# Pathophysiological Mechanisms of Antipsychotic-Induced Parkinsonism

Subjects: Neurosciences

Contributor: Elena E. Vaiman , Natalia A. Shnayder , Aiperi K. Khasanova , Anna I. Strelnik , Arseny J. Gayduk , Mustafa Al-Zamil , Margarita R. Sapronova , Natalia G. Zhukova , Daria A. Smirnova , Regina F. Nasyrova

Among neurological adverse drug reactions (ADRs) in patients with schizophrenia treated with antipsychotics (APs), drug-induced parkinsonism (DIP) is the most common motility disorder caused by drugs affecting dopamine receptors. One of the causes of DIP is the disruption of neurotransmitter interactions that regulate the signaling pathways of the dopaminergic, cholinergic, GABAergic, adenosinergic, endocannabinoid, and other neurotransmitter systems.

antipsychotic-induced parkinsonism | drug-induced parkinsonism | antipsychotics | dopaminergic system | dopaminergic receptor | adverse drug reaction

## 1. Dopamine D2 Type Receptors Blockade

Dopamine receptors in the brain are represented by two families: the D1 (D1 family receptors and D5 receptors), and the D2 (D2, D3 and D4 receptors). All currently available APs are able to antagonize dopamine D2 receptors, and the APs' therapeutic effects in psychosis are related to their action on the limbic system reducing dopamine transmission. Due to antagonism of dopamine D2 receptors in the striatum, neurons of gamma aminobutyric acid (GABA), encephalin and the subthalamic nucleus are disinhibited at the beginning of the indirect pathway without changing the direct pathway. Due to this, there is an increase in GABA inhibition in the thalamocortical projection by facilitating inhibition in the globus pallidus / reticular substantia nigra. This pathway is similar to the model of basal ganglia motor loop impairment in Parkinson disease (PD) [1].

It is assumed that the mechanism of action of APs is associated with the level of occupancy of the dopamine D2 receptors. This is confirmed by several reports that therapeutic doses of typical APs block D2 receptors in 70–89% of cases in young adults, while atypical APs block in 38–63% of cases [2].

## 2. Supersaturation ("Occupancies") of Striatal Dopamine D2/3 Receptors

The exact mechanism of AIP development is still unknown; nevertheless, the main theory is the dopamine receptors blockade. In animal models, about 70% of the occupancy of dopamine D2/3 receptors was recorded during AP therapy, which leads to the development of AIP [3]. The threshold levels of occupancy of dopamine D2/3

receptors in the striatum associated with the development of AIP in young adults, which is about 80%, have been demonstrated in studies using neuroimaging technologies (using positron emission tomography (PET) D2/3 receptor imaging) [4][5]. Dissimilarities in the severity of AIP development are associated with the occupancy density of dopamine D2/3 receptors, AP concentration, the rate of dissociation from the D2 receptor, the selectivity of dopamine receptors in the limbic system and striatum, and the activity of other receptors (for example, serotonergic, muscarinic) [6]. Therefore, typical APs are more associated with an increased risk of developing AIP than atypical APs [6][7][8]. However, such a high occupancy of dopamine receptors should not be considered unequivocally, because the occupancy of receptors is not equal to antagonism. For example, aripiprazole, which, in addition to dopamine receptors, interacts with serotonin (5-HT) types 1A and 2A receptors and rarely causes AIP, even with a dopamine receptor occupancy rate > 95% due to a weak antagonistic effect on dopamine receptors [9][10].

## 3. Influence of the Basal Ganglia of the Thalamocortical Motor Loop

The pathophysiology of AIP is associated with drug-induced changes in the motor chain of the basal ganglia secondary to blockade of dopaminergic receptors [1]. The central dopaminergic system is presented of the four pathways: mesolimbic, mesocortical, tuberoinfundibular, and nigrostriatal (**Figure 1**).

