Review Article

Epilepsy and dopaminergic system

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Abstract

Epilepsy is accompanied with a strong change in neuronal activity not only in excitatory (glutamatergic) and inhibitory (GABAergic) neurotransmission, but also in neuromodulatory agents. Dopaminergic system, as an important neuromodulatory system of the brain, has significant effect on neuronal excitability. In addition, this system undergoes many changes in epileptic brain. Understanding the effects of dopaminergic system in neuronal activities in epileptic brain and knowing the seizure-induced changes in dopaminergic system can shed light into finding the mechanisms involved in epileptogenesis and can help us in finding new treatments for epilepsy. In this review we briefly introduce dopaminergic system and its changes in brain areas which have role in epilepsy. Then, we will focus on the evidences showing the relationship between epilepsy and dopaminergic system.

Introduction

Epilepsy is among the most common neurological diseases which affects 1-2 percent of peoples (more than 50 million) all over the world (Graves, 2006). Epilepsy can be considered as occurrence of sudden, spontaneous and recurrent seizures. A seizure can define as an abnormal, synchronized hyperactivity in a group of neurons (Millichap, 2003). It usually accompanies with some behavioral manifestations (i.e. convulsive seizures). Outcome of seizures strictly depends on the brain regions that are affected by hyperactivity (Michael-Titus et al., 2007). Despite of a lot of progress in finding the mechanisms involved in epileptic seizures, there is not a definite treatment way for their complete suppression. Antiepileptic drugs can only reduce the rate of seizures in about 40 percent of patients (McNamara, 1994). Therefore, many studies are done to find new antiepileptic drugs.

One important change in epileptic brain is an imbalance in excitation to inhibition ratio (Engel and Pedley, 2008). Although this change is usually because of abnormal activity in glutamatergic and/or GABAergic neurons per se, however, neuromodulators such as dopamine can also affect this ratio by inducing some changes in the activity of glutamatergic and/or GABAergic neurons (Gonzalez-Islas and Hablitz, 2003; Slaght et al., 2002). Many evidences show that dopaminergic system has a critical role in controlling the neuronal activities during seizure. Previous studies have shown that significant changes occur in different aspects of dopaminergic system (such as release, metabolism and receptor binding of dopamine) following epileptic seizures both in human and laboratory animals (Bozzi et al., 2011; Waddington, 1993; Starr, 1996). In addition, dopaminergic neurons modulate the synaptic plasticity, a phenomenon that is also affected by seizure activity (Hansen and Manahan-Vaughan, 2014). Any abnormal variation in synaptic plasticity may change the neuronal responsiveness and leads to seizure induced impairment in different aspects of brain function of epileptic patients such as progressive hyper-excitabilities and cognitive
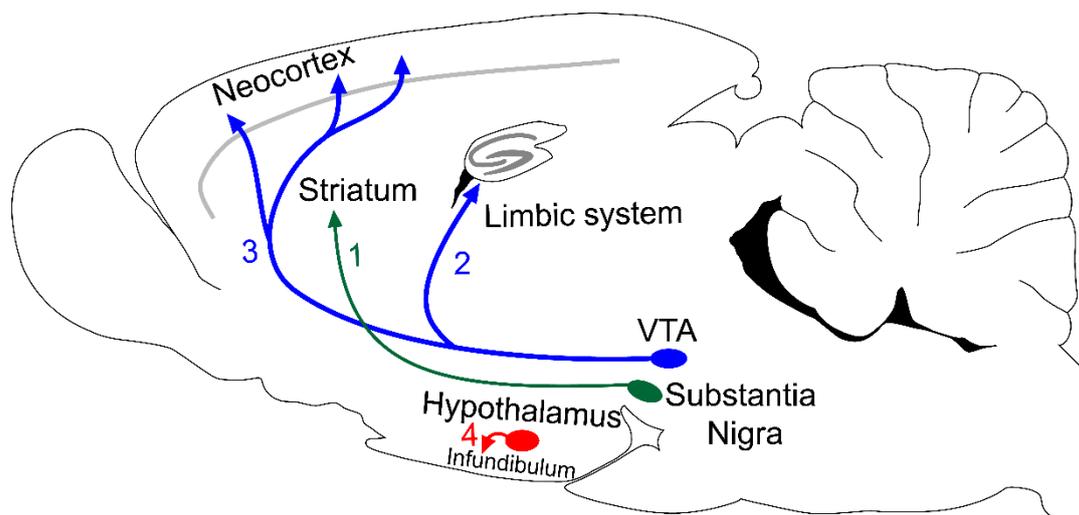
Fig.1. The main dopaminergic pathways of the adult rodent brain in the sagittal plane. The numbers show these pathways including: 1- Nigrostriatal pathway, 2- mesolimbic pathway, 3- mesocortical pathway and 4- tuberoinfundibular pathway.

