

# Adolescent Maturation of Cortical Dopamine

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Received: 11 November 2009/Revised: 14 January 2010/Accepted: 14 January 2010/Published online: 12 February 2010  
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**Abstract** Dopamine is a critical modulator of prefrontal cortical function, and it is known to be dysfunctional in schizophrenia. Current hypotheses on schizophrenia highlight developmental aspects and genetic predisposition for the disease; yet, symptom onset typically occurs during adolescence. Several aspects of prefrontal cortical circuits and their modulation by dopamine mature postnatally, as late as during adolescence. Here we review studies assessing the postnatal trajectory of dopamine control of GABA interneurons, a neuronal population that has been long suspected to be critical for schizophrenia pathophysiology. Dopamine modulation of fast-spiking interneurons changes dramatically during adolescence (postnatal day 45–50 in rats) with D2 agonists switching from being mildly inhibitory in prepubertal rats to strongly excitatory in young adult rats. In vivo recordings in adult rats reveal that deep-layer pyramidal neurons respond to endogenous DA release with suppression of firing while interneurons are activated. In adult rats with a neonatal ventral hippocampal lesion (NVHL), an extensively studied developmental model of schizophrenia, the maturation in the D2 modulation of interneuron physiology fails to occur, rendering a disinhibited prefrontal cortex. Abnormal interneuron maturation may therefore impair cognitive function in the adult animal.

**Keywords** Prefrontal cortex · GABA · Dopamine · Schizophrenia · Adolescence · Interneuron · Electrophysiology · Animal models

Anyone who has ever dealt with teenagers can tell that it is an age characterized by poor self-control, risk-taking, and inappropriate behaviors. There is a large amount of literature characterizing adolescent psychological processes (Dahl 2004; Galvan et al. 2007), and it is clear that adolescents are at risk for a number of mental health conditions including drug abuse and depression (Brenhouse and Andersen 2008; Brenhouse et al. 2008). However, the neural bases for such vulnerability and the changes involved in periadolescent brain maturation are only beginning to be understood. The prefrontal cortex (PFC) stands out as a brain region involved in adolescent behavior. Indeed, the PFC is critical for inhibitory control, decision making, and response selection, all processes that mature during adolescence. Furthermore, its malfunction can lead to risky behaviors and several psychiatric conditions that emerge during adolescence, such as schizophrenia and bipolar disorder. Here, we will review recent progress on understanding the maturation of PFC circuits during adolescence in several animal models.

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## Circuit Connectivity in the Prefrontal Cortex Changes During Adolescence

PFC function is determined by the interplay among several neuronal types and their modulation by afferents. As in any cortical region, pyramidal neurons are the primary PFC output, but their firing and its timing is tightly regulated by local inhibitory interneurons and by excitatory projections

from other pyramidal neurons. Thus, PFC function is likely to depend on a proper excitation-inhibition balance. Many aspects of such circuitry do change during adolescence (Andersen 2003). In nonhuman primates, the density of GABA interneuron processes increases during the prepubertal period, peaks during adolescence and then sharply declines (Anderson et al. 1995; Lewis 1997; Erickson and Lewis 2002). These data have been interpreted as evidence of a pruning process during adolescence that favors the selection of appropriate connectivity. Thus, the circuitry that underlies excitation-inhibition balance seems to be refined in its connectivity during this critical developmental period.

Excitation-inhibition balance is also controlled by neuromodulators. Among PFC neuromodulators, dopamine (DA) stands out because of its importance for working memory and decision making. Adequate, but not excessive, DA levels are required for proper PFC function, as demonstrated by the elegant work of the late Patricia Goldman-Rakic (Sawaguchi and Goldman-Rakic 1991; Sawaguchi and Goldman-Rakic 1994). This requirement takes the shape of an inverted U curve, and any departure from the optimal range will affect behavioral outcome (Murphy et al. 1996). DA contributes to PFC physiology by adjusting the efficacy of both excitatory and inhibitory synapses, so any postnatal changes in DA innervation would indeed affect PFC function. The density of TH fibers in macaques rises during the preadolescent period, peaking during adolescence and then decaying (Rosenberg and Lewis 1995). DA receptors also change postnatally. Early studies using autoradiography revealed that the density of D1, D2, and D4 receptors increases progressively until adolescence (postnatal day (PD) 45–50) in rats (Tarazi and Baldessarini 2000), and then at least D1 receptors are pruned (Andersen et al. 2000). More recently, when specific neuronal types were compared, it was found that D1 receptors increase transiently during adolescence in PFC cortico-accumbens projecting neurons (Brenhouse et al. 2008). Thus, in addition to changes in glutamate-GABA connectivity, the PFC innervation by DA also changes during adolescence. Considering all these anatomical changes, we postulated that synaptic physiology and its modulation by DA would also mature during adolescence in the PFC.

