Review Article

The Modulatory Role of Dopamine in Anxiety-like Behavior

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Abstract

Anxiety is an unpleasant physiological state in which an overreaction to a situation occurs. It has been suggested that different brain regions are involved in the modulation and expression of anxiety, including the amygdala, hippocampus, and frontal cortex. Dysfunction of neurotransmitters and their receptors can lead to many mood disorders like anxiety. There are evidences that dopamine plays an important role in anxiety modulation in different parts of the brain. Some evidence has shown that the mesolimbic, mesocortical and nigrostriatal dopaminergic system are involved in anxiety. Both dopamine D1 and D2 receptor mechanisms are important in mediating anxiety.

The activity of dopaminergic system is modulated by several neurotransmitters, including glutamatergic neurons from the medial prefrontal cortex (mPFC), GABAergic fibers from the nucleus accumbens (NAc) as well as the ventral pallidum and cholinergic fibers from the pedunculopontine nucleus and the laterodorsal tegmental nucleus. Thus, changes in the glutamatergic, and GABAergic, as well as mediated transmission in the mesolimbic, mesocortical and nigrostriatal dopaminergic system may influence anxiety-like behavior.

Keywords: Anxiety, dopamine, D1 and D2 receptor, mesocortical, nigrostriatal

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Introduction

Threatening stimuli evokes states of stress, anxiety or fear in animals. The level of anxiety exhibition is different in response to different stimulators.[1,2] In aversive condition, stress responses could result in individuals' homeostatic maintenance. Anxiety is a complex psychological state**,** which can be beneficial in some situations. It has been consistently shown that stressful life condition could induce anxiety-like behavior.[1,3–5] Potential threat results in a risk assessment behavior, comprising induction of arousal and attention, identification, and localization of danger to enable a transition from the "anxiety/defense" pattern to the more "goal directed" "fear/defense" pattern.[6,7] Walker, et al. (2003) revealed that this response system has both a slow onset and a slow offset. Also, they indicated that fear differs from anxiety in its time course, in having a rapid onset and offset.[8]

Many brain regions and different neurotransmitters are involved in the development of anxiety.[9] One of the most important neurotransmitters involved in behavioral responses to naturally anxiogenic environmental stimuli is dopamine, which plays a critical role in anxiety and fear.[10–12] Considering the involvement of dopaminergic system in the modulation of anxiety, the aim of this study is to review the participation of the dopaminergic system within many brain regions in the modulation of anxiety.

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The role of dopaminergic system in anxiety-like behavior

Anxiety can be considered even as a "normal" emotion and an adaptive component of the acute stress response under circumstances that threaten the integrity of the individual or can be a pathological state which disrupt the patient's life.[13,14] Experimental studies in animal models revealed that many brain regions acting in concert mediate the symptoms of anxiety, both normal and abnormal. However, some areas such as the hippocampus,[15,16] amygdala,[17,18] septum,[19,20] prefrontal cortex (PFC),[21,22] and NAc,[23,24] seem to be specially involved in anxiety-like behavior. Each of these regions has been related to the neurocircuitry of anxiety in humans.[4,25] A various mechanisms and neurotransmitter are involved in the regulation of anxious states.[14] It has been suggested that dopaminergic systems have central roles in regulation of anxiety-like behaviors.[26–33] Dopamine is the main catecholamine in the mammalian brain and influences variety of functions and has been revealed that dopamine has a role in pathophysiology of some mental disease including parkinson,[34–36] schizophrenia,[37–39] sleep-related disorders.[40,41] Also dopamine is involved in the regulation of locomotor activity,[42,43] cognition[44,45] emotion,[46,47] positive reinforcement,[48,49] food intake,[50,51] endocrine regulation, cardiovascular function,[52] catecholamine release, hormone secretion,[53,54] vascular tone, renal function,[55,56] gastrointestinal motility,[57] reward,[58,59] learning,[60–63] memory,[64,65] pain,[66,67] depression,[68,69] fear,[29,70] and anxiety.[71,72] Dopamine receptors were classified based on amino acid sequence homology and pharmacology.[73,74] Five different dopamine receptors have been identified, which are G protein-coupled,[75–78] and are categorized as belonging to one of the two classes nominated as D1-like (D1 and D5) or D2-like (D2, D3, and D4).[77,79,80] D1-like receptors can excite adenylatecyclase activity and increase cyclic adenosine monophosphate (cAMP). Autoreceptors, which are D2-like, have been recognized on the presynaptic terminals of dopaminergic neurons. Conversely, D2-like receptor activation either prevents or has no effect on cAMP levels.[81,82] Despite their opposing actions on adenylatecyclase activity, previous evidences have suggested that a synergistic inter-