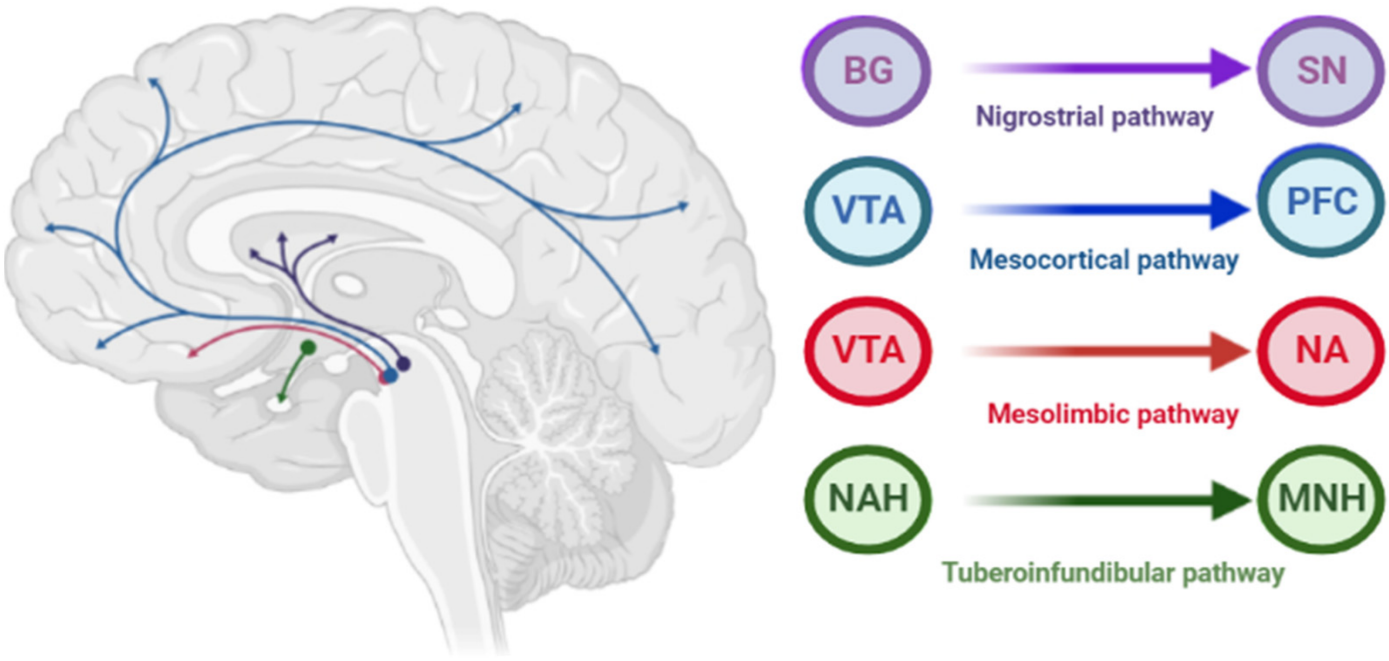


**Figure 1.** Pathways of dopaminergic neurotransmission. Note: VTA—ventral tegmental area; PFC—prefrontal cortex; NA—nucleus accumbens: SN—substance nigra; BG—basal ganglia (striatum); NAH—nucleus arcuatus (hypothalamus); MNH—middle nucleus (hypothalamus).

When dopamine D2 receptors blockade in the striatum, striatal neurons containing GABA and encephalin are disinhibited, affecting the indirect pathway and ultimately leading to a relative decrease in the activity of

thalamocortical circuits [1][11]. This effect may be mitigated by APs anticholinergic activity [12][13], as evidenced by the observation that clozapine has a low risk of developing AIP and also has a high relative affinity for muscarinic cholinergic receptors [12]. The reason for the decrease in sufficient concentrations of dopamine in the striatum may also be a decrease in the release of dopamine into the synaptic cleft [13]. Drugs that do not directly affect dopamine levels (valproic acid, calcium channel blockers) can induce DIP through other mechanisms, including modulation of GABA activity or mitochondrial dysfunction (**Figure 2**) [1][13][14][15][16].

