Research Article

SSRI and EPS: putative molecular mechanisms

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Introduction:

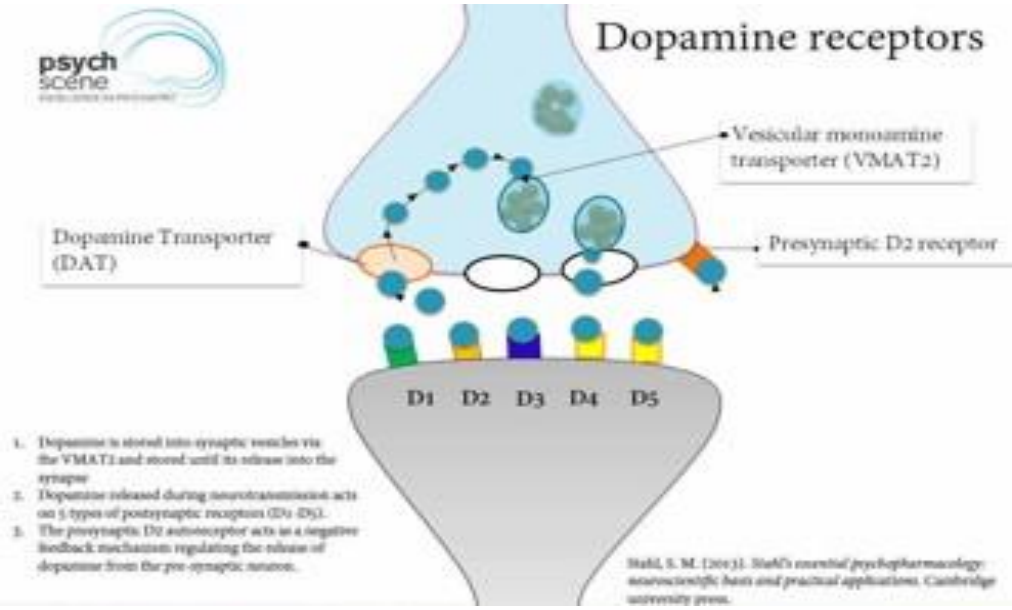
Selective Serotonin Re-Uptake Inhibitors (SSRI) are a class of antidepressant drugs widely used across the world because of their high index of therapeutic efficacy and optimal profile in terms of safety. However, there are several reports indicating that among its side effects are the occurrence of extrapyramidal dysfunction (EPS), including tremor, mild bradykinesia, akathisia, and dystonia.

Methods:

A search of PUBMED, MEDLINE, and online books was conducted for original research and review articles published in English between 1979 and 2018. Among the search terms were, second-generation antidepressants, SSRIs, fluoxetine, paroxetine, fluvoxamine, sertraline, citalopram, escitalopram, EPS, dopamine, serotonin, basal ganglia, pharmacokinetics, drug metabolism, and cytochrome P450. Only articles published in peer-reviewed journals were included, and meeting abstracts were excluded. The reference lists of relevant articles were hand-searched for additional publications.

In this review, by previous studies existing in literature, we aimed to analyze the putative underlying mechanisms related to dopaminergic and serotonergic pathways causative of inducing EPS by using SSRI in susceptible individuals.

Dopaminergic status and DA mechanisms:



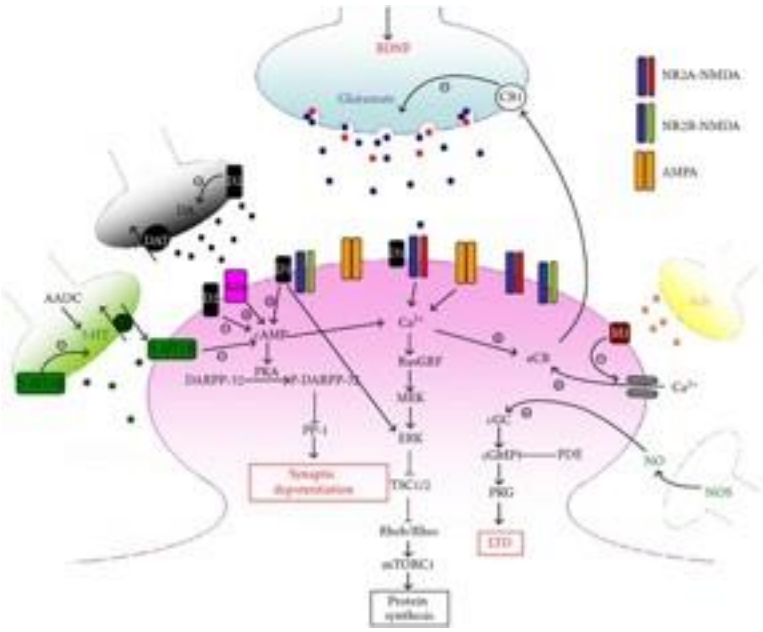
They are five types of dopamine receptors: D1, D2, D3, D4, D5:

