wiedemann 2004; Hsu et al 2005). A striking observation of these disparate fields related to brain reward is the extent to which abnormalities in these behavioral domains are seen in depression and other mood disorders. For example, most depressed patients prominently exhibit a reduced ability to experience pleasure (anhedonia) and loss of motivation, as well as abnormalities in several neurovegetative functions such as appetite, sleep, energy level, and circadian rhythms (American Psychiatric Association 2000).

Of course, these various brain areas cannot be thought of as distinct, since they function as parts of highly overlapping and interacting circuits (Figure 1). For example, the VTA and NAc receive strong glutamatergic inputs from several frontal cortical regions, hippocampus, and amygdala (see Hyman and Malenka 2001; Nestler 2001; Everitt and Wolf 2002; Kalivas 2004). Similarly, several peptidergic nuclei in hypothalamus send prominent projections to the VTA or NAc (see Saito et al

1999; Mignot 2004; Hsu et al 2005). All of these regions, in turn, receive innervation from VTA dopamine neurons, where dopaminergic transmission has been shown to profoundly affect the functioning of these regions in electrophysiological and behavioral paradigms (e.g., see Goldman-Rakic et al 2000; Louilot and Besso 2000; Pezze and Feldon 2004; Wittmann et al 2005). Additionally, the NAc directly innervates the hypothalamus (Heimer et al 1991; Baldo et al 2004).

The objective of this review is to summarize the growing evidence for a role of the NAc, and its dopaminergic inputs from the VTA, in the regulation of mood and motivation under normal conditions, and in mediating many of the prominent behavioral abnormalities seen in depression and other mood disorders. We highlight how research on the VTA-NAc reward circuit may provide novel targets for the development of new antidepressant treatments.

Mesolimbic Dopamine System in Mood Regulation

As mentioned above, the VTA-NAc pathway plays a critical role in reward. Virtually all drugs of abuse increase dopaminergic transmission in the NAc, and this is thought to contribute to the acute rewarding effects of the drugs (Wise 1998; Di Chiara et al 1999; Koob and Le Moal 2001). Some drugs also produce their rewarding effects in the NAc via dopamine-independent mechanisms. For example, opiates activate dopaminergic transmission in the NAc via actions in the VTA, but also directly activate μ opioid receptors on NAc neurons. As well, there is now considerable evidence that adaptations in the VTA-NAc in response to chronic drug administration mediate some of the pathological behaviors that characterize the addicted state (Hyman and Malenka 2001; Nestler 2001; Everitt and Wolf 2002; Kalivas 2004). Increasing evidence suggests that similar mechanisms in the VTA and NAc mediate acute responses to natural rewards under normal conditions as well as possibly compulsive responses under certain pathological conditions (e.g., over-eating, pathological gambling) (Kelley and Berridge 2002).

The possible involvement of the VTA-NAc pathway in mood regulation and depression is not well studied. The notion that this pathway may mediate depression-like behav-
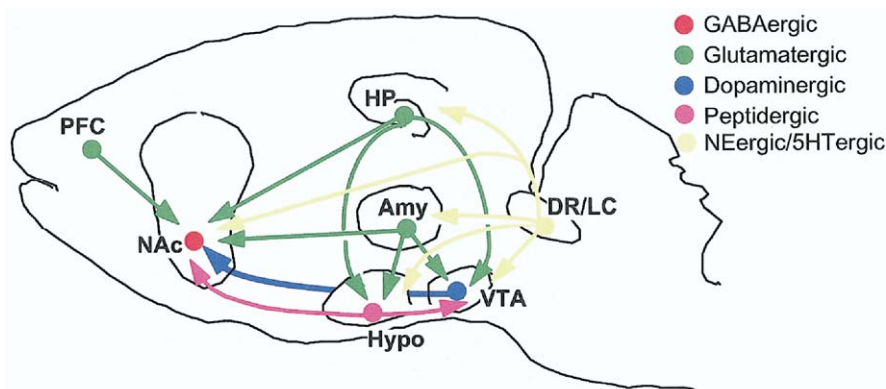

Figure 1. The neural circuitry of mood. The figure shows a highly simplified summary of a series of neural circuits in the brain that are believed to contribute to the regulation of mood. While most research in the depression field has focused on hippocampus (HP) and cerebral cortex (e.g. prefrontal cortex or PFC), there is the increasing realization that several subcortical structures implicated in reward, fear, and motivation are also critically involved. These include the nucleus accumbens (NAc), amygdala (Amy), and hypothalamus (Hypo). The figure shows only a subset of the many known interconnections among these various brain regions. The figure also shows the innervation of several of these brain regions by monoaminergic neurons. The ventral tegmental area (VTA) provides dopaminergic input to the NAc; inputs to most of the other brain areas are not shown in the figure. Norepinephrine (NE, from the locus coeruleus or LC) and serotonin (5HT from the dorsal raphe and other raphe nuclei) innervate all of the regions shown in the figure. In addition, strong connections between the hypothalamus and VTA-NAc pathway have been established in recent years. GABA, gamma-aminobutyric acid; DR, dorsal raphe.