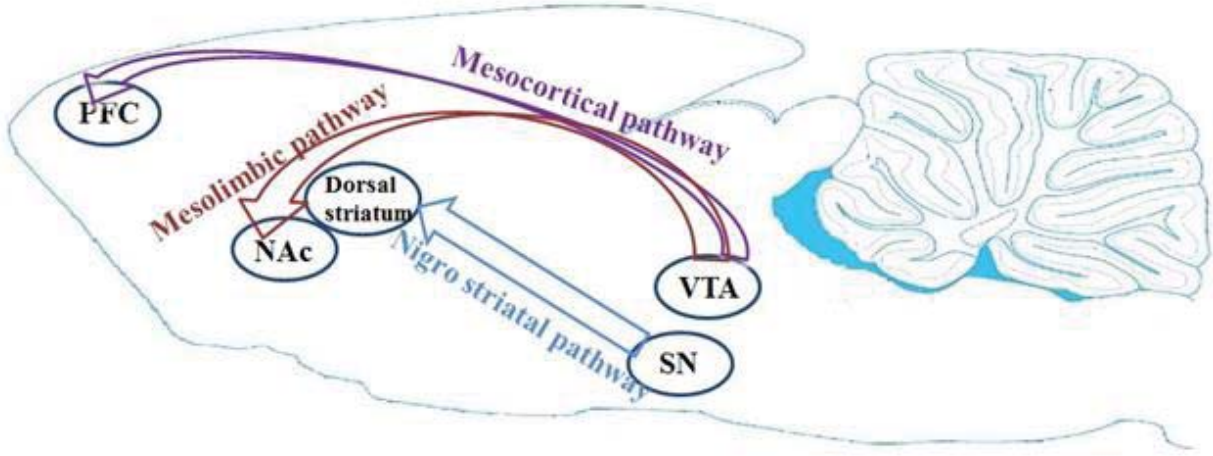

Figure 1. Schematic illustration of nigrostriatal, mesolimbic and mesocortical dopaminergic pathway. This pathway plays an important role in anxiety process.[62,94] The PFC and mesocorticolimbic dopaminergic pathway originate from the VTA.[147,163] The mesolimbic and mesocortical dopaminergic system are involved in mediating anxiety.[79] VTA: ventral tegmental area; SN: substantianigra; NAc: nucleus accumbens; PFC: prefrontal cortex.

action between D1 and D2 receptors is needed for the expression of most dopaminergic-related behaviors.[83–85] Alterations in dopamine transmission occurs following exposure to a wide variety of acute stressors.[79,86] It has been shown that both dopamine D1 and D2 receptors are important in mediating anxiety even it could be with different mechanism.[10,87–89] It has been reported that dopamine depletion would be the inducer of anxiety and depression-like behaviours,[72,90] while L-DOPA treatment could rebate these effects due to dopaminergic function modulation.[90] Dopamine is metabolized to 3,4-dihydroxyphenylacetic acid (DOPAC) in the terminal of synapses and mitochondria via monoamine oxidase. The level of dopamine and its metabolites, including the DOPAC/dopamine ratio (dopamine turnover) and MAO-A/B activity, are associated with anxiety-like behavior.[89,91–93]

Effect of dopamine neurons of various brain areas in anxiety-like behavior

Two important populations of dopamine neurons are 1) some dopaminergic neurons in substantia nigra (SN), which project to the dorsal striatum, giving rise to the nigrostriatal system, and 2) those in the VTA that project to limbic structures, mainly the ventral striatum [i.e., the NAc], and PFC, giving rise to mesolimbic and mesocortical pathways (Figure 1).[94] These systems are associated with different functions: the nigrostriatal system has a motor function, while the mesolimbic system has motivation and reward functions.[62,94,95] The pattern of dopamine release in the striatum and PFC is controlled by firing rates of dopamine cells in the substantia nigra pars compacta (SNc) and ventral tegmental area (VTA).[96] Moreover, different parts of the VTA/SN complex may have functional interactions, either via local connections or long-range feedback loops.[97–100] Some studies have indicated that the mesolimbic and mesocortical dopaminergic system are involved in mediating stress,[88] fear,[101] anxiety,[79,102] motivated behaviors, various types of reward and cognitive processes.[103] There are data showing that stress activates the mesolimbic dopamine system,[73,104] and an increase in dopamine level in the synaptic cleft, e.g. through inhibition of dopamine reuptake, which may induce anxiety-like behavioral effects.[73,105,106] The striatum contains dense dopaminergic innervations.[107] The dorsal striatum receives a major dopaminergic afferent from the SNc,[62] and the ventral striatum receives a major dopaminergic input from the VTA.[108] Dopaminergic neurons in the striatum play a main role in processing of reward,[62] and motivation.[108] In addition, the VTA is a main dopaminergic center in the brain, which projects dopaminergic pathways to several corticolimbic structures.[45,109,110] Dopamine containing neurons in VTA are about 60%.[111] Dopamine D1 receptors are expressed in moderate to low density in the VTA.[112] These receptors have a key role in the functional interaction between the VTA and its target sites, such as forebrain structures.[45,113] Furthermore the dopamine D2 receptors are highly expressed in the VTA of rodents.[112] Activation of the D2 autoreceptors leads to heighten potassium conductance that hyperpolarizes the plasma membrane of dopaminergic fibers.[114] The activation of D1 receptors located on the VTA dopaminergic neurons or non-dopaminergic nerve terminals increases D2 receptor-mediated inhibition through inhibitory neurons.[112] Some studies have shown that intra-VTA injection of D2 receptor antagonists, for example eticlopride or sulpiride, increase the extracellular dopamine in the VTA.[45,115] These studies may suggest that somatodendritic dopamine D2 autoreceptors in the VTA tonically inhibit the dopaminergic mesocorticolimbic pathway activity.[45] The VTA dopamine cells are activated in stressful condition[10] and anxiety,[116] and release dopamine in the NAc,[94] mPFC,[117] amygdala,[10] hippocampus,[45] and olfactory tubercule.[94]