It is possible to categorize dopamine receptors into two main subtypes:

• D1 like receptor family (D1; D5): the Gs protein is involved and adenylyl cyclase would be activated. The action of the enzyme causes the conversion of adenosine triphosphate to cyclic adenosine monophosphate (cAMP). As a consequence, by stimulating this class of receptors we obtain an excitatory effect downstream.

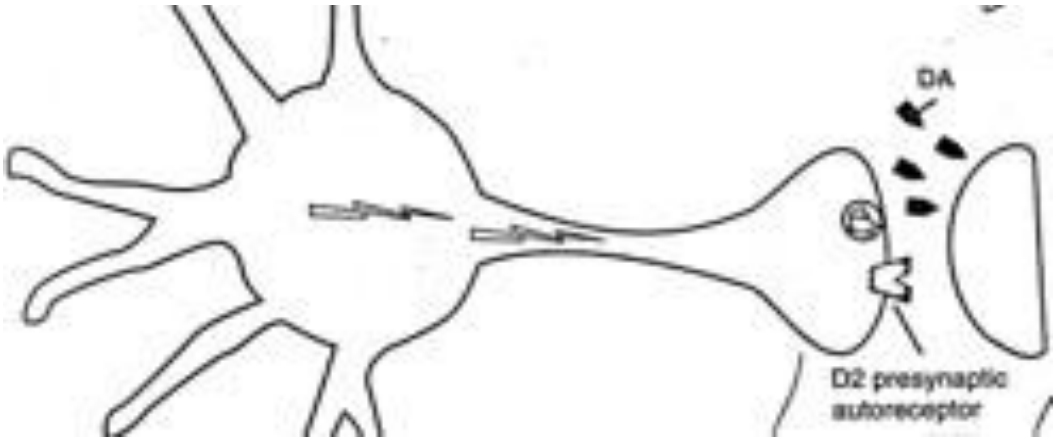
• D2 like receptor family (D2, D3, D4): which is the receptor combining with the Gi protein and its activated alpha-subunit then inhibits adenylyl cycles so that the concentration of cAMP is reduced. Therefore, inhibitory effects are carried out by stimulating these receptors.

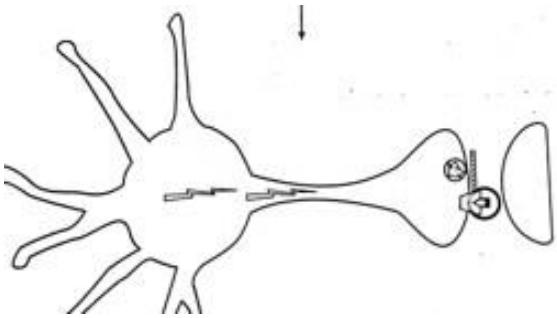
In addition, DA receptors may be located on presynaptic and post-synaptic neurons in the midbrain, striatum, n. accumbens and cerebral cortex.

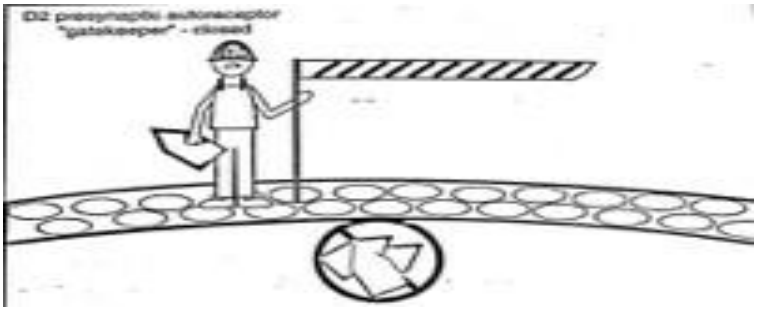


DA Presynaptic mechanisms:

On pre-synaptic dopamine neurons only D2 like receptor family are expressed as dopamine auto-receptors in axon terminals as well as somato-dendritic area providing feedback and regulating dopamine release. Hence, activation of dopamine autoreceptors decrease release of DA by inhibiting dopamine synthesis and enhancing dopamine reuptake by the dopamine transporter as well as regulating VMAT expression in presynaptic vesicles.