Table 1: Cell signaling pathways of dopaminergic receptors

Dopamine receptors	Coupled G proteins	Cellular effector	Signaling pathway	Reference
D1	$G_{\alpha s}/G_{\alpha olf}$	Adenylyl cyclase, Protein kinase A stimulation	Increasing cAMP	(Beaulieu and Gainetdinov 2011)
	$G_{\alpha q}$	Phospholipase C	Increasing inositol 3 phosphate/Diacylglyserol	(Clifford, Tighe et al. 1999)
D2/D3/D4	$G_{\alpha i}/G_{\alpha o}$	Adenylyl cyclase, Protein kinase A inhibition	Decreasing cAMP	(Beaulieu and Gainetdinov 2011)
	$G_{\beta\gamma}$	Phospholipase C, Ca^{2+} channnles	Increasing inositol 3 phosphate/Diacyl glyserol	
D5	$G_{\alpha s}$	Adenylyl cyclase, Protein kinase A	Increasing cAMP	(Sahu, Tyeryar et al. 2009)
	$G_{\alpha q}$	Phospholipase C	Increasing inositol 3 phosphate/Diacyl glyserol	

dysfunctions. Therefore, understanding the effects of dopaminergic system in neuronal activities in epileptic brain and knowing the seizure-induced changes in dopaminergic system can shed light into finding the mechanisms involved in epileptogenesis and can help us in finding new treatments for epilepsy. In this review we will briefly introduce dopaminergic system and its changes in brain areas which have role in epilepsy. Then, we will focus on the evidences showing the relationship between epilepsy and dopaminergic system.

Dopamine receptors

Dopamine is one of the most important modulatory neurotransmitters in the central nervous system which is released from dopaminergic fibers. There are four main dopaminergic pathways in central nervous system including: 1) the nigrostriatal, 2) mesolimbic, 3) mesocortical and 4) tuberoinfundibular systems (Fig. 1) (Koob, 1992). Based on sequence homology, pharmacology and second messenger activation, dopamine receptors are divided into two subfamilies: D_1 -like and D_2 -like receptors. The D_1-

like subfamily includes D_1 and D_5 receptors, while the D_2-like consists D_2, D_3 and D_4 receptors (Sibley et al., 1993; Vallone et al., 2000). Using mRNA analysis, it has been shown that D_2 like receptors are abundantly expressed in many brain regions, such as frontal cortex, olfactory bulbs, nucleus accumbens, hippocampus and amygdala. D_2 and D_3 dopamine receptors are also expressed in substantia nigra pars compacta and ventral tegmental area (VTA, the main anatomical regions that dopaminergic fibers give raise). In these areas D_2-like receptors indicate mainly a presynaptic location. D_1 -like receptors are expressed in striatum, frontal cortex, nucleus accumbens, substantia nigra and amygdala which are exclusively postsynaptic location (Civelli et al., 1991; Jackson and Westlind-Danielsson, 1994; Perez de La Mora et al., 2012; Cocker et al., 2014).

Numerous signal transduction pathways activated by dopamine receptors. Dopamine receptors belong to the family of seven transmembrane domain G-protein coupled receptors. Activation or inhibition of the cyclic adenosine monophosphate (cAMP) pathway and modulation of Ca^{2+} signaling are the best described effects mediated by dopamine receptors. D_1 -like receptors are generally coupled to $G\alpha_{s/olf}$ and stimulate the production of the second messenger cAMP which activates protein kinase A (PKA). In contrast, D_2 -like receptors are coupled to $G\alpha_{i/o}$ and negatively regulate the production of cAMP which leads to decreasing PKA activity (Table 1).