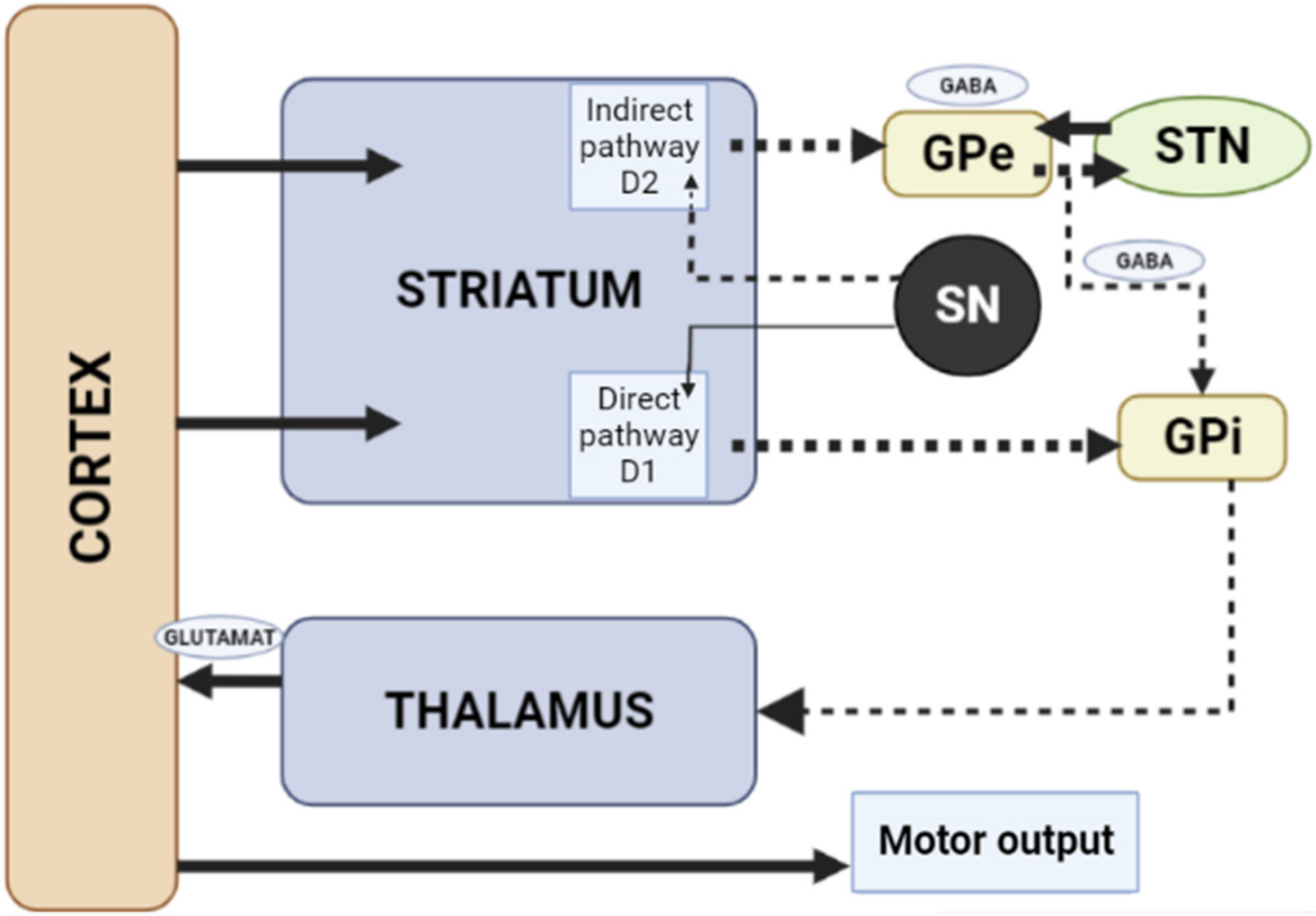


**Figure 2.** Schematic diagram of the excitatory and inhibitory ganglia involved in the development of AIP (Adapted from [17], Copyright year 2020, BMJ Neurol. Open). Note: Substantia nigra dopaminergic projections exert an exciting effect on stria-pallidal fibers of the direct pathway through dopamine D1 receptors, which leads to disinhibition of the thalamic nuclei and increased thalamocortical excitation, facilitating movements initiated by the cortex. The obstruction of voluntary movement occurs due to thalamic inhibition, due to the inhibition of stria-pallidal fibers in an indirect pathway through dopamine D2 receptors. The direct pathway is due to the activation of glutamate neurons in the sensorimotor cortex, and the indirect pathway is due to the activation of GABA-ergic neurons. The dotted line shows the inhibitory action due to the action of GABA. The straight line shows the excitatory effect due to the action of glutamate.

## 4. Fast-off-D Theory

In studies devoted to brain occupancy, radioactive clozapine has been proven to show rapid and transient occupancy of the dopamine D2 type receptors, dissociating in less than 60 s after administration, while radioactive haloperidol and chlorpromazine show long-term occupancy with slow dissociation in less than 30 min. Therefore, atypical APs are clinically more effective, having temporary occupancy of D2 type dopamine receptors and rapid dissociation to normal dopamine neurotransmission [18][19].

## 5. Role of Adenosine Receptors

Purine and adenosine interact with major neurotransmitter systems (glutamatergic cholinergic, GABA-ergic and dopaminergic) to modulate neuronal function in the central and peripheral nervous systems [20].

