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The Yin and Yang of Dopamine Release:

A New Perspective

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Abstract

Dopamine has undergone extensive investigation due to its known involvement in a number of neurological and psychiatric disorders. In particular, studies into pathological conditions have focused on the roles of high amplitude, phasically evoked dopamine release in regions such as the prefrontal cortex and striatum. However, research has shown that dopamine release can be more complex than just phasic release; thus, there is also a tonic, background dopamine release, with alterations in tonic dopamine release likely having unique and important functional roles. Unfortunately, however, tonic dopamine release has received relatively little attention. In this review, we summarize our recent studies and discuss how modulation of the dopamine system, both in terms of phasic activation and attenuation of tonic dopamine are important for the functions of brain regions receiving this dopamine innervation, and that imbalances in these dopamine release mechanisms may play a significant role in psychiatric disorders such as schizophrenia.

Keywords

Limbic System; Prefrontal Cortex; Nucleus Accumbens; Cognitive Functions; Animal Model; Schizophrenia

1. Introduction

Since its description in the brain by Carlsson in 1957 (Carlsson et al., 1957), the roles of dopamine (DA) have been extensively studied because of the demonstrated involvement of this transmitter system in multidimensional brain functions such as learning and memory (Grecksch and Matties, 1981), motivation (Everitt and Robbins, 2005), and emotional behaviors (Nader and LeDoux, 1999). Moreover, disruption of DA systems have been implicated in major neurological and psychiatric disorders including Parkinson's disease and schizophrenia (Hornykiewicz, 1966). In our recent studies, we provide a unique perspective on the functional relevance of DA system regulation, in which we suggest that a "decrease" of DA release may be as important as an "increase" of DA release in modulating behavior.

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2. Dopamine spike firing and dopamine release

DA neurons exhibit two distinct modes of spike firing: tonic single spike activity and burst spike firing (Grace and Bunney, 1984a; Grace and Bunney, 1984b). Tonic firing refers to spontaneously occurring baseline spike activity and is driven by pacemaker-like membrane currents of DA neurons (Grace and Bunney, 1984b; Grace and Onn, 1989). However, these DA neurons are under the influence of a very potent GABAergic inhibition, preventing some DA neurons from firing spontaneously in the basal condition (Grace and Bunney, 1979). Tonic firing of DA neurons has been shown to underlie the baseline tonic level of DA concentration within the striatum (e.g. 10-20 nM within the striatal region (Keef et al., 1993)). Studies suggest that this is mediated by an escape of DA from the synapse into the extrasyanptic space (Floresco et al., 2003; Grace, 1991). Therefore, the concentration of tonic extracellular DA is dependent on the number of DA neurons demonstrating spontaneous tonic spike activity (Floresco et al., 2003; Grace, 1991).

In contract, phasic activation of the DA system represented by the burst spike firing pattern is dependent on glutamatergic excitatory synaptic drive onto DA neurons from a number of areas, including the pedunculopontine tegmentum (PPTg) (Floresco et al., 2003; Futami et al., 1995) and the subthalamic nucleus (Smith and Grace, 1992). Burst spike firing triggers a high amplitude (e.g. hundreds of μM to mM levels), transient, phasic DA release intrasynaptically within the targeted areas (Floresco et al., 2003; Grace, 1991). This high amplitude DA release is nonetheless suggested to be subject to powerful, immediate reuptake into pre-synaptic terminals via DA transporters (Chergui et al., 1994; Suaud-Chagny et al., 1995), and therefore, phasic DA release would act transiently within the synaptic cleft and in very close proximity to the synapse (Floresco, et al., 2003; Grace, 1991; Chergui et al., 1994; Venton et al., 2003).

A series of electrophysiological studies by Schultz (Schultz et al., 1993; Tobler et al., 2003; Waelti et al., 2001) have shown behavioral correlates of tonic and bust spike firing of DA neurons. Thus, DA neurons exhibit burst spike firing that is triggered by presentation of unexpected rewards or sensory signals predicting such rewards (Schultz et al., 1993). In contract, studies have also revealed that a transient suppression of tonic spike firing in DA neurons occurs in response to the omission of expected rewards (Tobler et al., 2003) or aversive stimuli (Grace and Bunney, 1979; Ungless et al., 2004). Schultz suggests that these patterns of DA spike firing could be used as learning signals in the targeted brain structures (Waelti et al., 2001). Nevertheless, the distinct functional impact of DA release that occurs in response to burst spike firing versus suppression of tonic spike activity of DA neurons in the targeted area was unclear.