D_1 -like receptors, especially D_5 receptors, may also couple to $G\alpha_q$ and regulate phospholipase C (PLC). Activation of PLC leads to the production of inositol triphosphate (IP_3) and diacylglycerol that result to activation of PKC and an increased mobilization of intracellular calcium in response to IP_3 (Table 1). Alternatively, dopamine receptors have been shown to make heterodimers with a number of other G-protein coupled receptors (Clifford et al., 1999; Beaulieu and Gainetdinov, 2011). It has been shown that D_1/D_2 dopamine receptor heterodimers regulate calcium-dependent cell signaling in some neuronal populations. D_2 -like receptors also can regulate intracellular calcium levels by acting on ion channels or intracellular calcium stores that are mediated by the $G\beta\gamma$ subunits, separated from $G\alpha$ subunit after receptor activation, of heterotrimeric G proteins (O'Sullivan et al., 2008).

D_1 and D_2 -like receptors have different affinity to

dopamine. In rat central nervous system, the D_1 -like receptor have primarily low affinity, whereas the D_2 -like receptors have high affinity to dopamine agonist (Richfield et al., 1989).

Dopamine neurons have two firing patterns: phasic (spontaneous bursts, followed by pauses, 10–30 Hz) and tonic (regular firing patterns, 1–4 Hz). Tonic firing is defined as random spikes at an average rate of 4 Hz, but phasic mode is defined as transient increases in firing rate using random spikes with average firing rate of 20 Hz (Dreyer et al., 2010; Dreyer and Hounsgaard, 2013). These neurons shift from a tonic to phasic firing mode on encountering salient stimuli or unexpected appetitive stimuli like food, water and novelty.

The different firing patterns of dopaminergic neurons influence the balance between D_1 and D_2 receptor dependent pathways. It has been hypothesized that the tonic mode of dopamine firing maintains a basal dopamine tone in the range of nM that activates the higher affinity D_2-like receptors. Phasic dopamine firing induces a fast and transient rise in dopamine concentration in the range of μM to mM. This range of concentration enables the activation of the lower affinity D_1-like receptors. Therefore, phasic firing mode of dopamine neurons primarily increases D_1-like receptor occupancy, whereas D_2-like receptor occupancy is less affected. Phasic pattern reduces the average occupancy of D_2-like receptors by >40% compared to tonic firing (Dreyer and Hounsgaard, 2013).

Distribution of dopamine receptors

Different performance of neuromodulatory function of dopamine D_1- and D_2-like receptors may be related to various distributions of these receptors. As there is no specific ligands for all dopamine receptor subtypes, in situ hybridization is broadly used for measuring the dopamine receptor mRNAs in the brain (Missale et al., 1998). On the whole, the most widespread dopamine receptor is D_1 receptor (Dearry et al., 1990; Fremeau et al., 1991; Weiner et al., 1991). Distribution of various dopamine receptors in different brain areas has been reviewed in Table 2.

The role of dopamine receptors in seizure

Many studies on animal models showed the opposite actions of D_1-like and D_2-like receptor signaling in limbic epileptogenesis. D_1-like receptors signaling is

Table 2: Distribution of dopamine receptors in different brain areas				
Dopamine receptors	**Location**	**Distribution**	**Density**	**Reference**
D₁	Hippocampal formation	Molecular layer of CA1 Dentate gyrus Stratum moleculare stratum oriens	++ ++ + +	(Savasta et al., 1986) (Mansour et al., 1990)
	Cerebral cortex	Suprarhinal dopamine terminal Anteromedial dopamine terminal	++ ++	(Savasta et al., 1986)
	Basal ganglia	Pars reticulate ventral tegmental area Caudate-putamen Nucleus accumbens Globus pallidus Striatal GABAergic neurons	+++ ++ +++ +++ +++ +++	(Mansour et al., 1990) (Le Moine et al., 1991) (Gerfen et al., 1990)
	Hypothalamus	Lateral nucleus Ventromedial nucleus Arcuate nucleus Suprachiasmatic nucleus	+ + + +++	(Mansour et al., 1990)
	Midbrain	Superior colliculus	+++	(Mansour et al., 1990)
	Amygdala	Cortical nucleus Lateral nucleus Basalateral nucleus Medial nucleus Intercalated nucleus	+++ +++ +++ ++ +	(Mansour et al., 1990) (Levey et al., 1993)
	Olfactory bulb	internal granular layer Plexiform layer	+ +	(Levey et al., 1993)
D₂	Hippocampal formation	Stratum lacunosum Stratum moleculare Subiculum Pyramidal cell layer CA1, CA2, CA3 Granular cells of DG Molecular layer of DG Hilar region Subicular region	+++ +++ +++ + + + + +	(Mansour et al., 1990) (Khan et al., 1998)
	Cerebral cortex	All cortical regions	+++	(Khan et al., 1998)
	Basal ganglia	Nucleus accumbens Substantia nigra pars compacta Globus pallidus Olfactory nerve	+++ + +++ +	(Jackson and Westlind-Danielsson, 1994) (Levey et al., 1993)
	amygdala	Central nucleus	+	(Levey et al., 1993)
	Hypothalamus	Arcuate nucleus Supraoptic nucleus Suprachiasmatic nucleus Mammillary nucleus	+ + + +	(Khan et al., 1998)
D₃	Hippocampal formation	Stratum oriens of CA1 Stratum radiatum of CA1 Molecular layer of DG Subicular region	+++ +++ +++ +	(Khan et al., 1998)
	Cerebral cortex	All cortical regions	+++	(Khan et al., 1998)
	Basal ganglia	Nucleus accumbens Ventral pallidum Olfactory tubercle Islands of Calleja Dorsal striatum Substantia nigra pars compacta	+ + + + + +	(Bouthenet et al., 1991) (Diaz et al., 1994) (Bouthenet et al., 1991; Levesque et al., 1992; Sokoloff et al., 1990) (Diaz et al., 1994; Diaz et al., 1995)