Transmission of adenosine occurs through purinergic receptors coupled to the G-protein class P1, which is subdivided into four receptor subtypes: A1, A2A, A2B, and A3 [21]. A2A adenosine receptors are highly expressed by GABAergic neurons in the striatum, globus pallidus, and olfactory bulb [22], and are co-localized with dopamine D2 type receptors in the basal ganglia on enkephalin-expressing output neurons of the indirect pathway leading to the globus pallidus and substantia nigra [23][24], which are in dopaminergic nigrostriatal and mesolimbic neuronal pathways [25]. The A2A and D2 receptors are antagonists and regulate GABA neurons [26][27].

Most evidence suggests that due to intramembrane interaction, activation of the adenosine A2A receptor indirectly blocks the activation of dopamine D2 receptors, and stimulation of D2 receptors blocks the activation of adenylate cyclase caused by the A2A receptor [26]. Upon stimulation of A2A receptors, GABA is released, while upon stimulation of D2 receptors, it is suppressed in the globus pallidus [27][28]. Here is evidence that these receptors, on the contrary, can act as synergists, under certain circumstances (presence of certain isoforms of adenylate cyclase, interruption of previous long-term exposure to D2 receptor agonists), activation of the D2 receptors enhances the effects of A2A receptors [26]. A study by Parsons et al. [29] in rats showed that chronic administration of haloperidol activates striatal A2A receptors. The effect of haloperidol was selective for A2A receptors over other adenosine receptor subtypes. Notably, atypical APs did not affect A2A receptors' density [29]. A2A adenosine receptor antagonists suppress motor disorders such as catalepsy and locomotion induced by dopamine antagonists [30][31]. A2A receptor antagonists are effective in relieving muscle rigidity and tremor in AIP (**Figure 3**) [7][32][33].