iors was first proposed on the basis of studies with dopamine receptor antagonists (Wise 1982). Since that time, there have been sporadic publications reporting an association between the two over the past several decades (e.g., see Horger and Roth 1996; Di Chiara et al 1999; Espejo and Minano 1999; West et al 1999; Cyr et al 2001; Pallis et al 2001; Renard et al 2001; Yadid et al 2001; Jensen et al 2003; Nieoullon and Coquerel 2003; Rada et al 2003). These studies show that stress, in the context of animal models of depression, potently activates VTA dopamine neurons and stimulates dopaminergic transmission to its limbic targets including the NAc. There are also some reports that antidepressant treatments can alter dopaminergic activity in the VTA or its targets, and that experimental manipulation of dopaminergic transmission in the VTA-NAc pathway can regulate depression-like behavior in animal models. However, no consensus in the field has yet been established, partly because the depression field has focused largely on serotonergic and noradrenergic mechanisms in other brain circuits (e.g., hippocampus and cortex), while research of dopaminergic mechanisms and the VTA-NAc pathway has largely focused on addiction or schizophrenia. Certain antidepressant medications (e.g., bupropion and nomifensine), with proven efficacy in humans, are purported to act, at least in part, via promoting dopaminergic function. These drugs do have weak effects on dopamine systems in animals, however, it is far from proven that this explains their clinical efficacy, since long-term administration of drugs with much more profound activating effects on dopamine systems (e.g., cocaine, amphetamine) does not produce antidepressant effects in most people.

It is paradoxical that stress and other aversive stimuli mimic drug-induced activation of the VTA dopamine system, and it remains controversial as to the functional consequences of this regulation. One possibility is that activation of the VTA by stress represents a positive, coping mechanism by increasing an individual's motivation and drive to cope actively with the threat at hand. It is similarly striking that chronic exposure to stress causes many of the same longer-term adaptations in the VTA-NAc pathway as seen after chronic administration of a drug of abuse (see Fitzgerald et al 1996; Ortiz et al 1996; Everitt and Wolf 2002; Saal et al 2003). It is possible that chronic exposure to severe stress causes pathological adaptations in the VTA-NAc pathway that not only sensitize individuals to drugs of abuse—and thereby mediate the effect of stress in promoting drug addiction—but also contribute to other behavioral abnormalities relevant to depression and other mood disorders. Another possibility is that stress simultaneously activates brain regions in addition to the VTA (e.g., hippocampus, prefrontal cortex, amygdala) that affect the ways in which neural signals are "gated" through the NAc (e.g., West et al 2003) such that stress is not perceived as being rewarding, but can still cause adaptations that underlie sensitization.

There is now growing evidence for a role of specific molecular pathways in the VTA-NAc, first implicated in regulating drug and natural reward, in animal models of depression and antidepressant action. While much of this work is in relatively early stages of development, it has pointed to some novel strategies for antidepressant drug development. An interesting outcome of the work is the realization that some of the same molecular pathways implicated in depression and antidepressant action in hippocampus and frontal cortex also influence these phenomena at the level of the VTA-NAc, although very different effects are seen in these various regions.

CREB-Mediated Transcription in the VTA-NAc Pathway in Mood Regulation

The transcription factor CREB (cAMP response element binding protein) is stimulated in the NAc by exposure to several types of drugs of abuse or stress, and numerous studies have established that CREB activity in this region has a profound effect on an animal's responsiveness to emotional stimuli (Conti and Blendy 2004; Carlezon et al 2005). CREB function in the NAc is normally regulated by glutamatergic and dopaminergic inputs (Dudman et al 2003), suggesting that—by determining the set point of NAc neurons (Dong et al 2004)—it represents an emotional gate for behavioral responsivity. This view is now supported by a large body of data. Viral vector-mediated elevations of CREB within the rat NAc reduce the rewarding effects of cocaine, morphine, and sucrose (Carlezon et al 1998; Pliakas et al 2001; Barrot et al 2002), which indicates that a sustained elevation of CREB activity in the NAc produces anhedonia-like signs. In fact, this CREB phenotype appears to reflect a generalized numbing of behavioral responses to emotional stimuli, since animals with increased CREB function in the NAc also show reduced responses to a wide range of aversive conditions (Barrot et al 2002). Elevations of CREB within the NAc also make low doses of cocaine aversive—a putative sign of dysphoria or negative affect—and increase immobility behavior in the forced swim test, an effect that is opposite to those of standard antidepressants (Pliakas et al 2001). Similarly, overexpression of CREB in the NAc of inducible transgenic mice produces a depression-like phenotype (Newton et al 2002) and reduces the rewarding effects of cocaine (McClung and Nestler 2003).

