

Mini-Symposium

Braking Dopamine Systems: A New GABA Master Structure for Mesolimbic and Nigrostriatal Functions

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A new mesopontine structure exerting a strong influence on dopamine systems has recently been defined: the tail of the ventral tegmental area/rostromedial tegmental nucleus (tVTA/RMTg). This review presents a neuroanatomical, physiological, and behavioral overview of some of the recent and ongoing research on this brain region and its relationship with dopamine systems. The tVTA/RMTg sends dense GABA projections to VTA and substantia nigra neurons. The inhibitory influence of tVTA/RMTg on dopamine neurons is supported by both neuroanatomical and electrophysiology data. The latter studies also reveal the tVTA/RMTg as a substrate for morphine and cannabinoid action on dopamine cells. In primates, the tVTA/RMTg has been implicated in reward prediction error signals, through a basal ganglia–lateral habenula–tVTA/RMTg–dopamine–basal ganglia circuit. In rodents, the tVTA/RMTg has been shown to play a critical role in aversive behaviors, particularly those involving behavioral inhibition, such as freezing and avoidance. These findings highlight the functional importance of the tVTA/RMTg as a major GABA brake for dopamine systems.

Introduction

In the past, sporadic studies have noted distinctive characteristics of a brain region (Herkenham and Nauta, 1979; Scammell et al., 2000; Jhou, 2005; Perrotti et al., 2005; Ikemoto, 2007; Olson and Nestler, 2007; Ferreira et al., 2008; Geisler et al., 2008; Rotllant et al., 2010) that is now recognized as the “tail of the ventral tegmental area” (Perrotti et al., 2005) or “rostromedial tegmental nucleus” (Jhou et al., 2009a) (tVTA/RMTg). However, systematic study of this region was hampered by the lack of a coherent understanding of its anatomical and functional properties. This situation has now begun to change (Barrot and Thome, 2011; Lavezzi and Zahm, 2011; Bourdy and Barrot, 2012).

Anatomically, the tVTA/RMTg region (Fig. 1) has been shown to express a distinct pattern of afferents and efferents, including

strikingly focused afferents from the lateral habenula and strong projections to midbrain dopamine neurons, the dorsal raphe, and pedunculopontine nucleus (Jhou et al., 2009a,b; Kaufling et al., 2009, 2010a; Gonçalves et al., 2012), all regions that are implicated in motivated behavior. Rostrally, the tVTA/RMTg is bilaterally inserted deep into the posterior VTA, in a subregion of the paranigral nucleus and dorsolateral to the interpeduncular nucleus. In brain atlases, this part of the tVTA/RMTg is not yet differentiated from the VTA itself, and the tVTA/RMTg has strong neuroanatomical and functional links with dopamine systems, hence the designation as “tVTA.” More caudally, the tVTA/RMTg resides lateral to the median raphe, and partially embedded within the decussation of the superior cerebellar peduncle, at least in rats. This caudal half of the structure extends to the rostral edge of the pedunculopontine nuclei and shares homology with tegmental structures. Consistent with the nomenclature of other mesopontine structures and tegmental nuclei, it is thus designated as “RMTg.” However, both names refer to the same tVTA/RMTg continuum, which is proposed as a new GABAergic master brake for dopamine systems (Bourdy and Barrot, 2012).

The tVTA/RMTg expresses markers that distinguish it from surrounding regions. It includes high levels of the GABA-synthesizing enzyme GAD 67 (Perrotti et al., 2005; Olson and Nestler, 2007; Jhou et al., 2009a; Kaufling et al., 2009, 2010a), high levels of the μ -opioid receptor immunoreactivity (Jhou et al., 2009a, 2012; Jalabert et al., 2011), a prominent pattern of psychostimulant-induced Fos-related proteins (Scammell et al., 2000; Perrotti et al., 2005; Geisler et al., 2008; Jhou et al., 2009a;