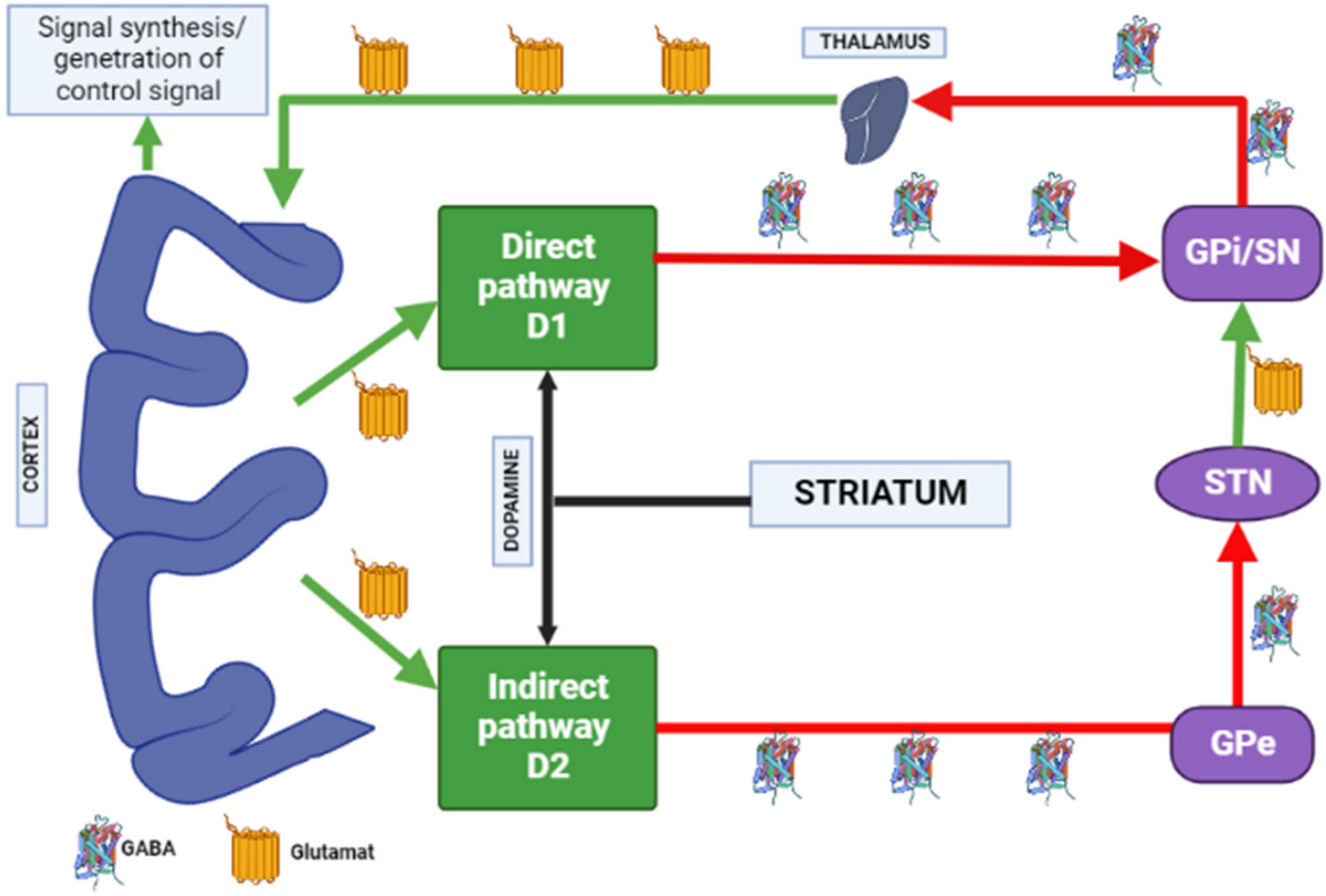


**Figure 3.** Distribution of A1 and A2A adenosine receptors in the human brain. Note: GPe—globus pallidus external; GPi—globus pallidus internal; STN—subthalamic nucleus; SN—substantia nigra; GABA—gamma aminobutyric acid.

## 6. Blockade of the Serotonergic System

The serotonergic system plays a crucial role in various physiological actions regulation, including psychoemotional, cognitive, sensorimotor, and autonomic functions [34][35][36]. Serotonergic neurotransmission is presented by several 5-HT receptors, which are classified into 7 families (5-HT1 to 5-HT7) and 14 subtypes (5-HT1A, 1B, 1D, 1E, 1F, 5-HT2A, 2B, 2C, 5-HT4, 5-HT3, 5-HT5A, 5B, 5-HT6 and 5-HT7) [37][38]. The 5-HT1E, 5-HT1F, and 5-HT5 receptors are associated with the Gi/o protein and inhibit adenylate cyclase activity, cyclic adenosine monophosphate (cAMP) formation, and protein kinase A (PKA) activity. The 5-HT2A, 5-HT2B, and 5-HT2C receptors are coupled to the Gq protein and increase phosphatidylinositol (PI) turnover by activating phospholipase C, thereby stimulating the protein kinase $C^{-}$ and $Ca^{2+}$/calmodulin cascade. The 5-HT4, 5-HT6, and 5-HT7 receptors are Gs-coupled and activate adenylate cyclase and PKA [36][37][38].