### **Periadolescent Maturation of Electrophysiological Responses to Dopamine in Pyramidal Neurons**

DA modulates the activity of PFC circuits via a variety of mechanisms. The available literature is not cohesive, with reports of both up and down regulation of glutamatergic and GABAergic responses by D1 or D2 family receptors. Many technical details may account for some of these

discrepancies, but it is clear that one needs to consider the cortical layer in which the modulation occurs and the age of the animal, among many other factors (Seamans and Yang 2004). In experiments from PFC slices (typically conducted in prepubertal animals), glutamatergic responses can be affected by presynaptic receptors modulating release (Gao et al. 2001), and postsynaptically by receptors that adjust the magnitude of AMPA and NMDA responses. As in many other brain regions, DA D1 receptors typically enhance NMDA responses while D2 receptors attenuate both AMPA and NMDA (Seamans et al. 2001b; Wang and O'Donnell 2001; Chen et al. 2004; Wirkner et al. 2004; Beazely et al. 2006). The potentiation of cell excitability by combined NMDA-D1 agonist administration is much stronger than the sum of their individual effects (Wang and O'Donnell 2001), indicating a synergistic interaction in the prepubertal (PD < 35) PFC. Thus, *in vitro* studies in slices from juvenile animals reveal a complex modulation of glutamate responses by DA, with a strong upregulation of NMDA responses being consistently observed.

As these modulations have been identified in slices from prepubertal animals, their nature in the adult brain remained to be explored. We have recently extended studies assessing the role of selective DA agonists on deep-layer pyramidal cell excitability in slices from both prepubertal (PD 28–35) and late adolescent/adult (PD > 55) rats. In pyramidal neurons, we assessed the effects of DA on cell excitability, measured as the number of action potentials evoked by a constant-amplitude depolarizing current pulse. As in slices from younger rats, NMDA, AMPA, and D1 agonists enhanced cell excitability in slices from adult rats, whereas D2 agonists reduced pyramidal cell excitability (Tseng and O'Donnell 2004). The glutamate and D1 effects were observed at lower concentrations than in young slices, with a dose-response curve shifted to the left, suggesting pyramidal neurons are more excitable in adulthood than they are prior to adolescence onset. These changes in modulation of NMDA responses are not likely to be derived from increased synaptic connectivity, as NMDA synaptic currents have been reported to acquire their adult profile prior to adolescence onset in monkeys (Gonzalez-Burgos et al. 2008). It is therefore proposed that the enhanced excitability may be due to the acquisition of new or an increase in the efficacy of existing modulatory factors.

The D1-NMDA interaction is also present in slices from adult PFC, but unlike prepubertal slices it is capable of driving persistent activity. Both D1 and NMDA receptors are critical for working memory functions, and it has been proposed that working memory entails sustained activity in a subset of PFC pyramidal neurons (Durstewitz et al. 2000; Durstewitz and Seamans 2006). Co-administration of a D1 agonist with NMDA into PFC slices from adolescent and

adult rats yields repetitive persistent depolarizations reminiscent of the up states recorded in vivo (Tseng and O'Donnell 2005). A low concentration of NMDA depolarizes deep-layer PFC pyramidal neurons and in some cases yields spontaneous action potential firing. Combining low levels of the D1 agonist SKF38393 with NMDA results in plateau depolarizations lasting several hundred milliseconds, but only in slices from rats older than PD45. Prior to that age, the depolarizations elicited by D1–NMDA co-administration last only tens of milliseconds, the range of simple synaptic responses (Tseng and O'Donnell 2005). Thus, prolonged depolarizations can be driven by D1–NMDA coactivation in the PFC of adolescent or adult, but not prepubertal rats. These results suggest that when DA signals coincide with strong glutamatergic depolarization in the PFC, NMDA responses are stronger, and this interaction becomes more efficient during the transition to adulthood.