Table 2:				
Dopamine receptors	**Location**	**Distribution**	**Density**	**Reference**
D_4	Hippocampal formation	Dentate gyrus Polymorphic layer of CA1, CA2, CA3 Entorhinal cortex	+++ + +++	(O'Malley et al., 1992)
	Cerebral cortex	Cerebral neocortex Medial frontal cortex layer II,III Layer IV,V Corpus callosum	+++ +++ + +++	(Defagot et al., 1997) (Khan et al., 1998)
	Amygdala	Anterior cortical Posterolateral cortical Basomedial	+++ +++ +	(Defagot et al., 1997)
	Basal ganglia	Substantia nigra Pars compacta Pars reticulata	+++ +++ +	(Defagot et al., 1997)
	Hypothalamus	Paraventricular nucleus Supraoptic nucleus	+++ +++	(Defagot et al., 1997)
	Thalamus	Reticular nucleus	+	
	Cerebellum	Purkinje cells Molecular layer Granular layer	+++ ++ ++	(Defagot et al., 1997)
	Midbrain	Superior colliculus Inferior colliculus	+++ +++	(Defagot et al., 1997)
D_5	Hippocampal formation	Pyramidal cells of hippocampus Dentate gyrus	+++ +	(Huntley et al., 1992)
	Cerebral cortex	Frontal areas Limbic cortical areas Occipital cortex	+++ +++ +	(Khan et al., 2000; Huang et al., 1992)
	Basal Ganglia	Pars compacta Pars reticulate Nucleus accumbens Globus pallidus Islands of Calleja, olfactory tubercle Septal area	+ + + + + +	(Khan et al., 2000)
	Hypothalamus	Hypothalamic arcuate Mammillary nucleus Supraoptic nucleus	+ + +	(Khan et al., 2000)
	Thalamus	Lateral dorsal nucleus Anterior ventrolateral Anterior dorsomedial lateral Posterior nucleus	+++ +++ +++ +++	(Meador-Woodruff et al., 1992; Trumpp-Kallmeyer et al., 1992; Khan et al., 2000)
	Cerebellum	Granule cell layer	+	(Khan et al., 2000)
	Midbrain	Inferior colliculus Oculomotor nucleus central nucleus Superior colliculus	+++ + +	(Khan et al., 2000)

generally pro-epileptogenic, whereas signaling from D_2-like receptors perform an anti-epileptogenic effect (Bozzi and Borrelli, 2013). Dopamine has inhibitory effect on excitability of hippocampal neurons through D_2-like receptors (Starr, 1996; Starr, 1993).

Drugs that stimulate dopaminergic system such as L-DOPA and anti-parkinson drugs (bromocriptine, pergolide), apomorphine and amphetamines have anti-epileptic and anti-convulsant effects (Starr, 1996). In epileptic patients, the anti-psychotic drugs (D_2-like antagonists) decrease seizure threshold and in patients without previous history of the disease promote the seizures. On the other hand, activation of dopamine D_1-like receptors exerts a proconvulsant effect and decrease the seizure threshold (Starr, 1996; Starr, 1993).