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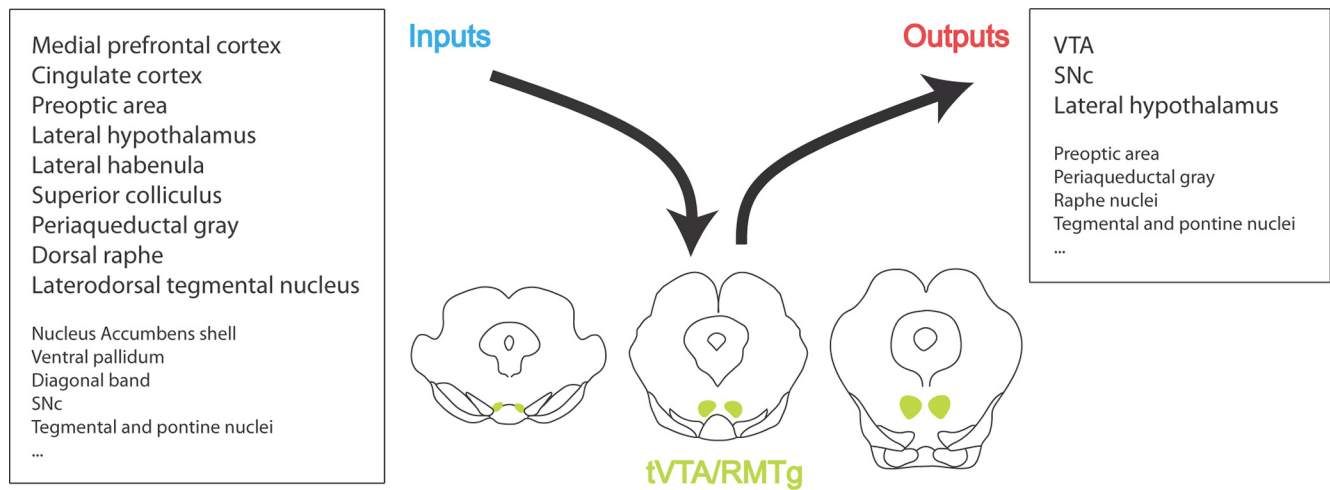


Figure 1. The tVTA/RMTg. The schema represents the rat tVTA/RMTg (in green) and lists its main afferent and efferent connections. Most afferent structures also innervate the VTA directly.

Kaufling et al., 2009, 2010b), and high levels of the neuropeptide nociceptin (Jhou et al., 2012).

In this review, we present some recent and ongoing work on the tVTA/RMTg and its links with dopamine systems.

Psychostimulants, aversive stimuli, and motor inhibition

Recent research on the tVTA/RMTg started from observations related to psychostimulant induction of FosB/ Δ FosB (Perrotti et al., 2005) and to the control of aversive responses (Jhou, 2005). The rat tVTA/RMTg showed a neuroanatomically delimited increase in the expression of Fos-related proteins following exposure to psychostimulants (Scammell et al., 2000; Perrotti et al., 2005; Geisler et al., 2008; Jhou et al., 2009a; Kaufling et al., 2009, 2010a, 2010b; Rotllant et al., 2010; Zahm et al., 2010; Cornish et al., 2012). This induction was observed with both acute and chronic exposure to psychostimulants, and with both self-administration and noncontingent administration. There is a strong selectivity of this molecular response, as the Fos-related induction was never observed with non-psychostimulant drugs (Perrotti et al., 2005; Kaufling et al., 2010b).

Changes in tVTA/RMTg neuron firing rates and/or cFos expression were also observed after some negative affective stimuli, such as footshocks, shock-predictive cues, omission of expected rewards, or food deprivation. Conversely, rewards and reward-predictive cues predominantly inhibited tVTA/RMTg firing (Jhou et al., 2009; Hong et al., 2011), a pattern inverse to that of most dopamine neurons (Schultz, 1998). Dopamine cells are implicated in many aspects of motivated behavior, including motor performance, cognition, affect, and learning, and the tVTA/RMTg may be implicated in a similarly wide range of functions. Fiber-sparing tVTA/RMTg lesions strikingly attenuated at least three distinct fear- and anxiety-related behaviors: conditioned freezing, unconditioned freezing, and open arm avoidance (Jhou et al., 2009b), suggesting a broad role in aversive behaviors, particularly those involving behavioral inhibition. The three altered behaviors may be triggered through distinct afferents to the tVTA/RMTg (for discussion, see Jhou et al., 2009b). Other behavioral aspects are being investigated, including a possible role for the tVTA/RMTg in the aversive properties of cocaine (Jhou et al., 2010).

The influence that the tVTA/RMTg exerts on behavior is likely related, at least in part, to the influence that this newly defined brain region exerts on dopamine systems.