### Periadolescent Maturation of Responses to Dopamine in Fast-Spiking Interneurons

As pyramidal cell activity is heavily controlled by GABA interneurons and interneurons are in turn also modulated by DA, it is important to understand the role of DA on local inhibitory processes. Although interneurons comprise a small proportion of cortical neurons, there are several different varieties (Flames and Marin 2005). Of particular importance in the control of pyramidal cell firing and high frequency oscillations are a subset of interneurons that can be identified by their content of the calcium-binding protein parvalbumin (PV) and electrophysiological features including high frequency firing. These are identified as fast-spiking interneurons (FSI) and include chandelier cells and basket cells. In slices from young rats, DA has a mixed set of effects on deep-layer FSI firing. Inhibitory post synaptic currents (IPSCs) recorded in pyramidal neurons (reflecting activity of interneurons) are enhanced in amplitude by D1 agonists and attenuated by D2 receptor activation (Seamans et al. 2001a). Recordings from FSI in slices from preadolescent rats revealed that D1, but not D2, receptors enhanced interneuron excitability (Gorelova et al. 2002). Thus, D1 and D2 family receptors affect local inhibition by controlling FSI firing and pyramidal neuron responses.

The complex DA modulation of interneuron firing also changes during adolescence. In all preadolescent recording studies, D2 receptors were not involved in the control of deep-layer FSI firing. We became aware of the possibility that this relationship changes during adolescence when assessing the DA modulation of AMPA and NMDA effects on deep-layer pyramidal cell excitability in adult slices. In those experiments, we found that the D2 attenuation of

NMDA effects was neither mimicked by blockade of protein kinase A (PKA) nor blocked by intracellular manipulations in the pyramidal cell that typically counter D2 effects (Tseng and O'Donnell 2004). In fact, the only agents that blocked the D2 agonist effect were GABA-A antagonists (Tseng and O'Donnell 2004). These data suggested that the D2 attenuation of NMDA responses involved recruitment of GABA interneurons. Indeed, D2 agonists increase cell excitability of FSI, but only in slices from adult (older than PD55) rats (Tseng and O'Donnell 2004, 2007b). A D2 recruitment of FSI in the adult PFC was also detected in experiments assessing synaptic responses in deep-layer pyramidal neurons to cortico-cortical afferent activation. In these experiments, whole-cell recordings were conducted in deep-layer pyramidal neurons while stimulating superficial layers at a distance of about 1 mm lateral to the apical dendrite of the recorded neuron. Such stimulation elicited AMPA-dependent EPSPs, which were attenuated by D2 agonists (Tseng and O'Donnell 2007a). The effect of the D2 agonist lasted even after washing out the drug. As D2 agonists can recruit interneurons, we tested whether GABA-A antagonists would attenuate the pyramidal cell response. Although neither picrotoxin nor bicuculline affected the early component in the D2 modulation of cortico-cortical synaptic responses, they blocked the late component (Tseng and O'Donnell 2007a). The data suggest that D2 receptors can attenuate inputs to pyramidal neurons by an early direct effect on pyramidal neurons, which is consistent with our previous observation that D2 activation attenuates AMPA responses (Tseng and O'Donnell 2004). In addition, D2 receptors further limit activity in PFC circuits by recruiting local interneurons which in turn may shunt synaptic responses. In recordings from prepubertal slices, only the early, direct component was detected (Tseng and O'Donnell 2007a), consistent with the notion that a D2 recruitment of FSI emerges during adolescence. The cellular mechanisms responsible for such a dramatic change are not yet clear. The acquisition of an excitatory response to D2 activation in interneurons, similar to that of D1 responses in interneurons suggests that the adult D2 response cannot involve Gi proteins, as Gi proteins oppose the effect of the D1-associated Gs proteins; the switch to a D2 excitatory effect may be related to the acquisition of a Gq response. In summary, the D1–NMDA interaction becomes more robust in the transition to adult stages, but this is countered by more efficient interneuron activation as both D1 and D2 receptors can drive FSI firing in the adult brain. Therefore, the dual effects of DA modulation on excitation-inhibition balance become refined during adolescence, with more effective highlighting of active (and thereby NMDA-driven) units and a more effective recruitment of local inhibitory processes.

### VTA Stimulation Activates PFC Interneurons In Vivo

In vivo recordings from anesthetized animals also suggest DA can activate interneurons. Electrical or chemical stimulation of the ventral tegmental area (VTA) causes rapid DA release in target regions in adult rats (Suaud-Chagny et al. 1992). Intracellular recordings from pyramidal neurons revealed that most pyramidal neurons stop firing action potentials following VTA stimulation (Lewis and O'Donnell 2000) or with intra-PFC administration of DA (Bernardi et al. 1982) in adult rats. A role of DA driving interneurons in adult rats was further supported by juxtacellular recordings from FSI, revealing that chemical stimulation of the VTA with NMDA (which evokes DA cell bursting) suppresses pyramidal cell firing and increases FSI firing (Tseng et al. 2006). Thus, endogenous release of DA within the adult PFC has a similar effect to what is reported in adult slices: most pyramidal cells are silenced while FSI are activated. There has not been so far a clear exploration of whether in vivo responses to mesocortical activation change during adolescence. We interpret these data reviewed above as indication of a noise-suppressing effect of DA. D1 potentiation of NMDA receptors would occur only on those pyramidal neurons already active when DA cell firing occurs; thus, this modulation would be observed in an awake animal in only the pyramidal neurons that are actively processing information relevant to the behavioral condition. The remaining pyramidal neurons would likely remain at their negative resting membrane potential, in which NMDA receptors are blocked by  $Mg^{++}$ . This effect of enhancing the activity of already active neurons is combined with a reduction in the activity of weakly activated pyramidal neurons, an outcome that would be achieved by activating FSI.