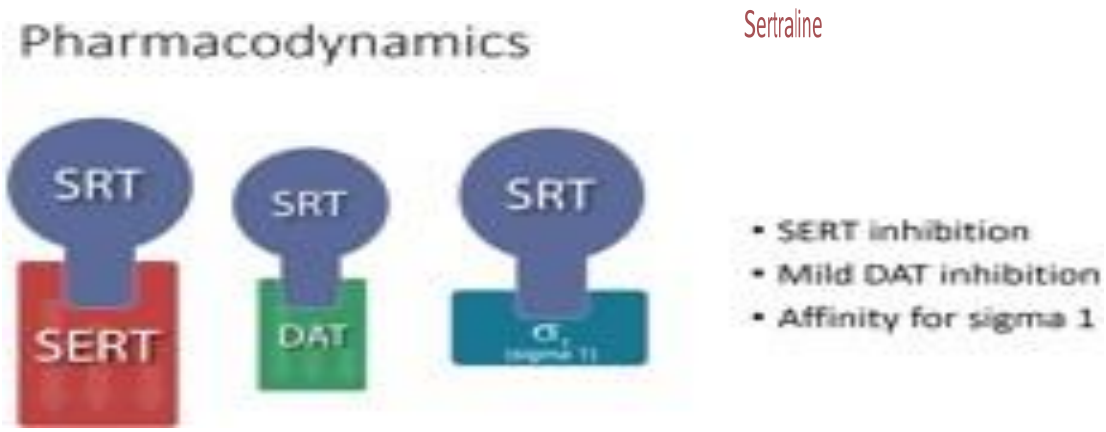


The molecular mechanism underlying the inhibition of dopamine release through terminal D2 autoreceptor is unknown. One possibility is that D2 autoreceptors inhibit the voltage-gated Ca2+channels in axon terminals, thus directly inhibiting Ca2+ -dependent release of dopamine. Patch-clamp studies on dopamine midbrain neurons in vitro have revealed a D2 receptor regulation of voltage-gated calcium currents (Cardozo and Bean, 1995) and axon terminal dopamine release is dependent on N and P/Q type calcium channels (Phillips and Stamford, 2000; Chen et al., 2006a).

Thus, presynaptic D2 receptors act as “gatekeepers” either allowing DA release when they are not occupied by DA or inhibiting DA release when DA builds up in the synapse and occupies these gatekeeping presynaptic auto-receptors. In the last case, occupancy of these DA2 receptors provides negative feedback input or a braking action upon the release of dopamine from the presynaptic neuron. As a result, lacking dopamine in the striatum may potentially lead to iatrogenic parkinsonism.

Each SSRI antidepressant may theoretically cause EPS by exerting its pharmacodynamic actions through Dopamine Transporter (DAT) in the striatum. For instance, sertraline is among SSRI the antidepressant that holds the highest affinity for DAT (weaker than SERT).

Therefore, high doses of sertraline daily (>100 mg/day) in susceptible subjects may potentially cause EPS by partial blocking of DAT in the striatum with subsequently increased amount of synaptic dopamine levels in the same area, whereas dopamine, in this case, activates D2 presynaptic inhibitory autoreceptors on the axonal terminal of dopaminergic neurons of the nigrostriatal pathway leading to a decrease in the synthesis and release of dopamine in the striatum.



In a study conducted on dopamine D2 receptors in the human brain by using positron emission tomography with [11C]raclopride (Penttila et al., 2004) it has been demonstrated that after repeated dosing of fluoxetine, D2 presynaptic receptor affinity decreased in the right medial thalamus, whereas in the left putamen there was a trend towards an increased affinity. Therefore, fluoxetine appears to have a regionally selective effect on the dopaminergic neurotransmission in various areas of the brain. These results suggested that the modulatory effects of these drugs on striatal dopamine function are different upon repeated dosing and further substantiate pharmacological differences between SSRI-class drugs.