Effect of dopamine neurons of the hippocampus in anxiety-like behavior

The hippocampus is the main part of the mesolimbic system that is involved in the modulation of fear and anxiety-related behaviors.[118–122] The hippocampus is vastly interconnected with the septum, and has main connections with the locus coeruleus, raphe nuclei, hypothalamus, amygdala and medial frontal cortex; regions that are involved in anxiety.[79] It is well known that the dorsal hippocampus plays a vital role in the learning and memory of spatial tasks,[123–125] while the ventral hippocampus is predominantly involved in the modulation of fear and anxiety.[126] In fact, the ventral sub-region of the hippocampus differs from the dorsal part in its anatomical connections.[127] The ventral hippocampus projects to the PFC, whereas the dorsal hippocampus does not.[126] Lesions of the ventral hippocampus induce anxiolytic-like effects similar to those observed after treatment with anxiolytic drugs in different animal models of anxiety.[119]

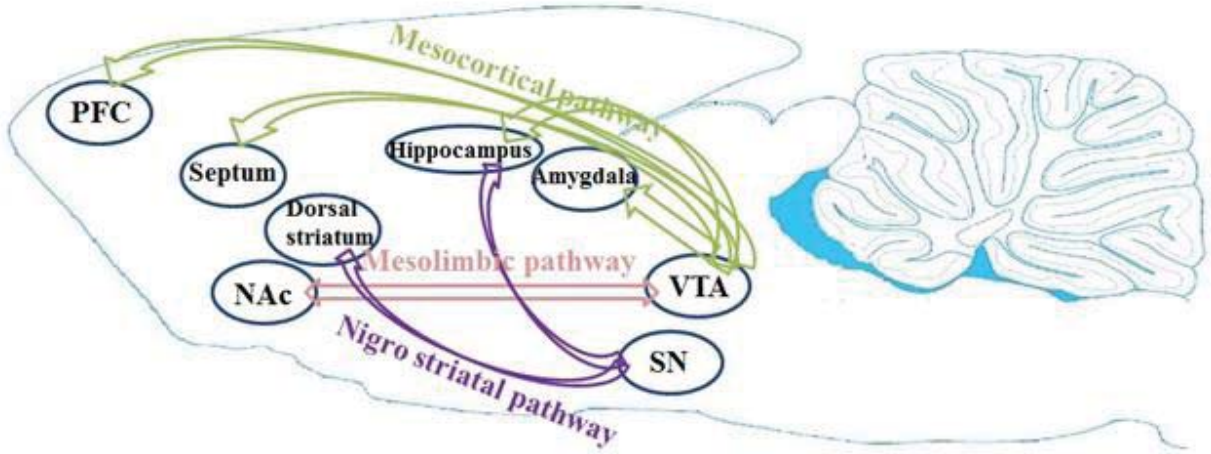

Figure 2. Schematic representation of the sites of actions of nigrostriatal, mesolimbic and mesocortical dopaminergic pathway. Nigrostriatal, mesolimbic and mesocortical dopaminergic systems are associated with different functions. Firing rates of the dopamine cells in the SNc and VTA control dopamine release in target structures such as the striatum and PFC.[23,63,65] VTA: ventral tegmental area; SN: substantianigra; NAc: nucleus accumbens and PFC: prefrontal cortex.

The hippocampus receives dopamine projections from the mesolimbic structures such as the VTA and SNc (Figure 2).[45,117,128,129] This phenomena seems to have a key role in the hippocampus plasticity.[123] Dopamine D1 and D2 receptors of the dorsal hippocampus (CA1) and ventral hippocampus are involved in anxiety-related behaviors.[74,79,130]

Effect of dopamine neurons in the amygdala in anxiety-like behavior

Amygdaloidal structure, which includes numerous sub-nuclei plays a main role in the integration and expression of anxiety,[131–137] stress,[138] fear conditioning, and emotional memory.[139] Structural changes in the basolateral amygdaloid (BLA) nucleus have been most implicated in anxiety situation. Stressful environment, elevated level of stress hormones and anxiety could lead to BLA nucleus hypertrophy, whereas experimental reduction of dendritic length results in decreased anxiety.[140–142] The mesocorticolimbic dopamine system function and associated mood state is regulated by VTA dopaminergic neurons, which are controlled by central amygdaloid (CeA) nucleus projections.[10,112] Several experimental investigations showed that the mesolimbic dopaminergic system has a critical role in amygdaloid modulation of fear and anxiety.[10,143] Under normal conditions, the activity of BLA nucleus is suppressed by the mPFC, but in stressful conditions, dopaminergic neurotransmission relieves BLA nucleus from cortical inhibition and leads to the development of anxiety responses.[10,144] Thus, this effect of dopamine decreases cortical inhibition and modulates the relation between important regions involved in anxiety in amygdala including BLA and CeA nuclei, which are central input and output station of amygdala.[10,87,112]

The amygdala is innervated by dopamine neurons originating from the VTA.[50] Anxiety, fear and other stressors can activate the VTA-derived dopaminergic pathways to the amygdala and adjacent bed nucleus of the stria terminals (BNST).[88] In mammals, dopamine receptor-mediated mechanisms play a critical role in the amygdaloid modulation of fear and anxiety.[10,12,143] Different kinds of dopamine receptors, which exit in the rats' amygdala are involved in anxiety modulation (Table 1).[10,101] Some evidences indicated that the intra amygdala D1 receptor activation or its blockade could cause either anxiogenic or anxiolytic effects in conditioned and unconditioned tests of anxiety.[10,18,87,145] Behaviorally, the intra-amygdala injection of dopamine D1-like receptor agonists and antagonists elicits anxiogenic and anxiolytic effects respectively on models of anxiety suggesting an anxiogenic role for D1 receptors in amygdala.[18,146] Furthermore, the amygdaloid dopamine D2 receptors play a vital role in the modulation of anxiety. The amygdaloid dopamine D2-like receptors are express in CeA nucleus of amygdala and have been suggested to be involved in anxiety-like behavior via VTA and BLA connecting modulations.[10,87,147] The Dopaminergic transmission (of unknown origin) in the vestibular nuclei and mesolimbic dopaminergic projections to the CeA nucleus and infralimbic are potential substrates for the D2-receptor-mediated dopaminergic transmission to influence vestibular function and anxiety.[12,148]