Conversely, reductions in CREB activity in the rat NAc, through viral vector-mediated expression of the dominant negative mutant mCREB, increases the rewarding effects of cocaine, morphine, and sucrose (Carlezon et al 1998; Barrot et al 2002; DiNieri et al 2005) and produces antidepressant-like effects in the forced swim test (Pliakas et al 2001) and learned helplessness paradigm (Newton et al 2002). Likewise, expression of mCREB in the NAc of inducible transgenic mice produces antidepressant-like effects (Newton et al 2002). Targeted deletion of predominant CREB isoforms in mutant mice also produces antidepressant-like effects (Conti et al 2002).

Increasing evidence indicates that CREB function in NAc also regulates anxiety-like behavior in rodents. Disruption of CREB function within the NAc, achieved by viral overexpression of mCREB, produces anxiety-like effects, whereas increased CREB function causes opposite changes (Barrot et al 2002, 2005). On the other hand, global knockdown of CREB reduces anxiety-like behavior (Valverde et al 2004), perhaps owing to CREB actions outside the NAc. The notion that elevated CREB function in NAc causes certain depression-like symptoms, while reduced CREB function in this region causes anxiety-like behavior, may seem paradoxical, but can be understood within the role CREB may play in this reward circuit under normal conditions. Our hypothesis is that CREB is a key regulator of the reactivity of brain reward circuits and thereby regulates individual sensitivity to emotional stimuli (Carlezon et al 2005). Short-term increases in CREB activity in NAc, induced by normal rewarding or aversive stimuli, would serve to dampen responses to subsequent stimuli and facilitate the ability to actively deal with the situation at hand (e.g., consumption of reward, escape from danger). Under more pathological conditions, however, larger and more sustained increases in CREB activity, induced by drugs of abuse or excessive stress, would lead to an excessive dampening of emotional

reactivity and to the behavioral phenotype outlined above. Conversely, sustained reductions in CREB activity, which are seen under conditions of social isolation (Barrot et al 2005), would heighten emotional reactivity and in the extreme be associated with a state of anxiety. This work highlights the notion that extreme increases or decreases in CREB function in NAc may be detrimental and contribute to the symptomology of different subtypes of depression (Carlezon et al 2005).

This role for CREB in the NAc in depression models is in stark contrast to CREB's activity in the hippocampus and other regions in many of the same behavioral models. In hippocampus, CREB appears to be an important mediator of antidepressant effects. Many antidepressant treatments increase CREB activity within this region (Duman et al 1997; Duman and Monteggia 2006), and direct elevation of CREB protein levels through the use of viral-mediated gene transfer produces antidepressant-like effects in rodents (Chen et al 2001). In contrast, in frontal cortex, activation of the cAMP pathway, which would be expected to increase CREB activity, can either promote or impair cognitive performance depending on the age of the animal (Ramos et al 2003). Recent evidence likewise suggests complicated effects of CREB at the level of the VTA in regulating drug reward, with differences seen depending on the particular subregion of the nucleus involved (Walters et al 2003; Pandey et al 2004; Olson et al 2005).

While the role of CREB in these latter regions in depression models has not yet been investigated, these studies highlight the very different behavioral consequences of CREB depending on the brain region involved. This may explain the difficulty in treating depression with drugs that produce global effects on the CREB pathway. For example, PDE4 (phosphodiesterase-4) inhibitors (e.g., rolipram) have been investigated as possible antidepressants (see Duman et al 1997). Such drugs, by inhibiting cAMP breakdown, would be expected to promote CREB function globally, with competing functional consequences expected. This would argue for targeting proteins (e.g., subtypes of PDE, RGS [regulators of G protein signaling] proteins, adenylyl cyclase, and many other signaling proteins) upstream of CREB that show much more selective tissue distributions. A corollary of this hypothesis is that similar specificity might be achieved by examining target genes of CREB that show greater tissue specificity than CREB itself. An example of such a CREB target, with potential implications for the treatment of depression, is the opioid peptide dynorphin.