DA Post-synaptic mechanisms:

On pre-synaptic dopamine neurons, either D1 and D2 like receptor families are expressed. However, so far only controversial evidence concerning direct or indirect effects of SSRI on dopaminergic post-synaptic modifications in the striatum has been found.

In rats, a study has shown that rapid exposure of dopamine to post-synaptic dopaminergic neurons leads to rapid and profound desensitization of DA1-receptor-stimulated adenylyl cyclase (Bates et al., 1991) that appears to be independent of the slower down-regulation of DA1 receptors.

On the other side, another study which has involved the use of serotonergic neurotoxin 5,7-dihydroxytryptamine (DHT) in mice treated with fluoxetine has shown that DHT injected into the brain region that is rich in dopaminergic terminals could change dopamine levels as well as serotonin at the injected region (Ludwig and Schwarting, 2007). However, intracerebroventricular injection of DHT has been reported to generally spare dopaminergic neurons. It suggests that the integrity of the serotonergic system is essential for the effect of fluoxetine on dopaminergic modulation.

In addition, other studies have shown that inhibition of dopamine reuptake generally causes immediate locomotor hyperactivity (Uhl et al, 2002), fluoxetine tends to reduce locomotor activity (Kobayashi et al, 2008, 2011a).

The exact mechanism by which repeated fluoxetine dosing influences dopaminergic neurotransmission has not been well established and studies on this topic are very few. According to previous rat experiments, fluoxetine may affect striatal dopamine function through increased expression and enhanced functional responsiveness of post synaptic D2 receptors (Ainsworth et al., 1998).

Serotonergic Status and 5-HT mechanisms:

There are two main 5-HT classes of serotonin receptors expressed in high density in the basal ganglia, particularly in the globes pallidus, and in the raphe nuclei:

-**5HT1** receptors, which are presynaptic, associated downstream with the inhibition of adenylyl cyclase as well as in opening of K+ channels

-**5HT2** receptors, which are postsynaptic, associated downstream with the stimulation of

Phosphoinositide-specific phospholipase C, closing of K+ channels.

5-HT presynaptic mechanisms:

The 5-HT1B/D receptor in rats and mice and the 5-HT1D receptor in human brain are located in high density in the basal ganglia, particularly in the globus pallidus and the substantia nigra.

Presynaptic 5HT1B receptors are autoreceptors, and detect the presence of 5HT, causing a shutdown of further 5HT release and 5HT impulse flow.

Functional studies indicate that the 5-HT1B and 5-HT1D receptors are located on presynaptic terminals of serotonergic neurons and modulate the release of serotonin. Release of 5-HT from the dorsal raphe nucleus also appears to be under the control of 5-HT1B/1D receptors, although it is unclear whether these receptors are located on serotonergic terminals or cell bodies.

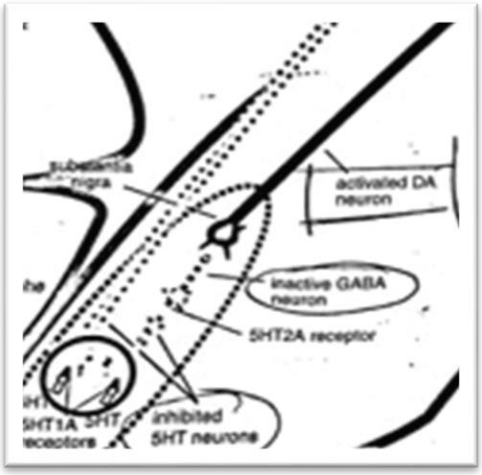
The presence of these receptors in high density in the basal ganglia raises the interesting possibility that they may play a role in diseases of the brain which involve the basal ganglia, such as Parkinsonism's.

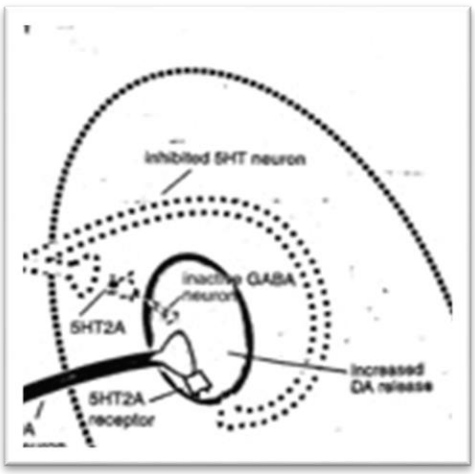
A putative mechanism that might explain how these receptors when stimulated increase dopamine release in is here showed:

Serotonin binding to 5HT1 receptors in the raphe nucleus inhibits serotonin release.