Effect of dopamine neurons in the septum in anxiety-like behavior

The septum is a region of the basal forebrain,[149] and plays an important role in anxiety,[16,150] fear, stress, emotions, aggression, and motivation.[151] The septum usually increases anxiety.[16] The septal region is compassed of two parts (lateral and medial septum) with different innervation and function.[19,152–155] Some studies indicate that the lateral septum enhances its neural activity when animals are submitted to a variety of stressful stimuli. Additionally, the lateral septum contains axon terminals and expresses receptors for different neurotransmitters/neuromodulators implicated with anxiety.[150] Several evidences indicated that lesion of the lateral septum produces anxiolytic effects.[151,156,157] In addition, the medial septum may play an important role in the regulation of anxiety.[16]

The VTA dopamine innervations to septum contact to perikarya and dendrites of septal fibers and induce excitatory and inhibitory postsynaptic responses.[123,158] A mild stressor significantly increased the septal dopamine levels, implicating a role for dopamine in sensory-related processing associated with the septal complex.[158–160]

Table 1. Effects of dopamine D1- and D2-like agonists and antagonists on anxiety.

Drug	Action	Animal model	Species (strain)	Site of injection	Dose range	Effect	Reference
SKF38393	D1 agonist	Elevated plus maze	Rat	BLA	0.25 µg/rat	Anxiogenic	88
SKF38393	D1 agonist	Head dips	Mouse	Hippocampus	4 µg/mouse	Anxiogenic	79
Apomorphine	D1/D2 receptor agonist	Elevated plus maze	Rat	Amygdala	0.001, 0.01 and 0.1 µg/rat	Anxiolytic	212
Apomorphine	D1/D2 receptor agonist	Elevated plus maze	Rat	Hippocampus	0.1 and 0.2 µg/rat	Anxiogenic	74
SCH23390	D1 antagonist	Elevated plus maze	Rat	BLA	0.5 and 1 µg/rat	Anxiolytic	88
SCH23390	D1 antagonist	Elevated plus maze	Rat	VTA	0.5 µg/rat	Anxiolytic	112
SCH23390	D1 antagonist	Elevated plus maze	Rat	NAc	0.5 µg/rat	Anxiolytic	194
SCH23390	D1 antagonist	Elevated plus maze	Rat	BLA	1 µg/rat	Anxiolytic	144
SCH 23390	D1 antagonist	Fear conditioning	Rat	BLA	1 and 2 µg/0.2 µL	Not effect	147
SCH23390	D1 receptor antagonist	Elevated plus maze	Rat	Hippocampus	0.01, 0.1 and 1µg/rat	Not effect	74
SCH23390	D1 antagonist	Elevated plus maze	Rat	Hippocampus	0.25, 0.5 and 1 µg/rat	Not effect	102
SCH23390	D1 antagonist	Head dips	Mouse	Hippocampus	0.5 µg/mouse	Anxiogenic	79
SCH23390	D1 antagonist	Elevated plus maze	Rat	Amygdala	0.5 and 1 µg/rat	Anxiogenic	212
Quinpirole	D2 agonist	Fear conditioning test	Rats	VTA	1 µg/0.2 µL	Anxiolytic	147
Quinpirole	D2 receptor agonist	Head dips	Mouse	Hippocampus	0.25 µg/mouse	Anxiogenic	79
Quinpirole	D2 receptor agonist	Elevated plus maze	Rat	BLA	0.03 and 0.05 µg/rat	Anxiogenic	88
Sulpiride	D2 antagonist	Fear conditioning	Rat	BLA	1 and 2 µg/0.2 µL	Anxiolytic	147
Sulpiride	D2 receptor antagonist	Elevated plus maze	Rat	BLA	5 µg/rat	Anxiolytic	144
Sulpiride	D2 receptor antagonist	Elevated plus maze	Rat	BLA	0.3 and 0.5 µg/rat	Anxiolytic	88
Sulpiride	D2 receptor antagonist	Head dips	Mouse	Hippocampus	0.25, 0.5 and 0.75 µg/mouse	Not effect	79
Sulpiride	D2 receptor antagonist	Elevated plus maze	Rat	NAc	0.25, 0.5, 0.75 and 1 µg/rat	Not effect	194
Sulpiride	D2 receptor antagonist	Elevated plus maze	Rat	Hippocampus	0.25, 0.5 and 0.75 µg/rat	Not effect	102
Sulpiride	D2 receptor antagonist	Elevated plus maze	Rat	VTA	0.2, 0.3, 0. 5, 0.7 and 1 µg/rat	Not effect	112
Sulpiride	D2 receptor antagonist	Elevated plus maze	Rat	Hippocampus	1, 2.5 and 5µg/rat	Not effect	74
Sulpiride	D2 receptor antagonist	Elevated plus maze	Rat	Amygdala	2 and 3 µg/rat	Anxiogenic	212
Raclopride	D2 receptor antagonist	Fear-potentiated startle	Rat	BLA	2.0–8 µg/side	Anxiolytic	10
Raclopride	D2 receptor antagonist	Shock-Probe Burying test	Rat	CeA	0.73, 2.4 µg/side	Anxiogenic	10
Eticlopride	D2 receptor antagonist	Conditioned freezing	Rat	CeA	1 µg/side	Anxiolytic	10

