● **REVIEW**

Dopamine as a growth differentiation factor in the mammalian brain

Koji Ohira[*]

Laboratory of Nutritional Brain Science, Department of Food Science and Nutrition, Mukogawa Women's University, Nishinomiya, Hyogo, Japan

Abstract

The catecholamine, dopamine, plays an important role in the central nervous system of mammals, including executive functions, motor control, motivation, arousal, reinforcement, and reward. Dysfunctions of the dopaminergic system lead to diseases of the brains, such as Parkinson's disease, Tourette's syndrome, and schizophrenia. In addition to its fundamental role as a neurotransmitter, there is evidence for a role as a growth differentiation factor during development. Recent studies suggest that dopamine regulates the development of γ-aminobutyric acidergic interneurons of the cerebral cortex. Moreover, in adult brains, dopamine increases the production of new neurons in the hippocampus, suggesting the promoting effect of dopamine on proliferation and differentiation of neural stem cells and progenitor cells in the adult brains. In this mini-review, I center my attention on dopaminergic functions in the cortical interneurons during development and further discuss cell therapy against neurodegenerative diseases.

Key Words: γ-aminobutyric acidergic interneuron; adult neurogenesis; cerebral cortex; dopamine; GABA; medial ganglionic eminence; migration; striatum

Dopamine (DA), one of the catecholamines, acts as a neurotransmitter in the central nervous system and is involved in motor control, attention, learning, enhancement of drug abuse, and certain types of neuropsychiatric disorders, such as schizophrenia, Huntington's, and Parkinson's diseases. DA binds to specific receptors, for example, D1-like and D2-like receptors, followed by intracellular signal transduction via G proteins to bring about secondary messenger cyclic adenosine monophosphate synthesis or inhibition. In contrast, DA has been reported to have a growth differentiation function as an alternate role. In this review, I focus on DA as a growth differentiation factor during development, in particular, in the differentiation and migration of cortical interneurons. I further discuss the assumed role of DA in the abnormal development of cortical neurons and cortical adult neurogenesis as prospects of regenerative medicine.

An electronic search of the PubMed and Google Scholar for papers published from 1980 to 2019 was performed, using the following words: "dopamine", "migration", "adult neurogenesis", "differentiation", "development", "cerebral cortex", "GABA", and "interneuron". Using these papers, the effect of DA on neural differentiation and migration during development was reviewed.

Biosynthesis of DA is based on tyrosine. The rate-determining step of DA synthesis is the conversion of tyrosine to L-DOPA by tyrosine hydroxylase. Thereafter, L-DOPA is rapidly converted to DA by aromatic L-amino acid decarboxylase and DA is concentrated into the secretory granules in the presynaptic terminal. DA released from the presynaptic sites binds to the specific metabotropic receptors (Foley, 2019).

It has been reported that DA regulates neuropeptide expression, such as dynorphin, enkephalin, and substance P, via promotion or suppression of DA receptors' signaling. These studies suggest that DA is not a simple neurotransmitter. During the early development of mammals, DA, tyrosine hydroxylase, DA receptors, and the DA-related signaling molecules, such as dopamine and 3′,5′-cyclic adenosine monophosphate-regulated neuronal phosphoprotein-32, G proteins, and adenylate cyclase, are expressed in the striatum primordium (Liu and Graybiel, 1999), which is the brain region that interacts most rapidly with the DA cells in the midbrain during development. In rodents, these molecules are observed in the striatum primordium from embryonic days 12–13 (E12–13). The striatum primordium at E12–13 has not yet differentiated into striatal neurons and mostly undifferentiated precursor cells express DA-related molecules (Liu and Graybiel, 1999), suggesting that DA can function as a growth differentiation factor. Nevertheless, the genetic depletion of DA-related molecules indicates that DA signaling may not significantly affect the development of the striatum, except for the D1 receptor (Liu and Graybiel, 1999). Thus, these studies suggest that DA signaling may not be involved in the regulation of striatal tissues during prenatal development but has a function in controlling the expression of some of the neural peptides.