3. Dopamine modulation of afferent input into the nucleus accumbens

To elucidate the functional relevance of DA system transmission in terms of the messages conveyed by burst firing versus suppression of tonic firing of DA neurons into the targeted regions, we investigated the influences of tonic and phasic DA release on the modulation of afferent inputs into the nucleus accumbens (NAcc), where a dense DA innervation from the ventral tegmental area (VTA) is present (Voorn et al., 1986). The NAcc is believed to regulate goal-directed behaviors (Mogenson et al., 1980) as it receives convergent synaptic inputs from limbic structures and the PFC (Finch, 1966; French and Totterdell, 2002). Thus, the NAcc is located where contextual and emotional information processed in limbic structures and motor planning processed in the PFC could be integrated (Grace, 2000).

Using in vivo electrophysiology combined with pharmacological manipulations of the DA system in the NAcc, we found that selective modulation of limbic and PFC inputs is mediated by DA D1 and D2 receptors, respectively (Goto and Grace, 2005). Thus, activation of D1 receptors facilitated limbic inputs into the NAcc without affecting PFC inputs, although

blockade of D1 receptors with a D1 antagonist did not yield significant effects on either limbic or PFC inputs. In contrast, we found that activation and inactivation of D2 receptors attenuated and facilitated, respectively, responses mediated by PFC inputs without affecting limbic inputs. This suggests that, unlike D1 receptor stimulation, striatal D2 receptors are under the influence of DA at the baseline condition, and can be modulated up or down from this state. Moreover, we also manipulated phasic and tonic DA release in the NAcc with activation and inactivation of the basal ganglia nuclei that regulate these distinct activity patterns as we recently reported (Floresco et al., 2003). Selective facilitation of limbic inputs was observed when phasic DA release (mediated by DA neuron burst firing) is increased, whereas, increases and decreases in tonic DA release selectively attenuated and facilitated, respectively, the PFC inputs. Taken together, these observations suggest that phasic DA release activates D1 receptors to facilitate limbic inputs, whereas tonic DA release has bi-directional effects on PFC inputs via D2 receptors, with increasing tonic D2 stimulation attenuating PFC afferent inputs and decreases in tonic D2 stimulation facilitating PFC inputs.

In addition to the physiological consequences of tonic and phasic DA system modulation, these distinct DA activity states were also found to exhibit behaviorally selective effects. Thus, using a behavioral cue discrimination task, we found that facilitation of limbic inputs into the NAcc by phasic DA release activating D1 receptors is required for learning of a response strategy in reinforcement learning, whereas a reduction of tonic DA stimulation of D2 receptors is essential to allow switching to a new response strategy once the criteria to achieve the goals is changed (Goto and Grace, 2005). Therefore, suppression of tonic spike firing of DA neurons by omission of expected rewards, which should result in a reduction of tonic DA release in the NAcc, may be used to selectively facilitate cortico-striatal information processing that mediates behavioral flexibility (Meck and Benson, 2002).

4. Impact of stress on dopamine-dependent synaptic plasticity

The PFC is another region that receives DA innervation from the VTA (Thierry et al., 1973). Unlike the striatum, this mesocortical DA innervation into the PFC is comparatively sparse; nonetheless, owing to the lower number of uptake sites and the high DA turnover in this region, DA still exerts prominent electrophysiological and behavioral effects in this brain region. DA release in the PFC has been shown to be critical for cognitive functions such as working memory (Goldman-Rakic, 1995). Moreover, alterations in DA release in the PFC are reported to occur upon exposure to stress. Thus, studies have shown that DA release in the PFC is increased under acute stress exposure (Gresch et al., 1994; Morrow et al., 2000), whereas when stress becomes chronic (e.g. over 2 weeks of stressful condition), a decrease of baseline DA release in the PFC is observed (Gresch et al., 1994). The impact of such increases and decreases in DA release on the induction of synaptic plasticity in PFC networks was examined as synaptic plasticity such as long-term potentiation (LTP) and depression (LTD) in the PFC: a process known to be DA-dependent (Otani et al., 2003). We found that LTP induction in hippocampal afferents into the PFC, which depends on D1 activation (Gurden et al., 2000), was facilitated with a short period of acute stress exposure, whereas when the exposure to stress is prolonged, LTP induction is impaired (Goto and Grace, 2006). As a result, there is an inverted U-shaped relation between the induction of synaptic plasticity in the hippocampal-PFC pathway and the duration of stress exposure, which is correlated with the amount of DA release during the stress exposure. While it is unclear whether the increase in DA release persists during the time of the LTP induction, the DA-induced changes in the phosphorylation of second messenger molecules such as CREB and DARPP-32 (Greengard, 1999), which are required for induction of LTP in this pathway (Hotte et al., 2007), are known to have effects that far outlast the period of DA receptor stimulation (Fig. 1A and 2B).