The opposite action of dopamine D_1- and D_2-like receptors signaling in epilepsy may be because of glutamate-dopamine interaction in limbic epileptogenesis. This hypothesis has been supported by studies in animal models in which activation of D_1-like receptors can activate glutamatergic neurons during seizure (Gangarossa et al., 2011).
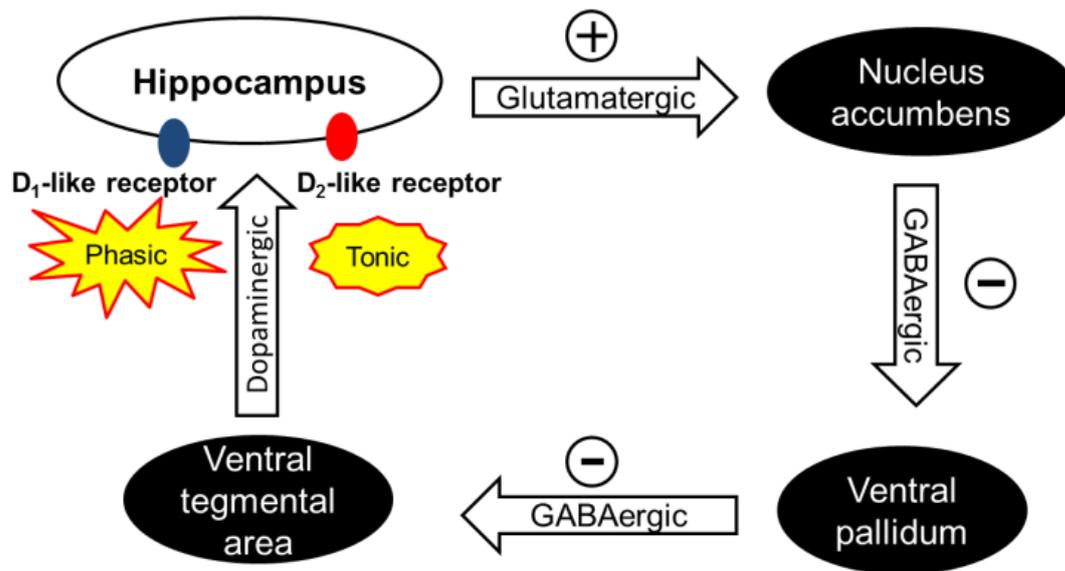
Epilepsy is accompanied with impairment in

Fig.2. Hippocampal-ventral tegmental area loop. Hippocamal glutamatergic neurons (through ventral subicular) projects to nucleus accumbens to stimulate its GABAergic projections to ventral pallidum, where inhibition of its GABAergic neurons makes a dis-inhibitory effect on ventral tegmental area and activates the dopaminergic fibers of VTA to affect hippocamus through D_1- (during phasic activity) and D_2-like receptors (during tonic activity) (Floresco et al., 2003b; Lisman and Grace, 2005).

controlling the dopamine level and expression of its receptors. The role of dopamine in epilepsy maybe due to these impairments. In addition, the level of dopamine and its metabolites is markedly changed according to the types of epilepsy and animal model (Starr, 1996). Most of animal models of temporal lobe epilepsy are accompanied with an increase in the firing rate of dopaminergic neurons and the level of dopamine in extracellular space (Cifelli and Grace, 2012).

The role of dopamine in epilepsy is also depends on the brain regions which involves in seizure generation and/or control. For example, hippocampus is one of the regions that involves in temporal lobe epilepsy. In this region, the concentration of D_2-like (especially D_4) is more than D_1-like receptors. During epilepsy, the amount of dopamine increases. Therefore, dopamine can inhibit the seizure activity through activating of hippocampal D_2-like receptors.

Another region that involves in epilepsy is the dentate gyrus. According to dentate 'gate' theory of temporal lobe epilepsy, seizures happen when the gate function of the dentate gyrus is interrupted such that excess excitation appears from or passes through the dentate gyrus to downstream regions (Heinemann et al., 1992; Lothman et al., 1992). In this region, similar to the hippocampus, D_2-like receptors play an anti-

epileptogenic role.

Changes in dopaminergic system in epilepsy
Epilepsy has been characterized as an imbalance between excitatory (glutamatergic) and inhibitory (GABAergic) transmission, however clinical and experimental evidences indicate the involvement of the major neuromodulatory systems, such as dopaminergic system, in epilepsy and seizure activity regulation.