Most of the evidence, as described above, was published before the middle 1990s. In the late 1990s, the important finding on the development of γ-aminobutyric acid (GABA) ergic interneurons in the cerebral cortex was reported: the tangential migration pathways of cortical GABAergic interneurons (Peyre et al., 2015). A part of the striatum primordium, the medial ganglionic eminence (MGE), is the source of cortical GABAergic interneurons. Cells in the lateral ganglionic eminence of the striatum primordium are differentiated into striatal neurons. Therefore, there are two distinct

migration pathways of cortical neurons (Peyre et al., 2015). Pyramidal neurons are generated in the ventricular zone of the developing cortex and move to the cortical parenchyma along the radial glia, whereas the tangential migration from the MGE results in cortical GABAergic interneurons. Therefore, up to the middle 1990s, nobody examined whether DA affects the development of cortical GABAergic interneurons derived from the MGE. In other words, the possibility remains that DA regulates the differentiation and migration of cortical GABAergic interneurons.

Most recently, DA has been reported to regulate the differentiation and migration of cortical GABAergic interneurons (Ohira, 2019). During the migration of cortical GABAergic interneurons from the MGE to the cerebral cortex, the MGE cells are stimulated by factors called motogenic factors, and begin to migrate along the cortical projection fibers (Peyre et al., 2015), which express the transiently expressed axonal surface glycoprotein-1 (TAG-1)/Contactin-2 adhesion molecule. Moreover, the interaction between semaphorin (Sema) and neuropilin (Npr) guides the MGE cells to the cerebral cortex (Peyre et al., 2015). Thus, the expressions of these migration-associated molecules should be spatiotemporally regulated during development. In the report, it was shown that the tyrosine hydroxylase positive axons from the substantia nigra entered the MGE region at E12.5 in mice, suggesting DA release in the MGE (**Figure 1**). In the primary cultures of the MGE cells, DA treatment increased the expression of the interneuron markers, Dlx2, glutamic acid decarboxylase 67, and Npr, as well as the D2 receptor, via DA-D1 receptor signaling. Dlx2 is essential to produce GABAergic precursor cells in the cerebral cortex (Peyre et al., 2015). Glutamic acid decarboxylase 67 is essential for the production of GABA from glutamate in the central nervous system. These results suggest that DA prompts the differentiation of the MGE cells to cortical GABAergic interneurons in the primary cultures.

Brain-derived neurotrophic factor (BDNF) is one of the motogenic factors for cortical GABAergic interneurons (**Table 1**) (Polleux et al., 2002). Interestingly, in the primary cultures of the MGE cells, the expression of BDNF mRNA was upregulated by the signaling of the D2 receptor, which is expressed by D1 receptor signaling (Ohira, 2019). Additionally, using organotypic slice cultures of E14.5 brains, DA-D2 receptor-BDNF signaling has been shown to increase in the number of migrating cortical GABAergic interneurons from the MGE (**Figure 1**). When both types of DA receptors are expressed on the same cell surface, D2 receptor signaling may be preferred, since the dissociation constant of the D2 receptor is smaller than that of the D1 receptor (Hunger et al., 2018). Administration of 6-hydroxydopamine, which can degenerate DA neurons in the substantia nigra, into E9.5 to E18.5 of pregnancy mice decreased the number of cortical GABAergic interneurons in E18.5 embryos. These results suggest that DA plays an important role in the development of cortical GABAergic interneurons and could harmonize the expressions of molecules for differentiation and migration of cortical GABAergic interneurons.

Another motogenic factor, hepatocyte growth factor/scatter factor (HGF/SF), has also been reported (Powell et al., 2001). Similar to neurotrophins, HGF/SF and its receptor, c-Met, are expressed in the cortex and ganglionic eminence as early as E13.5. In mutant mice of the urokinase-type plasminogen activator receptor, which is a converting enzyme of the inactive pro-form of HGF/SF, a subtype of cortical inter-

Table 1 Migration-related factors of GABAergic interneurons

Migration-related factors	References
BDNF-TrkB	Polleux et al. (2002); Steinecke et al. (2014)
HGF/SF-c-Met	Powell et al. (2001); Eagleson et al. (2011)
Semaphorin-Neuropilin	Marín et al. (2001); Li et al. (2019)
Slit-Robo1	Marín et al. (2003); Hernández-Miranda et al. (2011); McKinsey et al. (2013)