Dynorphin and κ Opioid Receptor Signaling in the VTA-NAc Pathway in Mood Regulation

The regulation of depression-like behavior by changes in CREB activity within the NAc appears to be mediated partly by dynorphin, an endogenous κ opioid receptor ligand (Carlezon et al 2005). Administration of κ agonists produces effects similar to those produced by increased CREB activity in the NAc, including increased immobility in the forced swim test (Mague et al 2003) and signs of anhedonia in reward models (Todtenkopf et al 2004). In contrast, κ antagonists produce antidepressant-like effects on their own (Mague et al 2003; McLaughlin et al 2003), attenuate the prodepressant-like consequences of elevated CREB expression within the NAc (Carlezon et al 1998; Pliakas et al 2001), and mimic the mCREB phenotype. One mechanism by which κ antagonists may produce antidepressant-like effects is by blocking the inhibitory actions that κ opioid receptors normally exert on VTA dopamine neurons (Shippenberg and Rea 1997). Indeed, intra-NAc administration of a κ antagonist is sufficient to cause an antidepressant-like effect in the learned helplessness paradigm (Newton et al 2002). These data suggest a scheme whereby excessive activation of CREB by chronic stress (or by drug withdrawal; see Shaw-Lutchman et al 2003) increases dynorphin expression in the NAc, which feeds back to decrease VTA dopamine function and trigger certain features of depression (Figure 2).

BDNF and Neurotrophin Signaling in the VTA-NAc Pathway in Mood Regulation

BDNF is another example of a protein that has very different effects in animal models of depression and antidepressant action depending on the brain region involved. BDNF is best characterized in hippocampus, where its induction by antidepressant treatments seems to be important for their behavioral activity (Duman et al 1997; Monteggia et al 2004; Duman and Monteggia 2006; but see Conti et al 2002, who show that CREB is important for BDNF expression in hippocampus but that neither is necessary for an antidepressant-like response).

Likewise, there is strong evidence for powerful effects of BDNF in the VTA-NAc pathway (Figure 3). BDNF, administered directly into the VTA or NAc, causes a profound increase in cocaine-induced locomotor activity and in cocaine reward in several behavioral paradigms (Horger et al 1999; Hall et al 2003;
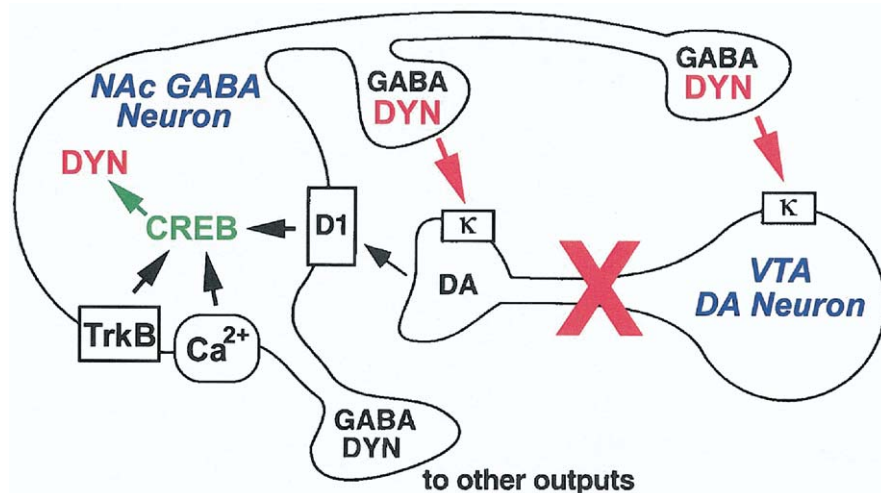