Several studies have suggested the presence of dopaminergic dysfunctions either in the brain of epileptic patient or in animal models of seizure and epilepsy (Starr, 1993; Starr, 1996; Bozzi et al., 2011). The involvement of dopamine in epilepsy is likely due to a dysfunctional control of dopamine levels or an alteration in expression of specific receptors. Any changes in dopamine levels and/or its specific receptors can alter the neuromodulatory action of dopamine on brain circuits especially in the limbic system. Different pattern of change may observe in the level of dopamine and its metabolites according to the type and animal model of epilepsy.

1- Epilepsy and dopamine level
The extracellular concentration of neurotransmitters changes in the brain of epileptic patients and

experimental animals (Goren et al., 2003). Many studies have focused on the hippocampus, because its involvement in the pathophysiology of the temporal lobe epilepsy, the prevalent type of seizure in adults. Several studies have suggested that seizure activity leads to enhancement of brain dopamine level.

In 2008, Meurs and his colleagues, measured the level of hippocampal extracellular dopamine using *in vivo* intracerebral microdialysis following seizures induced by different pharmacological agents including pilocarpine (the muscarinice receptor agonist), picrotoxin (the $GABA_A$ receptor antagonist) and R,S-3,5-dihydroxyphenylglycine (the group 1 metabotropic glutamate receptor agonist). Intrahippocampal administration of these three convulsive drugs significantly increased the dopamine dialysated concentration. These data confirmed many other studies which indicated the presence of higher level of dopamine in the brain of epileptic animals (Alam and Starr, 1996; Cavalheiro et al., 1994; Clinckers et al., 2004; Khan et al., 1999; Khan et al., 2000; Shih and McDonough, 1997; Smolders et al., 1997; Stragier et al., 2006). Therefore, increased network activity during seizure, results in increased level of extracellular dopamine.

In contrast to the above mentioned reports, there are another studied showing that the level of dopamine decreases in epileptic patients and animal models of seizure. Alcantara-Gonzalez et al. (2013), showed that extracellular levels of dopamine in hippocampus of kindled rat were significantly lower than control animals during interictal period. Similarly, it has been reported that the tissue content of dopamine in the amygdala of kindled animal (Engel and Sharpless, 1977), and in the epileptic focus (Mori et al., 1987) is decreased. The lower amount of dopamine in interictal period could be due to an increased turnover (Wilkison and Halpern, 1979) or due to inhibitory effect of D_2 autoreceptors on dopamine releasing.

In addition to experimental models, there are also evidences showing that dopaminergic neurotransmission alters in the epileptic patients. It has been shown that dopamine and its metabolite, homovanilic acid, is lower in temporal neocortex of patient with mesial temporal lobe epilepsy (Rocha et al., 2012) and temporal lobe epilepsy secondary to brain tumor or lesion compared with temporal neocortex from autopsies from died human due to different causes which had no history of neurological diseases (Mori et al., 1987; Pacia et al., 2001).

The reduction in tissue content of dopamine and homovalinic acid, may be as a result of decreasing in metabolism or release of dopamine, but not dopamine syntheses, because according to Pintor et al., (1990) no change is observed in tyrosine hydroxylase (TH) expression and activity. Other possibilities are a) an increase in the expression of monoamine oxidase, an enzyme that involves in the degradation of dopamine and b) an alteration of dopamine reuptake.

Changes in affinity of dopamine receptors can also affect the responsiveness of dopaminergic system during seizure. The expression of dopamine transporters increases in temporal cortex of patients with mesial temporal lobe epilepsy and temporal lobe epilepsy. It is interesting that this change positively correlates to the frequency of seizure (Del Sole et al., 2010). These effects may represent a compensatory mechanism to remove increased dopamine released as result of ictal activity.

2- Epilepsy and alteration in activity of dopaminergic neurons

It has been shown that epilepsy can change the activity of dopaminergic neurons. Pilocarpine- treated rats display an abnormally enhanced dopaminergic neuron drive in the form of an increase in activity of dopaminergic neuron population (Cifelli and Grace, 2012). In normal rats, the activity of VTA dopaminergic neurons is regulated by hippocampal-VTA loop which includes ventral subicular-nucleus accumbens-ventral pallidal-VTA pathway (Fig. 2) (Floresco et al., 2003). Therefore, during temporal-lobe epilepsy, the pathological hyperactivity of the hippocampal formation (including subiculum) can lead to increased VTA dopamine neuron activity. Since the phasic burst firing response of dopaminergic neurons depends on their spontaneous activity (Lodge and Grace, 2006), abnormally high levels of population activity would enable a phasic burst stimulus to elicit burst firing in a greater number of dopamine neurons, thereby putting the dopaminergic system in a hyper-responsive state in epileptic brain (Floresco et al., 2003; Lisman and Grace, 2005) (Fig. 2).