Effect of dopamine neurons of the medial prefrontal cortex (mPFC) in anxiety-like behavior

The mPFC of rodents is subdivided into anterior cingulate, precentral, prelimbic, infralimbic and medial orbital cortices.[22] These areas are involved in the control of emotional responses, and sending projections to various brain regions related to the expression of fear and anxiety.[161,162] The PFC and mesocorticolimbic dopaminergic pathway originate from the VTA.[109,147,163–165] The PFC dopaminergic system involved in anxiety-related behavioral via D1 or D2 activity, pharmacological stimulation or inhibition of dopamine receptors in the mPFC change anxiety-like state.[166–169]

Effect of dopamine neurons of the nucleus accumbens (NAc) in anxiety-like behavior

One of the major parts of ventral striatum and mesolimbic system is NAc.[23,94,170] The NAc is involved in motivation, reinforcement, defensive behavior, cognition, motor activity, sexual behavior, stress, fear and anxiety. The NAc has heterogeneous structure consist of the shell and core. The shell has a role in limbic and motor cortex connection. This connection could explain the involvement of shell in defensive behavioral responses to threatening stimuli.[24] Some neurotransmitter systems of the NAc may be involved in anxiety-related behavior.[23] The NAc received dopaminergic neurons from the VTA.[108,109,170,171] As medial and posterior sections of the VTA project to the medial portion of the ventral striatum (i.e. 'shell' of the NAc), whereas anterior and lateral parts of the VTA innervate the most lateral portions of the ventral striatum (i.e. the 'core' of the NAc).[94,172] The NAc can change the activity of VTA dopaminergic system via direct or indirect pathways. In a direct way, spiny fibers from the NAc project to the VTA and in an indirect way ventral pallidum is involved. It has been shown that there is a stressful environment that could increases dopamine in NAc.[112,152,173] Stress has also been shown to reorganize spine types on fibers of the NAc, an effect which may be relevant to altered motivational states characteristic of anxiety disorders.[4,174]

Interaction of dopaminergic system with other neurotransmitter in modulation of anxiety-like behavior

The balance between excitatory and inhibitory inputs and innate firing of dopaminergic neurons could regulate dopamine release of VTA in purposed regions.[117,175] The principle excitatory inputs to the VTA dopamine fibers are glutamatergic afferents from the mPFC,[62,117,176] whereas the major inhibitory inputs are GABAer-

gic, including local interneurons and projections from the NAc and the ventral pallidum.[177–181] Glutamatergic inputs activate AMPA- and NMDA-type ionotropic glutamate receptors in the dopamine cells. Agonist of AMPA and NMDA receptors could also induce the firing of dopaminergic neurons. In addition, blockage of NMDA receptor could inhibit dopamine firing-induced by electrical stimulation of glutamatergic afferents or application of ionotropic glutamate/aspartate.[182] Glutamate also activates metabotropic glutamate receptors (mGluRs), mainly type 1 mGluR (mGluR1), in the dopamine neurons. On the other hand, dopamine inhibits glutamate release and facilitates GABA release onto the dopamine neurons via activation of presynaptic D2 and D1 receptors, respectively.[62] Pedunculopontine nucleus (located in upper brainstem), and laterodorsal tegmental nucleus (located caudal to pedunculopontine nucleus) project and release acetylcholine to VTA. Cholinergic innervations induced dopamine release from VTA to NAc.[117,183] It has been shown that the release of glutamate with acetylcholine is important to produce specific patterns of activity in the dopaminergic neurons of the VTA.[117,184] Serotonergic system through serotonin (5-HT) receptor subtypes including 5-HT2A and 5-HT2C receptors modulates cortical dopamine activity. Stimulatory action of nicotine on the midbrain dopamine function could block by 5-HT2C receptor agonists. It has been reported that the level of extracellular dopamine in the accumbens shell and mPFC increased after 5-HT6 receptor agonist administration, which indicated the modulation effect of 5-HT6 receptors on dopamine transmission in the mesolimbic and mesocortical terminals.[112,185–189]

Interaction of dopaminergic system with glutamatergic system in modulation of anxiety-like behavior

The interaction between glutamatergic and dopaminergic systems in central nervous system (CAN) may be important in the modulation of anxiety-related behaviors (Table 2).[102,190] For instance, some study exhibited that NMDA receptor signaling in dopaminergic neurons of the VTA,[32] and CA1,[102] plays a key role in anxiety-like behaviors. A subcellular cross-talking between the dopaminergic and glutamatergic systems has been proven in terms of molecular assemblies: receptors of both systems tend to colocalize and NMDA transmission is increased when dopamine D1 is co-expressed.[57] The glutamatergic afferents activate ionotropic and metabotropic glutamate receptors in the dopamine cells.[62] Expression of the metabotropic glutamate receptor is high in the brain areas receiving dopaminergic inputs.[191] It has been revealed that metabotropic glutamatergic receptors interact with the dopaminergic and ionotropic glutamatergic interplay through the inhibition of a kinase, which is activated by dopamine receptor D1 that, in turn, activates AMPA receptors, providing a second mechanism of inhibition for excessive activation. It is interesting to note what happens within the glutamatergic system. It has been reported that after stimulating dopamine D1 receptors, the AMPARs and NMDARs undergo a different metabolic path, suggesting that a regulation takes place. It specially regulates the fate of different actors of the glutamatergic system.[57] Both *in vivo* and *in vitro* studies indicated that dopamine neurons firing induced by glutamatergic inputs can decreased by AMPA receptor antagonists.[192]