Using the in vitro slice preparation, we have provided data that has important implications with respect to the functional impact produced by a reduction in tonic, background DA release in the PFC (Matsuda et al., 2006). Thus, in the slice preparation where DA afferents are transected from cell bodies and a significant amount of residual DA is washed out during incubation, the background DA concentration would be expected to be significantly lower than that present in the intact, in vivo condition. We found that under such conditions, high frequency tetanic stimulation that is normally sufficient to induce LTP in vivo instead resulted in the induction of LTD. However, when a low concentration of DA was applied into the bath solution to mimic tonic background DA release present in vivo, high frequency stimulation now results in the induction of LTP, suggesting that the level of background tonic DA tone could determine the polarity of the synaptic plasticity that can be induced in PFC networks (Fig. 1A). A similar reduction in background DA tone is reported to occur within the PFC following chronic stress exposure (Gresch et al., 1994). Indeed, our preliminary evidence suggests that high frequency stimulation that normally induces LTP at hippocampal afferents into the PFC in the in vivo condition will instead result in the induction of LTD when animals are exposed to 2 weeks of chronic cold or restrain stress exposure (Goto et al., 2007).

5. Implications of tonic and phasic dopamine release in psychiatric disorders

Hypofrontality and attenuated DA release in the PFC have been proposed as pathophysiological factors in schizophrenia (Andreasen et al., 1992; Yang and Chen, 2005), with a particular association with the negative symptoms of this disorder (e.g. anhedonia, social withdrawal) (Andreasen et al., 1992). A similar hypofrontal condition is also reported in individuals with mood disorders such as depression (Galynker et al., 1998). Given that chronic stress is known to induce a depressive state and, therefore, has been employed as an animal model of depression (Katz et al., 1981), abnormal induction of LTD with attenuation of background tonic DA release in the PFC may be involved in negative symptoms of schizophrenia and depression (Fig. 1B).

Although hypofrontality has been proposed to be present in schizophrenia patients, there are some reports suggesting that PFC activity could be even higher in schizophrenia patients when compared to normal subjects in certain condition such as in performing comparatively easy working memory tasks (Callicott et al., 2003; Manoach, 2003). Thus, these studies suggest that an inverted U-shaped relation exists between working memory and activation of the PFC, and that schizophrenia patients may exhibit a lower working memory capacity compared to controls, leading to higher activation with simpler tasks (Fig 2A) (Manoach, 2003). Indeed, we have found a similar inverted U-shaped relation between LTP induction in the PFC and the effects of acute stress (Goto and Grace, 2006). In particular, we have also observed a shift of this inverted U-shaped relation toward greater acute stress vulnerability in an animal model of schizophrenia (Fig 2B) (Goto and Grace, 2006). In fact, it is known that schizophrenia patients exhibit a characteristic of greater vulnerability to stress, which has been correlated with susceptibility to relapse (Rabkin, 1980).

6. Conclusion

Increases and decreases in DA release can have markedly different effects on brain function, which can be both “Yin” and “Yang” depending on the state of the organism. Therefore, consideration of the bi-directional nature of DA changes is important for the normal functions of brain regions receiving DA innervation including the NAcc and PFC. An abnormal balance of DA release, especially in the PFC, may play a significant role in the pathophysiology of psychiatric disorders such as schizophrenia and depression.

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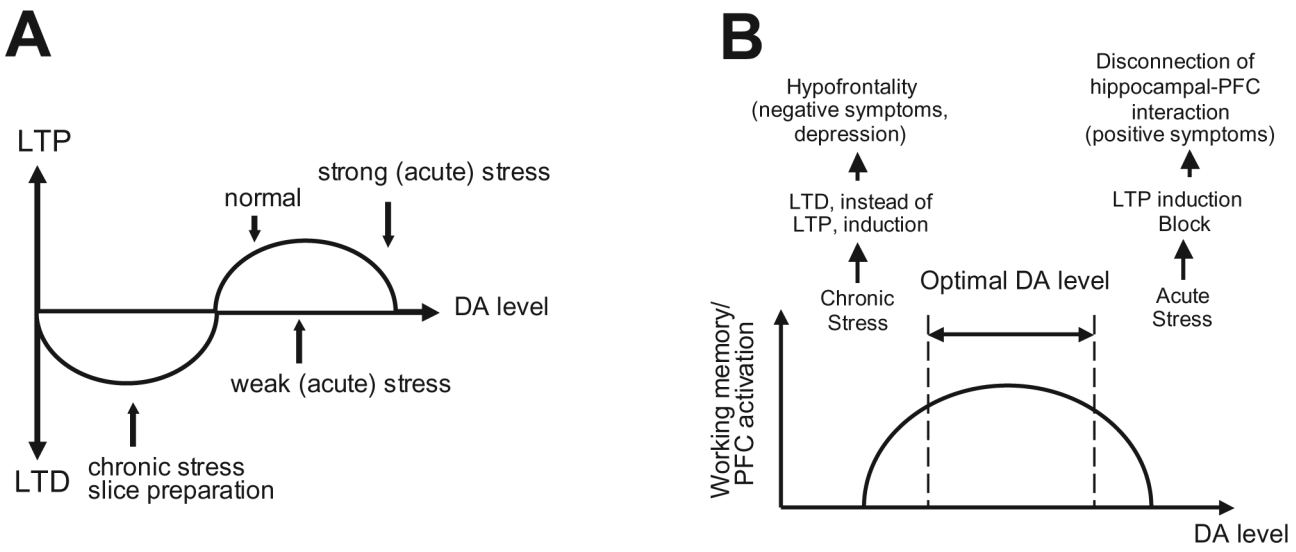