3- Changes in dopamine receptors in animal

models of seizure

In addition to changes in dopamine level, variations in dopamine receptors have also been reported both in epileptic patients and animal models of epilepsy. D_2- like receptor activation (which induces G_i protein activity) increases in different brain areas, including the ventral hippocampus of kindled rats (Alcantara-Gonzalez et al., 2013) and in other specific brain structures in kainic acid-induced seizures (Csernansky et al., 1988; Ando et al., 2004; Sato, 1983). In contrast, some studies showed reduced availability of D_2/D_3 receptors in the anterior caudate putamen of rats during the chronic phase of pilocarpine models (Yakushev et al., 2010).

4- Alteration in dopamine receptors and dopamine transporter in epileptic patients

There are a lot of reports on the abnormalities in dopamine receptors and transporters in the brain of epileptic patients. Most of studies show that the binding potential of D_2/D_3 receptor reduces in the brain of epileptic patient. For example, the decrease in D_2 receptor protein expression in the temporal neocortex (Rocha et al., 2012), decrement in binding potential of D_2/D_3 receptors in the ipsilateral temporal lobe, bilateral basal ganglia and irritative zone surrounding of the epileptogenic area (Werhahn et al., 2006) and in thalamus of patient with mesial temporal lobe epilepsy (Bernedo Paredes et al., 2015) have been shown. In addition, it has been reported that striatal D_1-receptor binding in autosomal dominant nocturnal frontal lobe epilepsy (Fedi et al., 2008) and binding potential of D_2/D_3 receptors bilaterally in the posterior putamen in the patients with juvenile myoclonic epilepsy are reduced significantly (Landvogt et al., 2010).

The observed decrease in D_2-spicific binding may be due to reduction of the receptors amount, decrease in receptor affinity and the increase in occupancy of the receptors by dopamine or due to dopamine promoted receptor internalization (Ginovart et al., 2004).

However, in contrast to the above mentioned reports, significant increase in D_2/D_3 receptor binding potential in the hippocampus (Bernedo Paredes et al., 2015), and higher expression of dopamine D_1 receptor and higher D_2-like induced activation of G proteins in the neocortex have been observed in patients with temporal lobe epilepsy (Rocha et al., 2012).

In the case of changes in dopamine transporter in epileptic patients, there are many controversies in results of previous studies. Some investigations show that dopamine transporter binding elevates in epileptic patient (Rocha et al., 2012; Sander et al., 2000; Del Sole et al., 2010); a phenomenon which may be a compensatory mechanism to remove released dopamine due to ictal activity (Meurs et al., 2008). On the other hand, there are also reports show that binding potential of dopamine transporter reduces in substantia nigra and midbrain in the patients with juvenile myoclonic epilepsy (Ciumas et al., 2008).

Dopamine and synaptic plasticity

Epileptic seizures are accompanied with changes in synaptic plasticity. Therefore, the phenomenons which are related to synaptic plasticity can be affected by seizure occurrence. Synaptic plasticity is one of the most important mechanisms that modifies the neural circuits in central nervous system. Synaptic plasticity is considered as the major cellular mechanisms that underlies learning and memory. Different kinds of long-lasting changes in the efficacy of synapses, includes long term potentiation (LTP), long term depression (LTD) and depotentiation, are influenced by dopamine (Zucker, 1989; Abraham and Bear, 1996; Malinow and Malenka, 2002).

In 1983, for the first time, two studies (Bliss et al., 1983; Krug et al., 1983) concurrently demonstrated that a depletion of catecholamine could modulate LTP in the dentate gyrus of freely moving rats. Among catecholamine transmitters, dopamine, has been recognized to play an important role in both synaptic plasticity and memory processes (Jay, 2003).