### Altered Interneuron Maturation in Rodent Models of Schizophrenia

The periadolescent maturation of PFC interneurons is likely to be important for the pathophysiology of schizophrenia. First, postmortem studies consistently reveal alterations in local GABA interneurons in the PFC and other cortical regions (Benes and Berretta 2001; Lewis et al. 2005; Hashimoto et al. 2008; Maldonado-Aviles et al. 2009). Second, florid symptom onset typically takes place by the end of adolescence. In addition, current theories on pathophysiological mechanisms emphasize the role of dysfunctional glutamatergic transmission, and DA remains the target of choice for pharmacological treatment. Thus, the circuitry responsible for excitation-inhibition balance in the PFC, which matures during adolescence and is modulated by DA, is a likely candidate to become dysfunctional in this and other neuropsychiatric disorders. This possibility

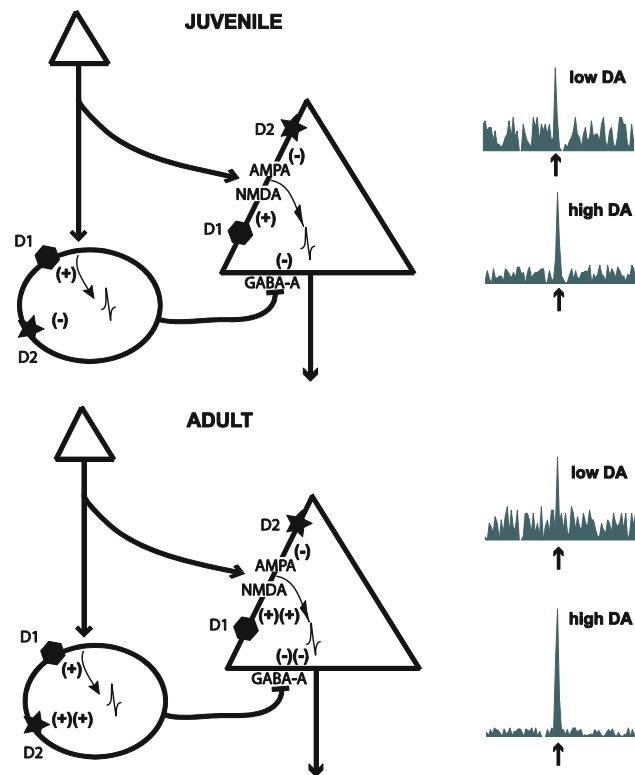
can be directly tested in animal models that can yield schizophrenia-like phenomena. We have studied over the past several years one such model: the neonatal ventral hippocampal lesion (NVHL). Rats with a NVHL exhibit a number of behavioral deficits that are relevant to schizophrenia, including altered social interactions (Sams-Dodd et al. 1997; Becker et al. 1999), disrupted working memory (Lipska et al. 2002; Marquis et al. 2008) and other cognitive impairments (Chambers et al. 1996), hyperlocomotion (Sams-Dodd et al. 1997), enhanced reactivity to stress and stimulants (Lipska et al. 1993; Wan et al. 1996), altered prepulse inhibition of the acoustic startle response (Lipska et al. 1995; Le Pen and Moreau 2002), among others. In addition, PFC connectivity is altered in adult rats with a NVHL (Flores et al. 2005), and markers of local inhibitory circuitry are particularly affected as revealed by reduced levels of the GABA-synthesizing enzyme GAD67 (Lipska et al. 2003) and increase in GABA-A receptors (Endo et al. 2007). Many of these alterations can be reversed with antipsychotic treatment (Le Pen and Moreau 2002), and they are in general not present before adolescence (Lipska et al. 1993). Interestingly, a medial PFC lesion in adult rats with a NVHL restored behavioral deficits and altered electrophysiological responses in the nucleus accumbens (Lipska et al. 1998; Goto and O'Donnell 2004), suggesting that an abnormally active PFC may be responsible for the NVHL effects.