Figure 2. CREB and dynorphin in the nucleus accumbens (NAc) in depression. The figure shows a simplified hypothetical scheme by which CREB induction of dynorphin (DYN) in the NAc contributes to certain symptoms of depression. CREB is activated by D_1 dopamine receptors (through activation of the cAMP pathway) or by Ca^{2+}- or TrkB-regulated signal transduction pathways, which leads to increased expression of DYN. DYN feeds back on κ opioid receptors located on the terminals and cell bodies/dendrites of VTA dopamine (DA) neurons. Stimulation of these κ receptors inhibits the VTA neurons, which may contribute to anhedonia and related symptoms of depression. Antagonists of κ receptors may thus block the consequences of CREB-induced increases in DYN activity, and exert antidepressant activity in some individuals. GABA, gamma-aminobutyric acid; CREB, cAMP response element binding protein; VTA, ventral tegmental area.
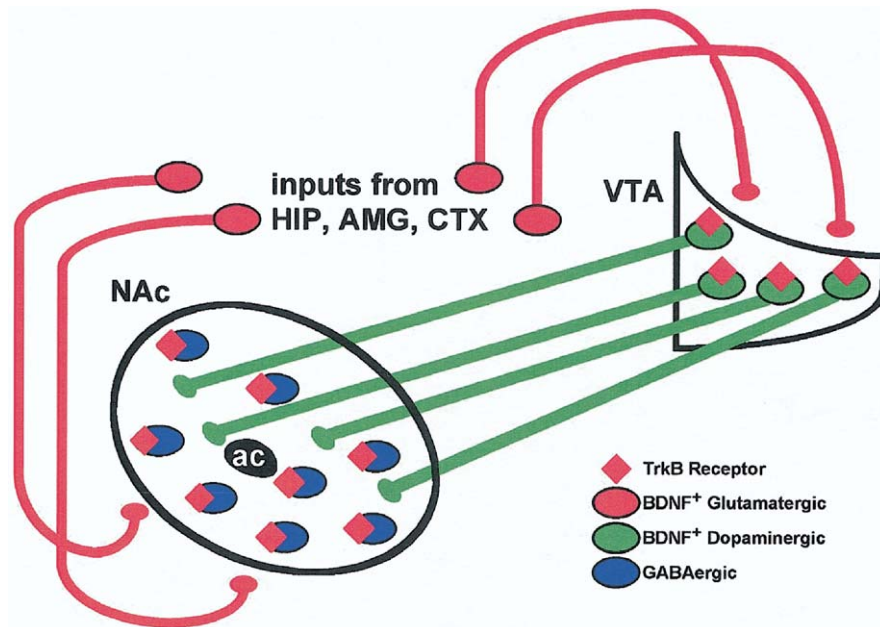
Figure 3. BDNF signaling in the VTA-NAc circuit. The figure shows a highly simplified depiction of the source of BDNF, and its actions, in the VTA and NAc. One major source of BDNF in both regions is provided by glutamatergic afferents from frontal cortex, hippocampus, and amygdala, which express high levels of BDNF. BDNF released from these afferents acts on TrkB receptors expressed on VTA and NAc neurons. VTA dopamine neurons express moderate levels of BDNF, and this may provide an additional source of BDNF in the VTA and NAc. In contrast, NAc neurons express very low levels of BDNF, and it remains unclear whether this source is physiologically relevant. BDNF, brain-derived neurotrophic factor; VTA, ventral tegmental area; NAc, nucleus accumbens; HYP, hypothalamus; GABA, gamma-aminobutyric acid; AMG, amygdala; CTX, frontal cortex.

Lu et al 2004). Other neurotrophins, such as NT3 (neurotrophin-3), seem to exert similar effects on this system (Pierce and Bari 2001). At the same time, intra-VTA BDNF exerts a depression-like effect in the forced swim test, while blockade of BDNF action in the NAc, by use of viral-mediated overexpression of a dominant negative mutant of TrkB (the receptor for BDNF), causes an antidepressant-like effect in the same test (Eisch et al 2003). Administration of BDNF into the VTA-NAc pathway also causes profound weight loss (Berhow et al 1995): this could be caused by a hyperdopaminergic (e.g., amphetamine-like) state or it could reflect reductions in the rewarding properties of food, a sign of anhedonia.

The finding that BDNF signaling in the VTA-NAc pathway promotes drug reward, but is also "pro-depressant" is surprising, in that by promoting mesolimbic dopamine function one might expect BDNF to also be antidepressant. Insight into this paradox comes from preliminary experiments using the social defeat model of stress, where animals subjected repeatedly to an aggressive animal develop a long-lasting behavioral syndrome characterized by several features of anhedonia seen in human depression, including decreased sucrose preference, decreased sexual behavior, decreased social interaction, and a general decrease in locomotor activity, some of which are reversed by chronic (but not acute) antidepressant administration (Berton et al 2006; see also Buwalda et al 2005). Interestingly, selective ablation of the BDNF gene from the VTA, achieved by viral expression of Cre recombinase in the VTA of mice homozygous for a floxed BDNF gene, is antidepressant in that animals no longer develop this behavioral syndrome in response to social defeat stress (Berton et al 2004). Our hypothesis is that BDNF signaling in the VTA-NAc is required for the establishment of important associations with negative emotional stimuli. Under normal conditions, this BDNF signaling is critical for the appropriate memories of potentially rewarding and dangerous settings. Under pathological conditions, however, this signaling may establish abnormal associations, which would lead to certain symptoms of depression even in the absence of true external threats.