5-HT1A receptors are localized in the raphe nucleus, hippocampus, amygdala, and lateral septum. Expression of 5-HT1A receptors occurs in the cerebral cortex, basal ganglia (striatum), and diencephalon (thalamus and hypothalamus) in low to moderate density [34][39][40]. Inhibition of adenylate cyclase activity by 5-HT1A receptors

leads to inhibition of the cAMP-PKA cascade. In addition, 5-HT1A receptors activate G-protein-gated inwardly rectifying potassium channels (GIRK), which hyperpolarize target neurons and suppress their activity [33][35][36][37]. Several studies on animal models have shown that 5-HT1A receptors are activated with the introduction of AP for dehydration, has a protective effect on the development of extrapyramidal syndrome (EPS) [41][42][43][44][45][46][47]. The 5-HT2A and 5-HT2C receptors are highly expressed in the cerebral cortex, olfactory tubercle and limbic system (nucleus accumbens, hippocampus), basal ganglia (striatum and substantia nigra). 5-HT2A/2C antagonists attenuate AP-induced EPS in PD patients [48][49][50] by increasing the level of released acetylcholine, dopamine metabolism, and Fos protein expression in the striatum [49]. 5-HT3 receptors constitute a heteropentamer consisting of subunits from 5-HT3A to 5-HT3E and function as a cation ($Na^+$, $K^+$, and $Ca^{2+}$) permeable channels [37][51]. Therefore, when 5-HT3 receptors are activated, postsynaptic membranes are depolarized, thereby exciting target neurons. Serotonin 5-HT3 receptors are located in the nerve endings of various neurons and induce the release of neurotransmitters (acetylcholine, glutamate, GABA and dopamine). Clinical studies have also shown that 5-HT3 receptor antagonists significantly reduce the frequency and severity of AP-induced EPS (e.g., AIP) in patients with chronic schizophrenia [52][53]. However, a recent study showed that serotonin 5-HT3 receptors do not affect the activity of cholinergic interneurons in the striatum [54]. Thus, the functional mechanisms of 5-HT3 receptors in EPS are still unclear. The expression of serotonin 5-HT6 receptors mainly occurs in the brain, in particular, in the basal ganglia (striatum and nucleus accumbens), limbic system (olfactory tubercles and hippocampus), and cerebral cortex [37]. According to the results of clinical studies, 5-HT6 receptor antagonists also have a protective property against the development of EPS [55][56]. The decrease in the incidence and severity of EPS in the presence of 5-HT6 antagonists was further confirmed by an electrophysiological study [54], reflecting a decrease in the activation of striatal acetylcholine neurons, thereby reducing the likelihood of developing EPS (**Figure 4**) [57].