BDNF: Brain-derived neurotrophic factor; GABA: γ-aminobutyric acid; HGF/SF: hepatocyte growth factor/scatter factor; TrkB: tropomyosin-related kinase B.
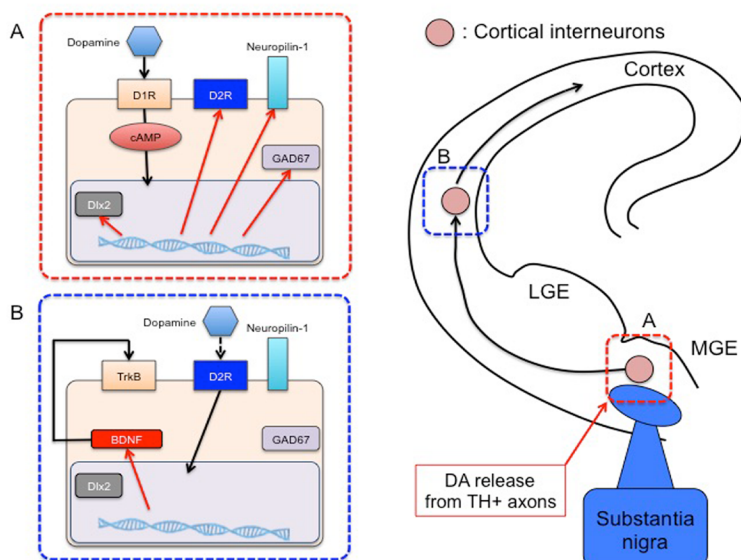
Figure 1 Schematic representation of the differentiation and migration of cortical interneurons by DA during development.
(A) MGE cells receive DA release from tyrosine hydroxylase positive axons of the substantia nigra, and differentiate into cortical interneurons. MGE cells express Dlx2, GAD67, Neuropilin-1, and D2 receptor (D2R) via D1R signaling. (B) Once the cells express D2R, D2R-BDNF-TrkB signaling moves the cortical interneurons to the cortex. BDNF: Brain-derived neurotrophic factor; cAMP: cyclic adenosine monophosphate; DA: dopamine; Dlx2: distal-less 2; GAD67: glutamic acid decarboxylase 67; LGE: lateral ganglionic eminence; MGE: medial ganglionic eminence; TH: tyrosine hydroxylase; TrkB: tropomyosin-related kinase B.

neurons decreased to 55–65% of the wild type level. It would be interesting to clarify the relationship between HGF/SF and DA.

Two pairs of repulsive molecules, Sema-Npr and Slit-Robo, have been reported to be involved in tangential migration (Marín et al., 2001). Npr1/2 is expressed in the migrating MGE cells, whereas Sema3A and Sema3F are expressed in the developing striatum. Subsequently, they function to sort migrating cortical GABAergic and striatal interneurons to their correct destination. The Npr1/2 expressing regions are just mantle layers of MGE, which are located in the ventral part of the internal capsule. These findings suggest that DA regulates the guidance of the MGE cell via the control of Npr expression.

The slit genes have been identified to encode the secreted molecules that function as factors for branching and repulsive pathfinding of axons and migrating neurons (Marín et al., 2003). In light of tangential migration, the slit mRNA is expressed in the ventricular zones (VZs) of the lateral ganglionic eminence and the MGE. The repulsive effect of Slit protein can determine the initial direction of cell migration from the VZs of the lateral ganglionic eminence and MGE to the outside of the regions. In the study, the expression of the slit receptor, Robo1, could not be changed by DA and DA receptor antagonists. In addition, since DA is released in the ventral region of the internal capsule apart from the VZ and the subventricular zone, the mechanism of Robo1 expression might not involve DA signaling. In summary, the expressions of factors promoting the migration of MGE cells, such as BDNF and Npr1, can be orchestrated by DA.

The following paragraph outlines the consequences of DA function decrease or loss during development. As described above, the number of cortical interneurons may decrease. In fact, a DA neuron deficit in the substantia nigra by 6-hydroxydopamine treatment during prenatal development results in a decrease in cortical GABAergic interneurons (Ohira, 2019). Cortical GABAergic interneurons, especially calbindin and parvalbumin-positive neurons, have been reported to induce the synchronized spiking of the gamma band (Nakazawa et al., 2012). Interestingly, during adolescence, DA can regulate functional maturation of GABAergic interneurons, especially, parvalbumin-positive interneurons in the cerebral cortex and hippocampus, including expression of GABA synthesizing enzymes and transporters, density of GABAergic synapses, and the projection pattern of GABAergic axons (Kilb, 2012). Thus, we assume that the decrease in cortical GABAergic interneurons, which is caused by a DA reduction, leads to cognitive deficits, hallucinations, and delusions. Indeed, such symptoms appear in schizophrenic patients (Nakazawa et al., 2012). The analyses of postmortem brain specimens from schizophrenic subjects have shown that the number of interneurons in the cerebral cortices, especially in the prefrontal cortices, decreases and abnormalities of gamma band neural activity are evident (Nakazawa et al., 2012). Some studies suggests that GABAergic deficits in schizophrenia patients progress during neurodevelopment (Fung et al., 2014; Gonzalez-Burgos et al., 2015; Glausier and Lewis, 2018). The genetic analyses of schizophrenia also provide evidence that DA-associated genes, such as catechol-O-methyltransferase and DA receptor genes, are related to schizophrenia. Therefore, DA signaling deficits during development might induce schizophrenia-like abnormalities.