The tVTA/RMTg and dopamine systems

The substantia nigra zona compacta (SNc) and VTA receive inhibitory inputs from multiple basal ganglia and basal forebrain regions (Somogyi et al., 1981; Bolam and Smith, 1990; Gonzales and Chesselet, 1990; Smith and Bolam, 1990; Fallon and Loughlin, 1995; Charara et al., 1996; Geisler and Zahm, 2005). SNc and VTA dopamine cells also receive inhibitory synapses from neighboring GABA neurons (Omelchenko and Sesack, 2009). Until recently, the potential inhibitory influence of the tVTA/RMTg on dopamine cells was unrecognized. Light microscopic observations, however, indicated that this projection was among the densest of afferents to the ventral midbrain and literally outlined the position of dopamine neurons (Ferreira et al., 2008; Jhou et al., 2009a; Kaufling et al., 2010a). Moreover, tVTA/RMTg axon varicosities formed multiple close appositions to the soma and dendrites of dopamine cells immunolabeled for the synthetic enzyme tyrosine hydroxylase (TH) (Jhou et al., 2009b; Kaufling et al., 2010a). These results suggested that dopamine neurons were the principal targets of tVTA/RMTg efferents.

To test this hypothesis, ultrastructural analysis was performed on tissue labeled by anterograde tract tracing from the tVTA/RMTg, and dual immunocytochemistry for tracer and either TH or GABA, in alternate sections. Within the VTA, ~83% of the synapses formed by tVTA/RMTg axons were onto dendrites immunoreactive for TH (Balcita-Pedicino et al., 2011). Despite the impression formed from light microscopic studies, no axosomatic synapses were found. Using postembedding immunogold, which is more sensitive than pre-embedding for the detection of GABA in axons, all tVTA/RMTg axons were found to be immunoreactive for GABA (Balcita-Pedicino et al., 2011). This finding was consistent with reports that the tVTA/RMTg represents a relatively pure GABAergic cell population (Perrotti et al., 2005; Olson et al., 2007; Jhou et al., 2009a,b; Kaufling et al., 2009, 2010a).

The remaining 17% of tVTA/RMTg synapses within the VTA were onto dendrites containing no TH signal detectable by the pre-embedding immunogold procedure used (Balcita-Pedicino et al., 2011). This finding suggests that some tVTA/RMTg axons contact non-dopamine neurons in the VTA, most of which are GABAergic (Nair-Roberts et al., 2008). This hypothesis is currently being investigated using pre-embedding immunogold, which is more sensitive than postembedding for detecting GABA in dendrites. To date, only a few tVTA/RMTg axons synapsing