The DA modulation of PFC circuits is impaired in this and other schizophrenia models. In vivo intracellular recordings reveal that VTA stimulation evokes an increase in firing in deep-layer PFC pyramidal neurons in adult rats with a NVHL (O'Donnell et al. 2002) instead of the suppression observed in naïve and control rats. Such increase could be due to enhanced excitability by DA acting directly on pyramidal neurons or by a poor recruitment of interneurons. Both conditions may actually occur. In vitro recordings in slices show enhanced effects of AMPA, NMDA, and D1 agonists on pyramidal cell excitability in adult NVHL rats compared to sham operated rats (Tseng et al. 2007). In addition, the periadolescent maturation of the D2 modulation of interneuron firing fails to occur in NVHL rats. Whole-cell recordings from FSI reveal that the D2 agonist quinpirole does not increase excitability in slices from adult NVHL rats (Tseng et al. 2008b). Thus, the combination of enhanced pyramidal excitability with a weaker DA recruitment of interneurons in NVHL rats would cause an imbalance in excitation-inhibition yielding a disinhibited state in cortical circuits.

### Conclusion

The modulation of PFC circuits responsible for excitation-inhibition balance changes during adolescence. These

changes are most evident upon activation of DA receptors, an observation that has been ascertained with both in vivo and in vitro electrophysiological studies. DA cells fire in bursts in the presence of unexpected reward or reward-predicting stimuli (Schultz 2004), and the consequence of this activity pattern is a rapid rise in DA levels (Gonon 1988). As DA is a critical modulator of glutamate and GABA synaptic activity in the PFC, burst firing and the ensuing phasic release have a strong impact on PFC-



**Fig. 1** Periadolescent maturation of DA actions on prefrontal cortical neuronal excitability. *Top*: Cartoon representing a pyramidal neuron (triangle) a fast-spiking interneuron (oval) in a prepubertal PFC, their excitatory afferents (small triangle) and their modulation by dopamine D1 and D2 receptors. In the pyramidal neuron, while D2 receptors attenuate AMPA responses, D1 enhance NMDA effects on cell firing. In the interneuron, D1 receptors enhance firing while D2 have a weak inhibitory effect. The consequence of this dual modulation is that activity of pyramidal neurons receiving strong inputs will be enhanced while everything else will be suppressed. The graphs to the right represent the activity of a hypothetical series of pyramidal neurons in conditions of low DA (and therefore without the mechanisms outlined to the left) and high DA, when the increase signal-to-noise becomes effective. The arrows point to the activity of the hypothetical pyramidal neurons receiving strong inputs. *Bottom*: Similar cartoon highlighting differences in the adult brain. D1 receptors are more efficient at enhancing NMDA responses and both D1 and D2 receptors enhance interneuron activity. The histograms to the right represent the hypothetical outcome of such enhanced D1–NMDA and D2–interneuron interactions: in conditions of high DA, the increase in activity of behaviorally relevant pyramidal neurons and the decrease in background activity become much more contrasted, allowing a better response selection

supported functions such as decision making and response selection. In the prepubertal PFC, a combination of enhancing ongoing, behaviorally relevant activity with suppressing weakly activated units may be achieved by the D1 synergistic effect with NMDA receptors and a recruitment of interneurons (Fig. 1). But in the adult PFC, both mechanisms become more effective, rendering a more efficient DA modulation of excitation–inhibition (Fig. 1) that could yield a more adequate response selection and minimize poor behavioral choices. In rodent models of schizophrenia, many of which yield altered interneuron function (Cabungcal et al. 2006; Homayoun and Moghaddam 2007; Tseng et al. 2008a, Feleder et al. 2010; Lodge et al. 2009), DA bursts may fail to provide an efficient control of excitation–inhibition balance, resulting in a noisy PFC that may resemble what is currently interpreted from imaging studies from schizophrenia patients; i.e., an exaggerated and inefficient activity responsible for the “hypofrontality” typically described in the disease (Callicott et al. 2000). Our work reveals that the adult PFC acquires a more efficient modulation of excitation–inhibition balance in the transition to young adult stages, but not in the NVHL model. A more thorough understanding of the mechanisms responsible for the maturation of PFC modulation by DA will undoubtedly allow the field to explore not only novel therapeutic approaches for schizophrenia and related disorders, but perhaps even to consider preventive strategies.

**Acknowledgments** The work reviewed here was supported by NIH Grant MH57683. I would like to thank Dr. Rose Marie Karlsson and Ms. Gwendolyn Calhoon for useful comments on the manuscript.

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