However, the increase of DA contents during development shows contrasting features. Cocaine inhibits DA transporters on the cell surface, causing DA release into the synaptic sites by the inhibition of DA reuptake into the nerve terminals. Consequently, DA contents in the synaptic sites are constitutively increased, and DA signaling is upregulated by cocaine treatment. In addition, when the DA concentration is increased by cocaine treatment, desensitization of DA receptors could occur, which would cause the same phenomenon as the decrease in DA concentration. Prenatal cocaine exposure disrupts brain development and induces lasting altered functions in cognition, known as "crack baby", that is, cocaine exposure during gestation is required to produce measurable central nervous system deficits in the offspring (Ross et al., 2015). Importantly, exposure of mouse embryos to cocaine from E8 to E15 decreases the number of cortical interneurons at E15 (Crandall et al., 2004). In addition, BDNF expression is decreased by cocaine treatment in the basal forebrain region of E15 mouse embryos (McCarthy et al., 2011). This suggests that excess DA disrupts the development of cortical interneurons, which is similar to the effects of the decrease in DA contents as described above. Taken together, adequate concentrations of DA are necessary for the development of cortical interneurons.

In stroke and neurodegenerative disease, there is profound impairment of the structures and functions of the brain. Treatment of the diseases is mostly via drugs. Moreover, thrombus in cerebral infarction can be dissolved or inhibited by drugs such as acetylsalicylic acid and clopidogrel, which can increase the survival of neurons around the infarct sites. However, their effects are very limited in terms of functional regeneration. Currently, research and development of therapeutic methods using stem cells, such as induced pluripotent stem cells and embryonic stem cells, are being actively conducted around the world as a treatment alternative to drugs. In addition to these, cell therapy using endogenous neural stem cells, which can produce all neural lineages, including neurons, astrocytes, and oligodendrocytes in the central nervous system, and neural progenitor cells, which have already become a lineage committed to giving rise to only one category of neural cell components, are going to be applied clinically. Previously, some of the endogenous neural stem cells and neural progenitor cells have been identified (for example, in the olfactory bulb, hippocampus, and hypothalamus). Interestingly, recent studies have reported neural stem cells and neural progenitor cells in the cerebral cortex (Ohira, 2018). One of the reports identified that neuronal progenitor cells in the adult cortex express the MGE markers, Nkx2.1 and MafB (Ohira et al., 2010), and these cells are also found in the cerebral cortex of aged animals (Okada and Ohira, 2017) and a certain drug can activate cortical neurogenesis (Ohira et al., 2013), suggesting that tissue stem/progenitor cells derived from the MGE may be maintained for the life of the individual and useful for cell therapy. DA has been reported to regulate

adult neurogenesis in the hippocampus (Veena et al., 2011; Hedlund et al., 2016; Tapia-Bustos et al., 2017). DA can promote the generation of and survival of new neurons in the hippocampal dentate gyrus, although there is controversy as to whether the D1 or D2 receptor can transduce the signal of DA (Choi et al., 2014; Takamura et al., 2014). The number of neural progenitor cells has been reported to be decreased in the hippocampal dentate gyrus of patients with Parkinson's disease. DAergic fibers were observed in the vicinity of hippocampal neural progenitor cells, and proliferation of the neural progenitor cells was reduced after the depletion of DA cells in the substantia nigra (Borta and Höglinger, 2007). Thus, the possibility that DA can increase cortical neurogenesis should be considered. Because cell therapy with stem cells is a promising modality to treat neurological disorders, it is important to elucidate the molecular mechanisms, including differentiation control by DA, underlying the differentiation of these cortical neural stem cells and neural progenitor cells.

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