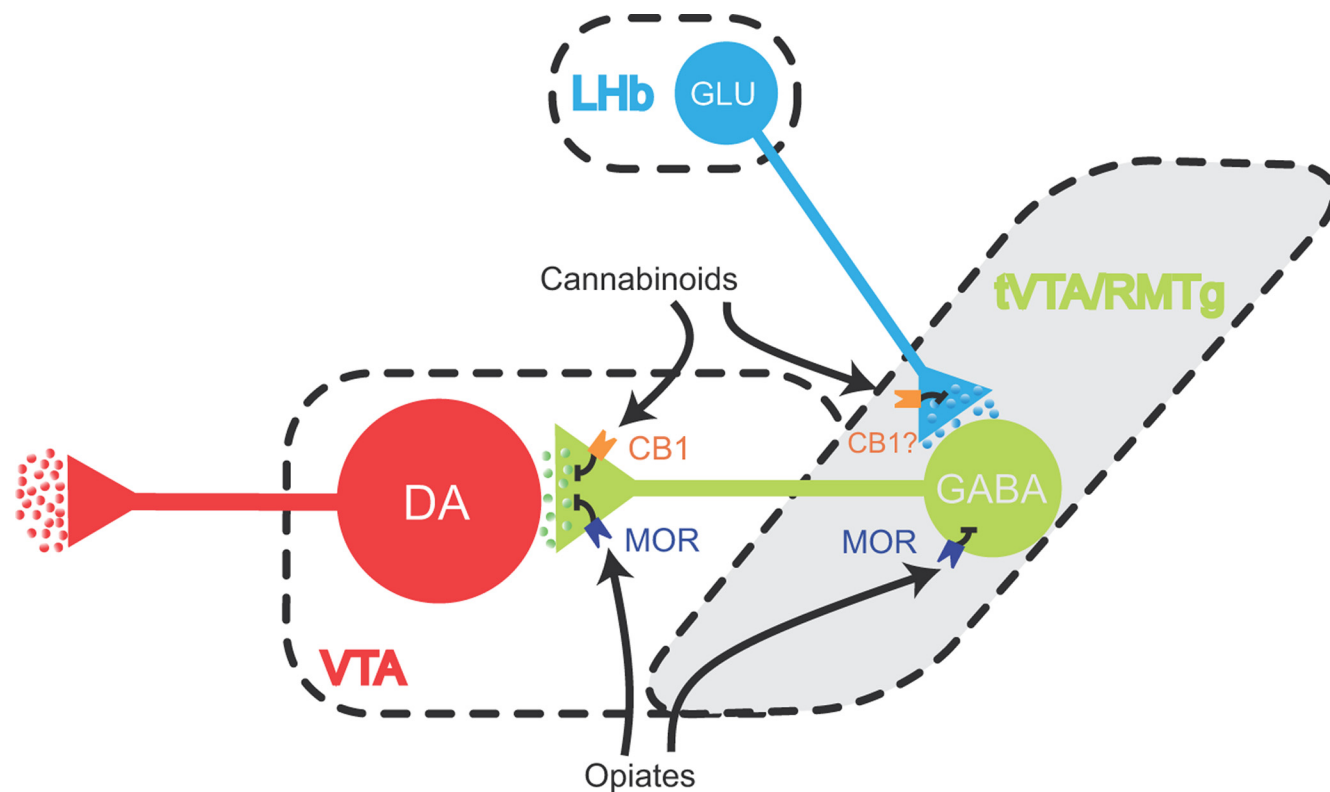


Figure 2. The tVTA/RMTg as a GABA brake for the dopamine system. The schema represents the tVTA/RMTg, its main glutamatergic input (lateral habenula, LHb), and its output to the nearby dopamine systems. Opiates and cannabinoids would recruit dopamine cells (DA) by blocking the GABA brake exerted by neurons of the tVTA/RMTg onto dopamine cells. CB1, cannabinoid receptors 1; MOR, μ -Opioid receptors.

onto GABA dendrites have been detected; additional sampling is needed to confirm these results. Such an outcome might indicate that the tVTA/RMTg also contacts glutamate-containing VTA neurons (Yamaguchi et al., 2007; Nair-Roberts et al., 2008). Alternatively, prior results may have included false-negative outcomes reflecting insufficient detection of low levels of TH. These possibilities are presently being examined.

Electron microscopy is now also being used to examine the tVTA/RMTg projection to the SNc. Although the findings are preliminary, all of the tVTA/RMTg axons observed to date synapse onto dendrites immunolabeled for TH and not onto unlabeled dendrites. Given that most SNc neurons are dopaminergic (González-Hernández and Rodríguez, 2000), this finding is not unexpected. Further investigation will include the dorsal portion of the SN reticulata, in particular the cell “bridges” where dopamine and non-dopamine cells intermingle. In this zone, it is possible that tVTA/RMTg axons will synapse onto non-dopamine neurons, although the density of this input is weak (Jhou et al., 2009b).

Collectively, these findings indicate that a substantial GABAergic projection from the tVTA/RMTg primarily targets dopamine neurons in the SNc and VTA. The placement of these synapses is mainly onto intermediate and proximal dendrites, and less commonly onto distal dendrites. The density of these synapses and their relatively proximal placement suggests that the tVTA/RMTg mediates a strong inhibitory influence on dopamine neurons throughout the ventral midbrain.

Dopamine systems are subject to an accelerator/brake control of their activity (Carlsson et al., 2001), which is critical for finely shaping dopamine responses. In agreement with neuroanatomical evidence, electrophysiological studies confirmed that the

tVTA-RMTg constitutes a major brake for dopamine systems: the inhibition of tVTA increases dopamine cell activity (Jalabert et al., 2011), and the stimulation of tVTA decreases it (Hong et al., 2011; Lecca et al., 2011, 2012; Matsui and Williams, 2011). Close attention was thus given to the tVTA/RMTg involvement in responses to drugs of abuse, more particularly opiates and cannabinoids, as well as in the processing of prediction error.

The tVTA/RMTg and opiates

Morphine is a potent opiate analgesic with a high addictive potential in some specific contexts outside medical usage (Shurman et al., 2010). A broadly accepted circuit model for morphine action on dopamine neurons suggests that morphine excites VTA-dopamine neurons by a disinhibitory mechanism involving neighboring GABA cells (Johnson and North, 1992). However, recent electrophysiological evidence has challenged this canonical model, by proposing an alternative inhibitory source, the tVTA/RMTg, for the excitatory effect of morphine on VTA-dopamine neurons (Fig. 2) (Jalabert et al., 2011; Lecca et al., 2011, 2012; Matsui and Williams, 2011; Bourdy and Barrot, 2012). Indeed, tVTA/RMTg cells express high levels of μ -opioid receptors (Jhou et al., 2009a, 2012; Jalabert et al., 2011), and *in vivo*, *ex vivo*, and optogenetic electrophysiological approaches demonstrated that morphine excites dopamine neurons by targeting receptors localized to tVTA/RMTg cell bodies as well as its terminals within the VTA (Jalabert et al., 2011; Lecca et al., 2011; Matsui and Williams, 2011; Lecca et al., 2012).