As was the case with treatments that globally target CREB, the fact that BDNF signaling in hippocampus produces effects that are opposite to those associated with the VTA-NAc pathway in

behavioral models of depression argue for caution in developing therapies for depression that exert a single effect on BDNF and its signaling cascade throughout the brain. However, we know that BDNF signals through a highly complex series of parallel but interacting intracellular signal transduction pathways, comprised of multiple subtypes of proteins, some of which show dramatic region-specific patterns of expression in brain. It will be interesting in future studies to identify such subtypes, and develop drugs that modify BDNF signaling, specifically within the hippocampus or the VTA-NAc and test their effects in animal models of depression. A recent study of phospholipase Cγ (PLCγ), one of BDNF's effector proteins, shows the potential of targeting these signaling cascades. Viral-mediated overexpression of PLCγ in the VTA can cause either prodepressant- or antidepressant-like effects in several behavioral paradigms depending on whether the anterior or posterior subregion of the VTA is targeted (Bolanos et al 2003). Given the vast number of proteins that are involved in BDNF signaling cascades, there would appear to be great promise for approaches that exploit regional differences in the expression of factors that are directly upstream or downstream of BDNF.

Hypothalamic Feeding Peptides in the VTA-NAc Pathway in Mood Regulation

A role of the hypothalamus in reward mechanisms dates back to the late 1960's, when animals were shown to self-stimulate the lateral hypothalamus (see Wise 1996). This has been explained in part by the fact that dopaminergic fibers from the VTA to the NAc pass through the lateral hypothalamus, but dopamine-independent mechanisms of reward in this region have also been implicated. Dramatic advances in the study of feeding behavior have provided additional connections between the hypothalamus and reward mechanisms. Numerous peptides, each of which is expressed in a discrete subpopulation of hypothalamic neurons and regulates eating behavior, show strong projections (in some cases their strongest projections) to the NAc or VTA (Saito et al 1999; Mignot 2004; Hsu et al 2005), and have been implicated in rewarding responses to drugs of abuse (Fulton et al
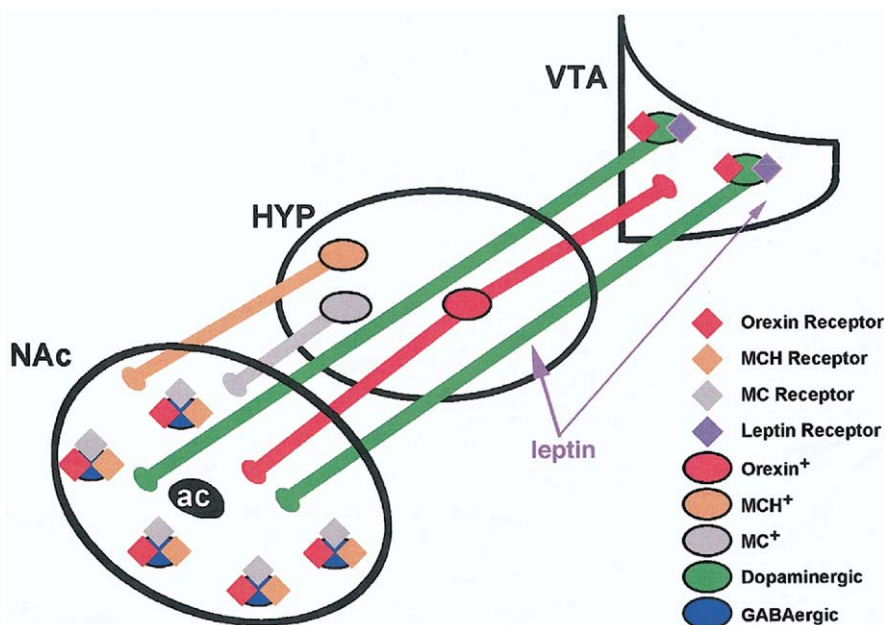
Figure 4. Innervation of the VTA-NAc circuit by hypothalamic feeding peptides. The figure shows examples of prominent innervation of the VTA or NAc by peptides classically studied for their role in hypothalamic feeding mechanisms. Orexin, expressed in lateral hypothalamus, innervates VTA and NAc, among many other brain regions. MCH (expressed in lateral hypothalamus) and MC (expressed in arcuate nucleus of hypothalamus) provide very dense innervation of the NAc. Leptin, presumably derived from peripheral fat, acts on leptin receptors in the VTA (in addition to its classic action on leptin receptors in hypothalamus). Each of these peptides has been shown to regulate drug reward and more recent evidence shows that they affect depression-related behaviors as well. VTA, ventral tegmental area; NAc, nucleus accumbens; MCH, melanin-concentrating hormone; MC, melanocortin; HYP, hypothalamus.

2000; Shalev et al 2001; Kelley and Berridge 2002; Kiefer and Wiedemann 2004; Hsu et al 2005) (Figure 4). This information has raised the interesting possibility that there are separate but interacting mechanisms that regulate physiological need for food (mediated within the hypothalamus) and the desire for food (mediated within the NAc), although such distinctions remain highly speculative.