In addition to its role in reward, dopamine has been shown to be essential role in learning and memory especially in mesohippocampal pathway (Jay 2003). Neuronal activities in different hippocampal subregions such as dentate gyrus, CA1 region and subiculum are modulated by activation of dopamine receptors (Frey et al., 1993; Grace et al., 2007). However, it is not completely clear that how do the two different classes of dopamine receptors modulate different forms of synaptic plasticity. Following dopamine denervation, different kinds of plasticity, LTP and LTD are lost in different parts of CNS (Centonze et al., 1999; Calabresi et al., 2000a; Paillé et al., 2010). In recent years, many studies focus on

dopaminergic system and dopamine receptors' role in synaptic plasticity; nevertheless, many controversial results have been reported.

D_1-like receptors antagonist inhibits the expression and maintenance of late LTP, whereas the D_1-like receptor agonist induces both the early and late phases of LTP. Previous studies also demonstrated that in D_1 knockout mice, late LTP was absent and spatial memory impaired (Kusuki et al., 1997; Calabresi et al., 2000b; Gurden et al., 2000; Kerr and Wickens, 2001; Huang et al., 2004; Matsuda et al., 2006; Schotanus and Chergui, 2008; Zhou et al., 2009). But some studies have showed that D_1-like receptors manipulation had no effect on LTP and LTD (Huang and Kandel, 1995; Swanson-Park et al., 1999; Kulla and Manahan-Vaughan, 2000; Thomas et al., 2000; Abe et al., 2008; Xu and Yao, 2010). *In vitro* studies on CA1 synapses showed that both the early and late phases of LTD are dependent on D_1/D_5 receptor activation. Consistent with this *in vitro* data, D_1-like receptors agonist and antagonist facilitates and inhibits LTD induction, respectively (Gurden et al., 2000; Lemon and Manahan-Vaughan, 2006). Interestingly, D_1-like receptor manipulation also affects depotentiation (a form of plasticity that is the reversal of previous potentiation) both *in vitro* and *in vivo*. Application of D_1-like receptors agonist decreased depotentiation and antagonist prevented inhibition of depotentiation (Otmakhova and Lisman, 1998).

Activation of D_2-like receptors has suppressive effect on LTD in the hippocampal CA1 region of rats (Chen et al., 1995). Previous studies on corticostriatal synapses showed LTP was enhanced in slices using D_2-like receptor antagonist or in mice lacking D_2-like receptors (Matsuda et al., 2006; Rocchetti et al., 2015). In one study, Rocchetti et al. (2015) showed that the genetic deletion and the pharmacologic blockade of D_2-like receptors in mice severely impaired both N-methyl-D-aspartate receptor (NMDAR)-dependent LTP and LTD in CA1, and decrease learning and memory performance. Recently, the deficiency of depotentiation has been shown in patients with Parkinson's disease who lack nigrostriatal dopaminergic projections (Rocchetti et al., 2015). Another study on hippocampal synapses showed that depotentiation was induced through activation of D_4 receptor but not D_1/D_5 receptors (Kwon et al., 2008).

In addition to above mentioned effects of D_2-like receptors on synaptic plasticity in normal conditions, these receptors can also modify seizure-induced potentiation in kindling model of epilepsy. Previous studies showed that kindling can induced synaptic potentiation (Sutula and Steward, 1986; Gilbert and Mack, 1990; Mohammad-Zadeh et al., 2007) and this effect can be prevented by application of low-frequency stimulation (Mohammad-Zadeh et al., 2007; Zeraati et al., 2010; Asgari et al., 2016; Ghorbani et al., 2007; Ghotbedin et al., 2013; Sadegh et al., 2007; Jahanshahi et al., 2009; Shahpari et al., 2012). This phenomenon depends to activation of D_2-like receptors, so that administration of D_2-like receptor antagonist can remove the preventing effect of low-frequency stimulation (Rezaei, 2016).

These variations in effects of dopamine on synaptic plasticity may be based on difference in brain regions, dopaminergic innervation, expression of dopamine receptors or protocols of LTP or LTD induction.

Conclusion

Dopamine as one of the most important neuromodulators in the brain has very important effects on neuronal excitability. As the main aim of using the anticonvulsive therapeutic manners (such as antiepileptic drugs or brain stimulations) is to reduce the excitation to inhibition ratio in neuronal activity, thus, it is necessary to understand the role of dopaminergic system on neuronal activity in epileptic brain. In addition, by increasing our knowledge on the effects of dopamine on synaptic plasticity in both normal and epileptic conditions, we can shed lights on determining the mechanisms which may be responsible in seizure-induced impairments in synaptic plasticity-dependent phenomenon.

Acknowledgments

Conflict of interest

The authors state that there is no conflict of interest.

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