Exploring the sources of inhibitory and excitatory drives onto dopamine neurons is critical for understanding the impact of network activity on the integrative properties of dopamine neurons in response to morphine. In addition to potent tonic GABA

modulation (Paladini and Tepper, 1999), VTA-dopamine neurons receive glutamatergic inputs from diverse brain nuclei (Geisler et al., 2007; Dobi et al., 2010). Evidence indicates a critical role for VTA glutamate receptors in morphine rewarding properties (Carlezon et al., 1997; Harris et al., 2004), and the crucial role of the inhibition/excitation balance for the *in vivo* effects of morphine on dopamine neurons has recently been demonstrated (Jalabert et al., 2011). The influence of tVTA/RMTg in morphine-induced activation of VTA-dopamine neurons was assessed by intra-VTA infusion of morphine after selective inactivation of the tVTA/RMTg (Jalabert et al., 2011). In this condition, morphine failed to increase dopamine activity, which demonstrated that tVTA/RMTg tonic activity was necessary for morphine-induced responses of VTA-dopamine neurons. These *in vivo* results were confirmed *ex vivo* by a study demonstrating that GABA projections from the tVTA/RMTg were inhibited by opioids, which consequently disinhibited VTA-dopamine neurons (Matsui and Williams, 2011). However, this GABA-related disinhibition did not preclude a role for VTA glutamatergic transmission in the morphine effect. Indeed, blocking VTA NMDA and AMPA receptors prevented morphine-induced excitation of VTA-dopamine neurons (Jalabert et al., 2011). This outcome showed that VTA glutamatergic transmission is necessary for the *in vivo* excitatory effect of morphine.

These recent findings were extended by assessing the functional consequences of increasing the excitatory control of VTA-dopamine neurons on morphine-induced responses (M. Jalabert, C. Glangetas, L. Groc, and F. Georges, unpublished data). Based on previous *ex vivo* electrophysiological studies (Ungless et al., 2001), the VTA was assessed 24 h following a single acute cocaine injection. The results established that cocaine experience potentiates morphine-induced excitation of VTA-dopamine neurons *in vivo*, suggesting that the intrinsic excitability of VTA-dopamine neurons may be important for scaling morphine responses. Given that morphine has a high addictive potential in specific situations (Shurman et al., 2010), it would be important to assess whether the excitatory context of dopamine neurons may tune the addictive potency of morphine.

The critical role of the tVTA/RMTg in opiate action is also supported by behavioral data. The injection of a μ -opioid receptor agonist into the tVTA/RMTg markedly reduced pain responses to subcutaneous formalin injections (Jhou et al., 2012), and infusions of μ -opioid agonists or GABA agonists into the tVTA/RMTg supported self-administration and conditioned place preference (Jhou et al., 2012). These data suggest that tVTA/RMTg inhibition can be reinforcing. Conversely, activation of the tVTA/RMTg—as obtained through optogenetic stimulation of afferents from the lateral habenula—has been shown to promote behavioral avoidance (Stamatakis and Stuber, 2012).

Interestingly, some functional properties recently attributed to the tVTA/RMTg have also been ascribed to VTA GABAergic neurons (Cohen et al., 2012; Tan et al., 2012; van Zessen et al., 2012), raising questions about whether these two populations are similar or separate. The insertion of the rostral part of the tVTA/RMTg within areas that are designated in brain atlases as VTA may add to the confusion. While most studies have not attempted to distinguish the tVTA/RMTg from nearby sites, some studies do show substantial differences. Anatomically, VTA GABA neurons exhibit prominent projections to the forebrain (Van Bockstaele and Pickel, 1995; Carr and Sesack, 2000a, 2000b) that the tVTA/RMTg lacks (Jhou et al., 2009a; Kaufling et al., 2010b). Conversely, the tVTA/RMTg receives an intense lateral habenula synaptic input that is several-fold greater than the habenular pro-