Recent work has begun to draw connections between these hypothalamic feeding peptides and depression. Of particular note is melanin-concentrating hormone (MCH), which is a major orexigenic (pro-appetite) peptide expressed in a subset of lateral hypothalamic neurons. The MCH_1 receptor, the only subtype expressed in rodents, shows dramatic enrichment in the NAc (Saito et al 1999), and recent evidence supports the view that this hypothalamic-NAc pathway, mediated via MCH, is important in reward. Direct administration of MCH into the NAc stimulates feeding behavior, whereas blockade of the MCH_1 receptor in this region decreases feeding (Georgescu et al 2005). Moreover, several MCH_1 receptor antagonists, administered systemically or directly into the NAc, exert antidepressant-like effects in the forced swim test (Borowsky et al 2002; Georgescu et al 2005). A similar antidepressant-like phenotype is observed in mice lacking MCH, while a prodepressant-like phenotype is seen in MCH-overexpressing animals (Georgescu et al 2005). Taken together, these data provide a strong case that MCH antagonists, by disrupting MCH signaling to the NAc, may provide a highly novel mechanism for antidepressant medications. Such drugs would also reduce weight, which could be useful in a subset of depressed patients.

Several other feeding peptides should be considered in this regard as well. Orexin (hypocretin), another peptide expressed in lateral hypothalamus, is thought to increase feeding primarily by promoting a state of wakefulness and alertness (Mignot 2004). Orexin neurons project widely throughout brain and provide strong innervation of the VTA, where orexin stimulates dopaminergic neurons via orexin OX_1 receptors and may promote drug reward (Nakamura et al 2000; Korotkova et al 2003). OX_1 receptor agonists, which are in development to promote wakefulness and alertness, warrant evaluation as potential antidepressant agents (see Allard et al, 2004). Given the involvement of

orexin in regulating sleep-wake cycles, it would also be worth investigating whether abnormalities in orexin signaling may be related to the disparate types of sleep abnormalities reported in depression. Orexin deficiency is believed to cause narcolepsy, and patients with narcolepsy have a high incidence of depression (Daniels et al 2001).

Melanocortin (melanocyte stimulating hormone, MSH) produces its central effects largely through the MC_4 receptor, and this receptor is highly enriched within the NAc (see Hsu et al 2005). Abnormalities in behaviors that reflect drug reward have been documented in mice with altered levels of the MC_4 receptor, an effect mediated at least partly by the NAc (Hsu et al 2005). Drugs aimed at the MC_4 receptor could hold some potential in the treatment of depression. Indeed, a nonpeptide MC_4 antagonist shows some antidepressant- and anxiolytic-like effects in animal models (Chaki et al 2003).

These are examples of just some of the prominent hypothalamic feeding peptides that deserve attention in the depression field. Other examples include leptin, CART (cocaine- and amphetamine-regulated transcript), NPY (neuropeptide Y), CRF (corticotrophin releasing factor), and ARP (agouti-related peptide), among many others (e.g., Heilig 2004) . Of particular note is that perturbation of these various hypothalamic feeding peptide systems could well produce very different effects in different subtypes of depression. It is conceivable that individuals whose depression is characterized by reduced activity and weight gain would respond differently to such agents than individuals who exhibit increased activity, anxiety, and weight loss.

Clock and Other Circadian Genes in the VTA-NAc Pathway in Mood Regulation

Abnormal circadian rhythms have long been described in depression and other mood disorders (American Psychiatric Association 2000). Many depressed patients report their most serious symptoms in the morning with some improvement as the day progresses. This may represent an exaggeration in diurnal fluctuations in mood, motivation, energy level, and responses to rewarding stimuli that are seen commonly in the healthy popu-

lation. The molecular basis for these rhythms seen under normal and pathological conditions remains poorly understood.

Most research on circadian rhythms has focused on the suprachiasmatic nucleus (SCN) of the hypothalamus, which is considered the master circadian pacemaker of the brain (Okamura et al 2003). Here, circadian rhythms are generated at the molecular level by Clock (a Pas domain containing transcription factor) dimerizing with Bmal; the dimer induces the expression of Per (Period) and Cry (Cryptochrome) genes, which in turn feedback to repress Clock-Bmal activity. In addition, Clock-Bmal, Per, and Cry regulate the expression of many other genes, which presumably drive the many circadian variations in cell function. This Clock-Per cycle in the SCN is entrained by light and appears to be essential for matching circadian rhythms with the light-dark cycle. More recent research, however, has indicated that control of circadian rhythms is far more complicated than this simple model. Thus, Clock, Bmal, Per, and Cry genes, as well as several related genes, are expressed broadly throughout the brain, including in the VTA and NAc, although little is known about their function outside the SCN.