In particular, dopamine D1 manipulation results into a specific phosphorylation profile of NMDA receptors in different sub regions of the neuronal cell, although the AMPA and metabotropic glutamatergic receptors were found to be unchanged in their phosphorylation state after dopamine D1 experimental challenge. The PSD-95 has been shown to be the scaffolding proteins that control the relationship between the D1 and NMDA receptors.[193] Under physiological conditions, PSD-95 uncouples dopamine D1 and NMDA allowing the internalization of NMDA, which interrupts the glutamatergic signal.[57]

Interaction of dopaminergic system with cholinergic system in modulation of anxiety-like behavior

The regulation of dopamine release by acetylcholine may modulate anxiety-like behavior in mice.[79] Some evidences demonstrated the involvement of dopamine transmission through D1 and D2 receptors of the NAc shell,[194] dorsal,[79] and ventral hippocampus,[74] in the anxiogenic-like effect of nicotine. Cholinergic inputs of laterodorsal tegmental nucleus control the pattern of dopamine cell firing.[94] The dopamine neurons generally exhibit excitatory responses to acetylcholine via activation of nicotinic,[94,96] and muscarinic acetylcholine receptors.[62] It is suggested that dopamine is involved in anxiogenic-like effect of nicotine. As dopamine neurons express different subtypes of nicotinic acetylcholine receptors (nAChRs), stimulation of postsynaptic M5 muscarinic acetylcholine receptors activitate dopamine neurons.[62,94] Some studies indicated that dopamine is released by nicotine,[195] induces anxiety-like behavior,[196] which is reduced via blockade of the D1 and D2 receptors by dopamine antagonists.[74,79] Zarrindast, et al. (2010), showed that systemic injection of apomorphine is able to induce anxiolytic-like effect in elevated plus maze, through D2 receptor subtype. The possibility may exist that apomorphine acts on presynaptic D2 receptors and in turn decreases dopamine release through nicotine.[74] Thus, dopamine post-synaptic receptor activation should be involved in the anxiogenic-like behavior of nicotine.[74,79]

Interaction of dopaminergic system with GABAergic system in modulation of anxiety-like behavior

It has been reported that GABAergic system is participated in modulation of anxiety-like behavior via interacting with other neurotransmitter systems such as opioidergic and dopaminergic systems in some specific brain areas including the ventral hippocampus, NAc and CeA nucleus.[23,101,197] A large number of synapses onto dopaminergic neurons of SNc are GABAergic, so it is suggested that GABA strongly inhibits the activity of dopamine neurons.[198] In VTA, the inhibition effect of GABA is lower than SNc. NAc/striatum and the ventral pallidum/globuspallidus (external segment) have a GABAergic feedback projections into the VTA/SNc.[62,177,178] Recent evidence employing an optogenetic approach indicates that the GABAergic feedback from the NAc/striatum projects more densely to non-dopamine neurons.[173,199] The dopamine neurons also receive GABAergic inputs from local GABA neurons within the VTA,[200] or from substantia nigra pars reticulata (SNr).[179] Both $GABA_A$ and $GABA_B$ receptors mediate the inhibitory action of GABA on the dopamine cells.[200] It has been reported that dopaminergic activity of nigrostriatal neurons are increased by $GABA_A$ receptors activity, while mesolimbic dopaminergic neurons' activity decrease in consequences of $GABA_B$ receptors stimulation. $GABA_B$ receptor-mediated inhibition is achieved by activation of G protein-gated inwardly rectifying K+ (GIRK) channels.[201] GABA release onto the dopamine neu-

Table 2. A summary of dopamine receptor pharmacology in animal models of anxiety.