jection to the VTA (Balcita-Pedicino et al., 2011). Even more critically, injections of small (nanomolar) quantities of μ -opioid receptor agonist or GABA agonist that produced reinforcement or analgesia in the tVTA/RMTg did not produce these effects when injected into the VTA (Jhou et al., 2012). This may seem surprising considering the prior reports of reward or analgesia after larger intra-VTA injections of μ -opioid receptor agonists (Morgan and Franklin, 1991; Nader and van der Kooy, 1997; Zangen et al., 2002), and considering that opiates can act directly on tVTA/RMTg terminals within the VTA to recruit dopamine neurons (Jalabert et al., 2011; Matsui and Williams, 2011). However, very small injections strongly limit the drug spread, affecting a restricted part of the considered structure. Such small injections into the VTA might affect a subset of cells or terminals only, which may not be enough to elicit detectable behavioral consequences. On the other hand, tVTA/RMTg injections would target GABA cells with widespread projection fields into the VTA (Jhou et al., 2009a; Kaufling et al., 2010), which may result in the secondary disinhibition of a much larger population of dopamine cells. These results and the partial inclusion of the tVTA/RMTg within the posterior aspects of VTA also raise the possibility that some of the behavioral data from the last decade showing antero-posterior differences in the behavioral influence of the VTA might be related to tVTA/RMTg targeting (Ikemoto et al., 1998, 2006; Zangen et al., 2002, 2006; Rodd et al., 2004, 2008; Shabat-Simon et al., 2008; Linsenbardt and Boehm, 2009; Hauser et al., 2011). This question may be particularly relevant concerning the action of opiates, ethanol, and cannabinoids.

The tVTA/RMTg and cannabinoids

Not only opiates, but cannabinoids also are known to activate dopamine neurons by disinhibition (Lüscher and Ungless, 2006), i.e., by depressing GABA release and therefore shifting the balance between excitatory and inhibitory inputs impinging on dopamine cells (Marinelli et al., 2006; Lobb et al., 2010; Morikawa and Paladini, 2011). As mentioned above, the tVTA/RMTg, as a major source of GABA in the VTA, powerfully contributes to this balance. Hence, the strength of tVTA/RMTg-induced inhibition of dopamine cells was correlated with their spontaneous discharge rate (Lecca et al., 2012), and inactivation of the tVTA/RMTg increased the firing rate of dopamine neurons (Jalabert et al., 2011). The recent characterization of tVTA/RMTg neurons also sheds new light onto the mechanisms by which cannabinoids excite dopamine neurons (Fig. 2). Indeed, these drugs depress tVTA/RMTg neurons' activity and strongly reduce the inhibition exerted by tVTA/RMTg afferents (Lecca et al., 2011, 2012). Patch clamp experiments also showed that the cannabinoid agonist WIN55212-2 depressed IPSCs evoked in VTA dopamine cells by stimulation of tVTA/RMTg afferents through a presynaptic mechanism (Lecca et al., 2012), suggesting that tVTA/RMTg terminals express cannabinoid receptors 1 (CB1).

The endocannabinoid system plays a major role in mechanisms of addiction: CB1 agonists promoted reinstatement of extinguished drug-seeking behavior (the equivalent of relapse in humans) for a number of drugs of abuse (Fattore et al., 2003, 2005; López-Moreno et al., 2004; Spano et al., 2004; McGregor et al., 2005; Justinova et al., 2008; Gamaledin et al., 2012). Conversely, CB1 antagonists (i.e., rimonabant) reduced the rewarding effects of most drugs of abuse (Colombo et al., 1998; De Vries et al., 2001; Navarro et al., 2001; Cohen et al., 2002; Rigotti et al., 2009). However, rimonabant was withdrawn from the market for increased risk of depression and suicide (Christensen et al., 2007). From this lesson, we learned that CB1 receptor blockade