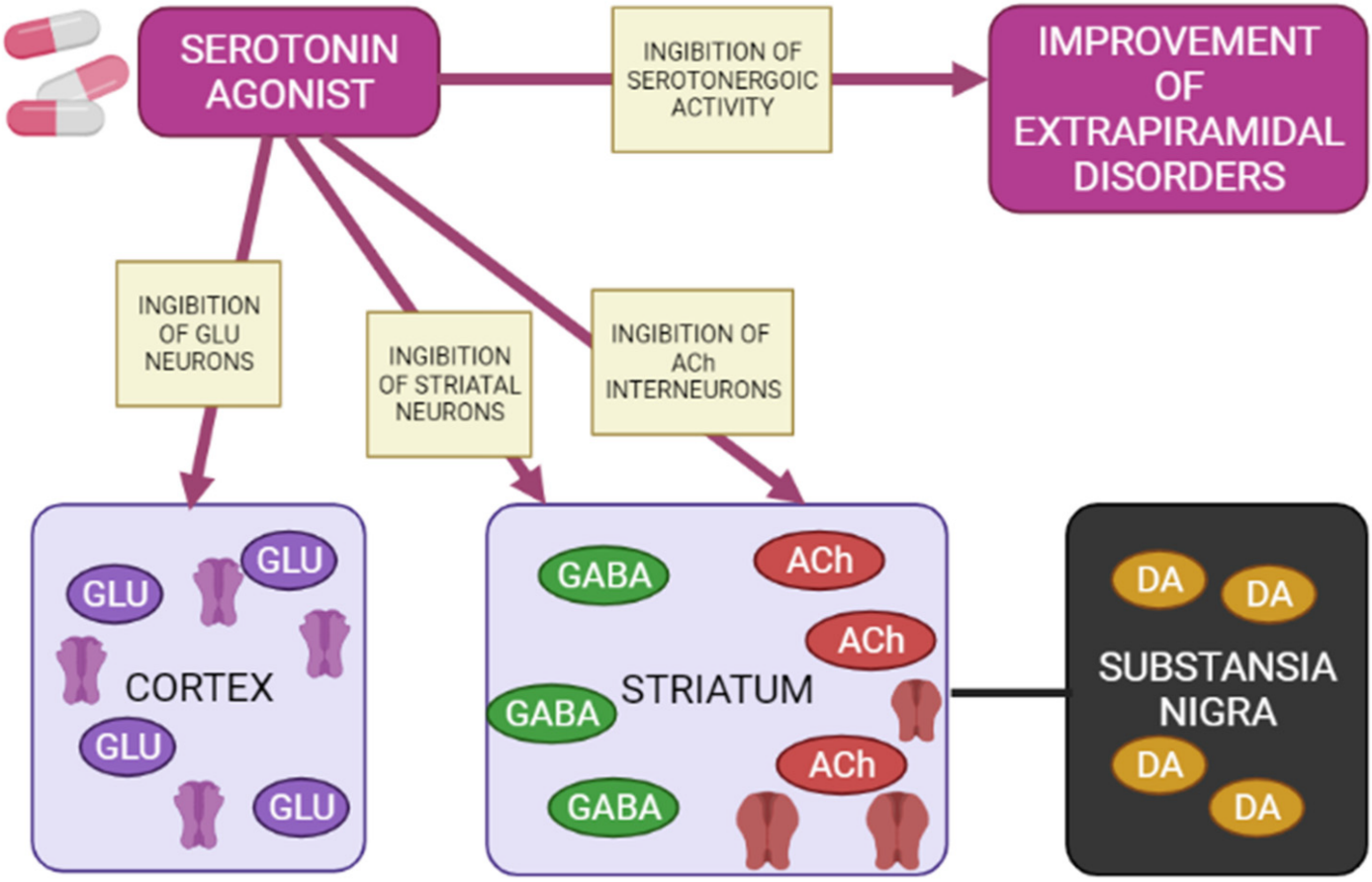


**Figure 4.** Mechanisms of action of a 5-HT1A agonist in modulating extrapyramidal motility disorders (Adapted from [57], Copyright year 2012, Adv. Biol. Psychiatry). Note: GLU—glutamate; GABA—gamma aminobutyric acid; Ach—acetylcholine; DA—dopamine.

Agonists of postsynaptic and presynaptic serotonin 5-HT1A receptors lead to a de-crease in the manifestations of extrapyramidal movement disorders. This is explained by hyperpolarization GABA medial spine neurons or indirectly by inhibition acetylcholinergic and glutamatergic interneurons in the striatum. In addition, when presynaptic 5-HT1A autoreceptors are stimulated, the serotonergic activity of neurons in the nuclei of the sutures is inhibited, reducing the functions of 5-HT2A/2C, 5-HT3 and 5-HT6 receptors, as a result of which the symptoms of extrapyramidal movement disorders improve.

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