Drug	Action	Animal model	Species (strain)	Site of injection	Dose range	Effect	Reference
SKF38393 + Nicotine	(D1 receptor agonist) + (An active alkaloid of tobacco)	Head dips	Mouse	(Dorsal hippocampal) + (i.p.)	(4 µg/mouse) + (0.5 mg/kg)	Anxiogenic	79
SKF38393 + histamine	(D1 receptor agonist) + (Histamine)	Elevated plus maze	Rat	Co-injection in BLA	(0.125 µg/rat) + (1 and 2.5 mg/kg)	Anxiolytic	88
Apomorphine + Nicotine	(D1/D2 receptor agonist) + (An active alkaloid of tobacco)	Elevated plus maze	Rat	(Ventral hippocampus) + (i.p.)	(0.02, 0.1 and 0.2 µg/rat) + (0.6 mg/kg)	Anxiolytic	74
Apomorphine + morphine	(D1/D2 receptor agonist) + (Opioid)	Elevated plus maze	Rat	(CeA) + (i.p.)	(0.1, 0.2 and 0.3µg/rat) + (4 mg/kg)	Anxiolytic	101
SCH23390 + Nicotine	(D1 receptor antagonist) + (An active alkaloid of tobacco)	Head dips	Mouse	(Dorsal hippocampal) + (i.p.)	(0.125, 0.25 and 0.5 µg/mouse)+ (0.5 mg/kg)	Anxiolytic	79
SCH23390 + Nicotine	(D1 antagonist) + (An active alkaloid of tobacco)	Elevated plus maze	Rat	(Ventral hippocampus) + (i.p.)	(0.01 µg/rat) + (0.6 mg/kg)	Anxiolytic	74
SCH23390 + Nicotine	(D1 receptor antagonist) + (An active alkaloid of tobacco)	Elevated plus maze	Rat	(VTA) + (CeA)	(0.25 µg/rat) + (1 µg/rat)	Anxiolytic	112
SCH23390 + Nicotine	(D1 receptor antagonist) + (An active alkaloid of tobacco)	Elevated plus maze	Rat	(NAc) + (CeA)	(0.125 and 0.25 µg/rat) + (1 µg/rat)	Anxiolytic	194
SCH23390 + morphine	(D1 receptor antagonist) + (Opioid)	Elevated plus maze	Rat	(CeA) + (i.p.)	(0.5–1.5 µg/rat) + (6 mg/kg)	Anxiogenic	101
SCH23390 + histamine	(D1 receptor antagonist) + (Histamine)	Elevated plus maze	Rat	Co-injection in BLA	(0.25 mg/rat) + (5 and 7.5 mg/rat)	Anxiolytic	88
SCH23390 + MK801	(D1 antagonist) + (NMDA receptor antagonist)	Elevated plus maze	Rat	Co-injection in dorsal hippocampal	(0.5 µg/rat) + (0.5 g/rat)	Anxiolytic	102
Quinpirole + Nicotine	(D2 receptor antagonist) + (An active alkaloid of tobacco)	Head dips	Mouse	(Dorsal hippocampal) + (i.p.)	(0.25 µg/Mouse) + (0.5 mg/kg)	Anxiogenic	79
Quinpirole + histamine	(D2 receptor antagonist) + (Histamine)	Elevated plus maze	Rat	Co-imjection in BLA	(0.01 µg/rat) + (1 and 2.5 mg/kg)	Anxiolytic	88
sulpiride + Nicotine	(D2 receptor antagonist) + (An active alkaloid of tobacco)	Head dips	Mouse	(Dorsal hippocampal) + (i.p.)	(0.5 and 0.75 µg/mouse) + (0.5 mg/kg)	Anxiolytic	79
Sulpiride + Nicotine	(D2 receptor antagonist) + (An active alkaloid of tobacco)	Elevated plus maze	Rat	(Ventral hippocampus) + (i.p.)	(1 µg/rat) + (0.6 mg/kg)	Anxiolytic	74
Sulpiride + Nicotine	(D2 receptor antagonist) + (An active alkaloid of tobacco)	Elevated plus maze	Rat	(VTA) + (CeA)	(0.7 µg/rat) + (1 µg/rat)	Anxiolytic	112
Sulpiride + Nicotine	(D2 receptor antagonist) + (An active alkaloid of tobacco)	Elevated plus maze	Rat	(VTA) + (CeA)	(0.7 µg/rat) + (1 µg/rat)	Anxiolytic	194
Sulpiride+ morphine	(D2 receptor antagonist) + (Opioid)	Elevated plus maze	Rat	(CeA) + (i.p.)	(0.5–1.5 µg/rat) + (6 mg/kg)	Anxiogenic	101
Sulpiride + histamine	(D2 receptor antagonist) + (Histamine)	Elevated plus maze	Rat	Co-injection in BLA	(0.1 mg/rat) + (5 and 7.5 mg/rat)	Anxiolytic	88
Sulpiride + MK801	(D2 receptor antagonist) + (NMDA receptor antagonist)	Elevated plus maze	Rat	Co-injection in dorsal hippocampal	(0.12, 0.5 and 0.75 µg/rat) + (2 µg/rat)	Anxiogenic	102

rons can be inhibited through both $GABA_A$ and $GABA_B$ receptors which may be responsible for phasic firing of dopamine neurons.[180,198,202–204]

The tail of the VTA (tVTA), also named the rostromedial tegmental nucleus (RMTg), is recently defined as a midbrain structure that considered to send a GABAergic input on the dopamine systems.[203,205,206] Anatomical properties of tVTA, make it suitable for conveying different kinds of signals to dopamine neurons and participate in behavioral responses.[206] Also, there is a putative GABAergic connection with the dopamine fibers within the CeA nucleus. It is known that the amygdala is under a powerful GABAergic control of the mPFC. Dopamine D1 and D2 receptors in the CeA and BLA nuclei attenuate the mPFC inhibition in dopaminergic activity by unknown mechanism.[10]

Interaction of dopaminergic system with cannabinoid system in modulation of anxiety-like behavior

Cannabinoids may interact with several neurotransmitter systems; such as the dopaminergic system.[128] The CB1 receptor stimulation might prevent the release of different neurotransmitters (dopamine, norepinephrine, and serotonin) involved in triggering stress induced response, thus reduce it.[207,208] Cannabinoids modulate monoamine synthesis and release dopamine by the activation of CB1 receptors.[128,209] Neurons expressing dopamine D1 receptors also express cannabinoid CB1 receptors but the exact roles of them in behavior is not understood yet.[86] In the central nervous system, endogenous cannabinoids compounds activate cannabinoid CB1 receptors, which are located pre-synaptically in several brain regions such as PFC, hippocampus, amygdala, basal ganglia and VTA.[86,94,210,211]A dopaminergic and endocannabinoid interactions in different parts of the brain like amygdala, NAc and striatum are involved in different behavioral responses.[86] It has been suggested that D1 and D2 dopaminergic receptors' activities are involved in the anxiety induction.[212]