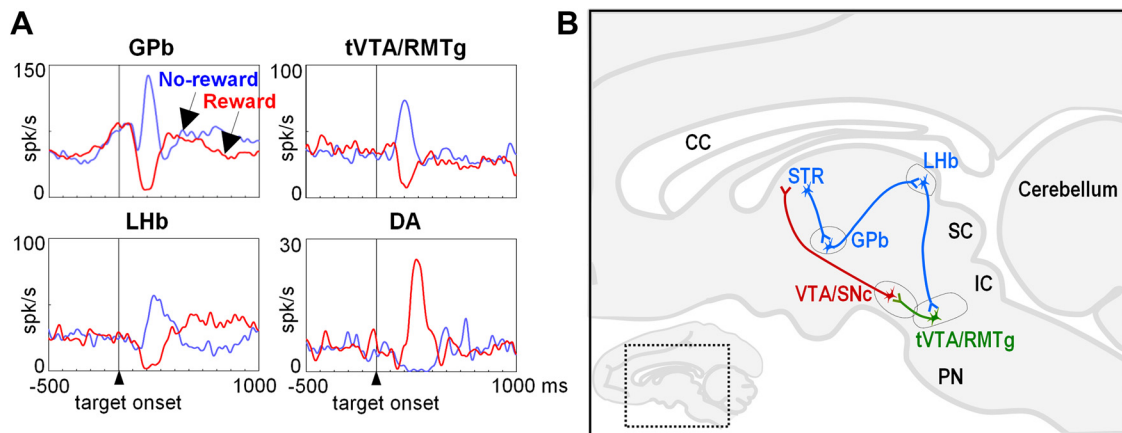


Figure 3. The tVTA/RMTg as part of the reward prediction error circuit. **A**, Responses of representative GPb, lateral habenula (LHb), tVTA/RMTg, and dopamine neurons (DA) to the visual target onset in the 1DR task (Hong et al., 2011). The averaged activity of each neuron, expressed as a spike (spk) density function, is shown separately for the reward trials (red) and no-reward trials (blue) as the response to the onset of the target. **B**, Neuroanatomical schematic of the reward prediction error circuit in the monkey. CC, Corpus callosum; GPb, borders of the globus pallidus internal segment; IC, inferior colliculus; PN, pontine nuclei; SC, superior colliculus; STR, striatum.

decreases the motivation to seek sources of reward, including natural ones (Horder et al., 2010) and induces states of anhedonia and enhanced sensitivity to aversive stimuli or punishment, which might lead vulnerable individuals to depression.

The tVTA/RMTg is in the ideal position, being a possible hub between aversion- and reward-responding brain regions, to function as a switch between opposite motivational states and to relay information to dopamine neurons (Lavezzi and Zahm, 2011; Bourdy and Barrot, 2012). Under these circumstances, the tVTA/RMTg terminals on VTA cells might be targets for endocannabinoid-mediated short- and long-term forms of synaptic plasticity. Electrophysiological evidence supports this hypothesis and indicates that endocannabinoids regulate the strength of these afferents and ultimately adjust dopamine neuron firing (Pistis et al., unpublished data). Hence, by decreasing GABA release from tVTA/RMTg terminals, the endocannabinoids might sensitize dopamine neurons toward excitatory inputs evoked by rewarding stimuli, such as those associated with drugs of abuse. This might result in enhanced firing activity and dopamine release in terminal regions (Melis and Pistis, 2012; Melis et al., 2012), and possibly behavioral sensitization or reinstatement of drug-taking behavior. Conversely, deficits in the endocannabinoid tone on tVTA/RMTg synapses are expected to promote GABA release and depress dopamine cell firing. This enhanced inhibitory control on dopamine neurons might dampen their responses to natural rewards or addictive drugs, or increase those toward aversive stimuli, ultimately leading to reduced motivation or to maladaptive responses to aversion and punishment.

This hypothetical mechanism could also bear relevance for gender- or strain-specific vulnerability to addictive drugs. It is noteworthy that the appetitive properties of addictive drugs result from activation of brain reward pathways and suppression of responses in neural circuits mediating aversion (Riley, 2011). Individuals susceptible to addiction might experience reduced responses to the aversive component intrinsic to several addictive drugs, such as alcohol (Rezvani et al., 2010) and cannabinoids (Quinn et al., 2008), or to negative consequences of compulsive drug intake (Riley, 2011). In this regard, experiments in alcohol-preferring rat strains or in female rats—more vulnerable than male counterparts to cannabinoid self-administration (Fattore and Fratta, 2010)—may provide information on the strength of

tVTA/RMTg afferents and of endocannabinoid-mediated synaptic depression, and on how these parameters may correlate with the vulnerability to addiction. These hypotheses concerning the endocannabinoid system and tVTA/RMTg function are presently under investigation.