Figure 1.

Based on findings from animal studies, several models can be derived to account for some of the observations made regarding possible underlying biological mechanisms of psychiatric disorders such as schizophrenia. **(A)** In the normal condition at a moderate level of DA tone, long-term potentiation (LTP) is induced with high frequency activation of PFC afferent fibers such as those arising from the hippocampus and participating in memory-guided behavior. A brief exposure to stress would increase DA release in the PFC, and thereby facilitate DA-dependent induction of LTP, whereas if the stress exposure is severe, an excess in DA release could occur, leading to impairment of LTP (e.g. via stimulation of extrasynaptic DA receptors). In contrast, in the case of chronic stress, where a significant decrease in DA tone is produced, PFC networks would preferentially shown LTD. Such a condition is likely to be present in the in vitro slice preparation, in which the DA tone would be expected to be low. **(B)** Acute stress induces excessive DA release, which in turn over-stimulates D1 receptors in the PFC. As a result, information processing mediated by hippocampal-PFC interactions, which depends on LTP, would be disrupted. In contrast, attenuated DA tone, which could be produced by chronic stress exposure, would also interfere with proper information processing in the hippocampal-PFC pathway due to the abnormal induction of LTD. Indeed, this LTD may contribute to suppression of PFC activity (i.e. hypofrontality).

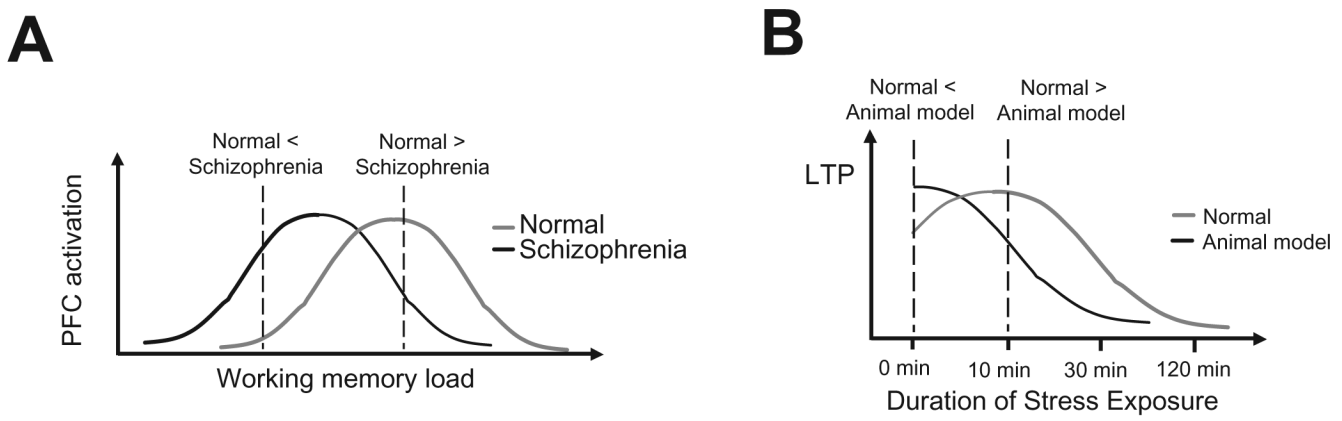

Figure 2.

Alterations in the inverted U-shaped relationships could contribute to the pathophysiology of schizophrenia. **(A)** Studies suggest that the relationship between working memory and PFC activation may also present as an inverted U-shape. In this example, schizophrenia patients would exhibit normal PFC activation only with a low working memory load. However, as the working memory load increases, PFC activation fails to compensate and becomes lower than that of normal subjects. Therefore, the hypofrontal condition reported in schizophrenia may be a function of working memory capacity of the PFC. Adapted from Manoach, 2003. **(B)** Our studies revealed that, in a developmental disruption model of schizophrenia, a similar inverted U-shaped relationship may exist with respect to LTP in PFC networks and stress exposure, with the schizophrenia model showing a leftward shift in the debilitating aspects of stressful stimuli. Adapted from Goto and Grace, 2006.