Interaction of dopaminergic system with opioidergic system in modulation of anxiety-like behavior

Morphine-induced anxiolytic-like effects may be mediated by interacting with other neurotransmitter systems such as GABAergic and dopaminergic system in some specific brain areas including the ventral hippocampus, NAc and CeA nucleus.[23,101,197] Morphine blocks inhibitory effect of GABA on VTA dopaminergic activity, thus increases dopamine release.[101,213] Rezayof, et al. (2009) reported that the CeA nucleus dopaminergic mechanisms, possibly via D1/D2 receptors, might be involved in the modulation of morphine-induced anxiolytic-like behavior in rats.[101] Opioids can increase dopaminergic transmission to the NAc by inhibiting the GABAergic interneurons in the VTA.[214,215] Chronic administration of opiates decrease the size of dopaminergic neurons of VTA and subsequence dopamine release while, increase volatility of neurons.[216] *In vivo* studies in morphine-dependent rats indicated that opiates hyperpolarize local GABA interneurons and decrease inhibitory effect of GABAergic synapses on the VTA dopamine neurons.[216,217] Olianas, et al. (2012) report that activation of μ- and δ-opioid receptors in mouse mPFC increase dopamine D1-like receptor signaling.[213]

Interaction of dopaminergic system with histaminergic system in modulation of anxiety-like behavior

Histaminergic system has been shown to be involved in the modulation of anxiety-like behaviors. It has been indicated that various stressful situations increase the turnover of histamine in the rodent brain.[88] The amygdala receives histaminergic afferents derived from the tuberomammillary nucleus of the hypothalamus.[218] BLA nucleus has a lot of histamine H1, H2 and H3 receptors.[88,219] In their study, Bananej, et al. (2012) showed that the dopamine D1 and D2 receptors in the BLA nucleus may be involved in the anxiogenic-like effects induced by histamine.[88]

In conclusion, several studies have assessed the involvement of dopamine receptor mechanism in anxiolytic-like and anxiogenic-like behaviors in animal models.[102] This review was an attempt to explore the role of dopamine receptors in modulation of anxiety.

Several evidences show that dopaminergic system in the VTA,[116] NAc,[152] mesolimbic,[104] amygdala,[10,12,143] and hippocampus,[79] play a critical role in the modulation of anxiety-like behavior. Anxiety-like behavior are accompanied by alterations in mesolimbic dopamine function,[220] such as increase in dopamine level and its metabolite, enhancement of dopamine responses to cues and psychostimulants, as well as induction of dopamine neuron burst firing. Some evidences suggest that dopaminergic mechanisms in the mesolimbic circuit comprising the VTA, NAc, and amygdala are novel targets for the pharmacological treatment of anxiety.[147,221,222]

It seems that the cholinergic and dopaminergic receptors interact with each other to regulate the anxiety-related behaviors of rats in the VTA,[112] NAc,[194] hippocampus,[74] CeA,[112] and BLA nuclei.[144] It has been revealed that nicotine modulates anxiety by induction of VTA dopamine neurons activity.[223,224] Zarrindast, et al. (2012) suggested that nicotine-evoked anxiety-induced by nicotine may be mediated via the activation of D1 and D2 dopamine receptors in the NAc.[194] Some studies indicated that NMDA receptor signaling in the dopaminergic neurons of the VTA plays a pivotal role in anxiety-like behaviors.[32,102] The existence of D2 receptors in glutamatergic nerve terminals of VTA and BLA suggested that dopamine controls the activity of VTA dopaminergic neurons in these two regions.[112] There are glutamatergic projections from the BLA nucleus to the NAc.[194,225] Several investigators reported that hippocampus NMDA and dopamine D1 but not D2 receptors are involved in the expression of anxiety-like behaviors.[79,102,226–229] Moreover, it has been shown that CB1 receptor signaling through either post- or pre-synaptic mechanisms regulate dopaminergic pathways directly or indirectly.[94,211,230–232] Interestingly, the existence of both CB1 and D1 receptors in same sites shows that they may have synergic function in behavior and other responses.[86] It has been shown that the endocannabinoid system is a relevant negative modulator of the behaviors, which are mediated by dopaminergic systems.[128,233] Some researches revealed that the dopaminergic mechanism in the CeA nucleus may be involved in mediating morphine-induced anxiolytic-like effects. Rezayof, et al. (2009) reported that the blockade of the dopamine D1 receptors of the CeA nucleus inhibited morphine induced anxiolytic-like effect. They suggested that dopaminergic system of the CeA nucleus, through both dopamine D1 and D2 receptors, may be involved in mediation of morphine-induced anxiolytic-like effects.[101] Furthermore, GABA fibers via either $GABA_A$ or $GABA_B$ receptors,[180,203,204] serotonergic neurons through the 5-HT2 and 5-HT6 receptors,[112] and histaminergic cells by H receptors,[88] contribute with dopamine neurons in modulation of anxiety behavior. Therefore, it can be suggested that interaction of dopamine neurons with cholinergic, glutamatergic systems and etc. in different parts of brain may influence anxiety-like behaviors.

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