There is now increasing evidence that circadian genes can also regulate brain reward. The first indication of this function came from studies in *Drosophila*, which showed that behavioral sensitization to cocaine is dependent on expression of Per, Clock, Cycle, and other circadian genes (Andretic et al 1999). More recently it was reported that rewarding responses to cocaine are reduced in mice lacking Per genes (Abarca et al 2002). In contrast, cocaine reward, as well as baseline and cocaine-induced locomotor activity, are markedly enhanced in mice lacking Clock, and these abnormalities are associated with a dramatic increase in the activity of VTA dopamine neurons (McClung et al 2005a). Preliminary studies suggest that Clock mutant mice also display less depression-like behavior in the forced swim test and reduced brain stimulation reward thresholds, also suggestive of an elevated affective state (McClung et al 2005b). Together, these studies are consistent with an important influence of Clock and other circadian genes, at the level of the VTA-NAc pathway, in the regulation of mood and suggest that abnormalities in circadian gene function could contribute to certain symptoms of depression.

Beyond Clock, there has been interest in NPAS2 (neuronal Pas domain protein-2) for a role in mood regulation. NPAS2 is homologous to Clock and, like Clock, dimerizes with Bmal to regulate the expression of Per, Cry, and many other genes in a circadian fashion (Reick et al 2001). Interestingly, NPAS2 is not expressed in the SCN. Instead, it is expressed in several limbic regions of brain and is, in fact, highly enriched within the NAc (Garcia et al 2000). NPAS2 knockout mice show increased anxiety-like behavior and deficits in fear conditioning. In addition, the mice show deficits in the ability to entrain to nonlight stimuli, such as food (Dudley et al 2003). It has been suggested that NPAS2 is a critical mediator of circadian rhythms in emotional responses via actions in limbic regions of brain such as the NAc. This important hypothesis requires further investigation.

Taken together, these early studies support the hypothesis that circadian genes may function abnormally in depression and other mood disorders. This work also suggests that drugs aimed at influencing particular target genes for these circadian transcription factors, which are expressed within distinct brain circuits, deserve attention as targets for possible new treatment agents for depression.

Future Directions

A major need of future research is to better define the detailed circuitry of the numerous and diverse molecular pathways

discussed above. Both the VTA and NAc are heterogeneous structures, which contain distinct cell types with distinct afferent and efferent neuronal connections. As just one example, dynorphin is localized to one of two major subtypes of GABAergic projection neurons that populate the NAc (see Carlezon et al 1998). These cells project directly onto VTA dopamine neurons. In contrast, induction of CREB activity by stress and drugs of abuse occurs in both major subtypes of NAc projection neurons (Barrot et al 2002; Shaw-Lutchman et al 2003). The cellular specificity of most of the other molecular signals covered in this review has not yet been identified. Likewise, the VTA and NAc have well-delineated subregions—i.e., core and shell divisions of the NAc and rostral versus caudal poles of the VTA—with clear topographical differences in afferent and efferent connections and behavioral outputs (e.g., see Barrot et al 2002; Olson et al 2005). We need to understand how various molecular pathways of interest map onto these subregions as well. Ultimately, these layers of anatomical specificity will provide further insight into the role of the mesolimbic dopamine system in depression related phenomena.

The several lines of research outlined in this review argue in favor of broadening the range of neural circuits that are thought to be involved in depression and antidepressant treatment. At the very least, the VTA-NAc and related reward circuits are likely involved in the manifestation of many of the most prominent symptoms of depression, which involve impairments in reward and motivation, and their improvement during treatment. Less certain is whether primary abnormalities in the reward circuitry are involved in the etiology of depression, although the same can be said for hippocampus, cortex, and any other region, since the primary site of pathology in the brain that causes depression remains unknown. Also unknown is whether available antidepressant treatments produce some of their therapeutically relevant effects directly at the level of the mesolimbic dopamine system or indirectly via other regions.

Regardless of the role of the VTA-NAc in the etiology of depression and in the mechanism of action of current antidepressants, advances in understanding how specific molecular pathways within the VTA-NAc and other reward regions regulate mood and motivation provide fundamentally novel avenues by which to search for antidepressant medications with new mechanisms of action. The search for such novel antidepressants over the past several decades has been extremely disappointing to date, and molecular targets in reward regions may meet the same fate. Nevertheless, the need for such medications is great, and we believe there is compelling evidence to include molecular pathways in the VTA-NAc circuit in this important search.

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