Placing tVTA/RMTg into prediction error pathways

The above-mentioned properties of the tVTA/RMTg suggest roles in a variety of motivational processes, consistent with emerging evidence placing it in a critical location among the pathways processing reward prediction errors (RPEs). Neurons from the lateral habenula in the monkey are excited by a visual stimulus that indicates the absence of reward and inhibited by a stimulus that indicates the presence of reward (Matsumoto and Hikosaka, 2007). This negative reward signal contributes to the well known reward coding of dopamine neurons (Christoph et al., 1986; Matsumoto and Hikosaka, 2007). The suggestion that the RPE signal in dopamine neurons may come from the lateral habenula triggered research to examine the neural elements of reinforcement learning connected to the lateral habenula and dopamine areas (Fig. 3A). It was hypothesized that the globus pallidus internal segment (GPi) could play a critical role, considering the fact that the major input to the lateral habenula comes from the GPi (Parent et al., 2001). To test this hypothesis, antidromic stimulation was used to identify GPi neurons that projected to the lateral habenula, in combination with a behavioral saccade task known as the one-direction-rewarded (1DR) to control the level of motivation. The results showed that lateral habenula-projecting neurons were located mainly along the borders of the GPi (GPb) and displayed firing patterns different from movement-related GPi neurons. A majority of GPb neurons encoded a negative RPE similar to that observed for lateral habenula cells, while some other neurons encoded a positive RPE. A detailed analysis showed that only the negative-RPE-coding neurons discriminated the reward/no reward meaning of the saccade target earlier than the lateral habenula. These results led to the suggestion that the GPb-to-lateral habenula projection was excitatory (Hong and Hikosaka, 2008a). Consistent with this idea, the electrical stimulation of the GPb triggered a short-latency excitatory response in lateral habenula neurons (Hong and Hikosaka, 2008b).

While the suppressive influence of the lateral habenula on the dopamine system was established, a more detailed circuit hypothesis emerged in the following years from several laboratories.

It was suggested that a little-known structure, the tVTA/RMTg, receives lateral habenula inputs and projects to dopamine neurons in rodents (Jhou et al., 2009a,b; Kaufling et al., 2009, 2010; Omelchenko et al., 2009; Balcita-Pedicino et al., 2011). To determine the function of this suggested circuit, antidromic and orthodromic recording techniques were used between the lateral habenula, tVTA/RMTg, and dopamine areas, in combination with injection of a retrograde tracer into the dopamine cell area in the monkey. Antidromically and orthodromically activated neurons were recorded while the monkey was performing the 1DR task. Results showed that tVTA/RMTg neurons were localized in the paramedian tegmental area, caudal to the VTA, extending caudally toward the pedunclopontine tegmental nucleus along the lower border of the superior cerebellar peduncle decussation (Hong et al., 2011). Physiologically, those neurons receiving inputs from the lateral habenula showed a similar activation pattern to lateral habenula neurons (Fig. 3B) and sent their suppressive signals to dopamine cells. In addition, many tVTA/RMTg neurons showed tonic responses resembling the “state value” signals in the dorsal raphe (Bromberg-Martin et al., 2010), which is one of the targets of the tVTA/RMTg. Interestingly, about half of the tVTA/RMTg neurons discriminated the reward/no reward conditions earlier than the lateral habenula, suggesting that the tVTA/RMTg may receive some reward-related inputs originating from areas other than the lateral habenula.

These results support the hypothesis that the negative RPE signal of the lateral habenula originates from the basal ganglia and is sent to the tVTA/RMTg. The tVTA/RMTg in turn translates this negative RPE into a dopamine-positive RPE, while transmitting additional motivational signals to non-dopamine networks, therefore reinforcing rewarding actions and discouraging actions leading to failure. This hypothesis gains support from a recent study in mice showing that stimulation of lateral habenula inputs to the tVTA/RMTg is sufficient to induce behavioral avoidance (Stamatakis and Stuber, 2012). This observation suggests that the circuit outlined above represents a shared mechanism across species.

Concluding remarks

The elucidation of a new brain region is a relatively rare event in the present age of neuroscience. Such discoveries have the potential to rapidly advance our knowledge, as evidenced by the speed with which new data have emerged regarding the tVTA/RMTg and as evidenced by the importance of these revelations for understanding the functional operation of reward and aversion systems. The tVTA/RMTg has proved itself to be a major source of inhibitory regulation of SNc and VTA dopamine neurons whose substantial influence was missing from previous models of reinforcement learning. This brainstem region and its ascending projections serve as substrates for activation of dopamine cells by different drugs of abuse, thus contributing to their rewarding and/or aversive properties. Furthermore, the tVTA/RMTg provides a key node in the circuitry by which dopamine neurons acquire information predictive of reward and punishment. Because of these essential roles, it is possible that dysfunction of the tVTA/RMTg contributes to the pathophysiology of mental disorders such as major depression and addiction. Moreover, the tVTA/RMTg may serve as a potentially useful site for therapeutic intervention in these conditions. It is hoped that what is learned in the next few years through advanced study of this critical brain structure illuminates understanding of how regulatory systems control motivated behavior.

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