1) In the striatum, reduced serotonin release means that 5HT2A receptors on GABAergic and dopaminergic neutrons are not stimulated, which in turn means that dopamine release is not inhibited.

2) Similarly, in the brainstem, reduced serotonin release means that 5HT2A receptors on GABAergic interneurons are not stimulated and therefore GABA is not released. Thus, dopamine can be released into the striatum.



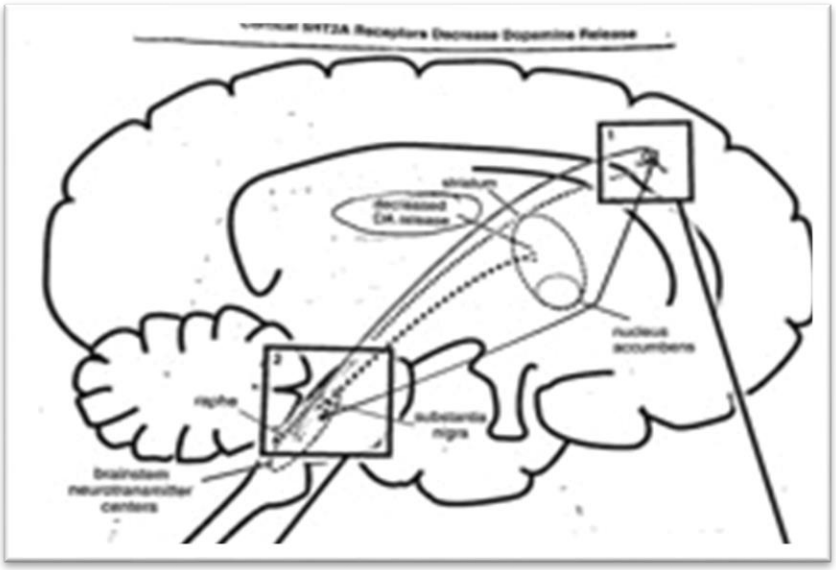


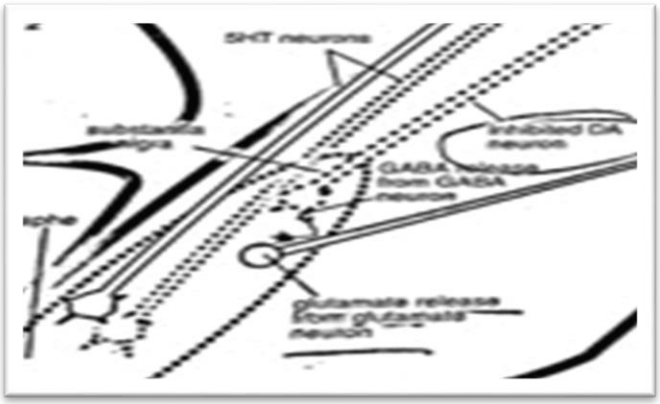
5-HT postsynaptic mechanisms:

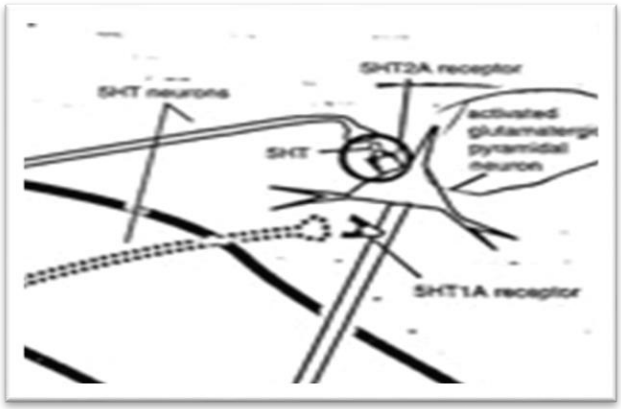
All 5-HT2a receptors are postsynaptic, and this class of serotonergic receptors are located in many brain regions.

When they are located on cortical pyramidal neurons and are stimulated by serotonin can lead to decreased dopamine release in the striatum.

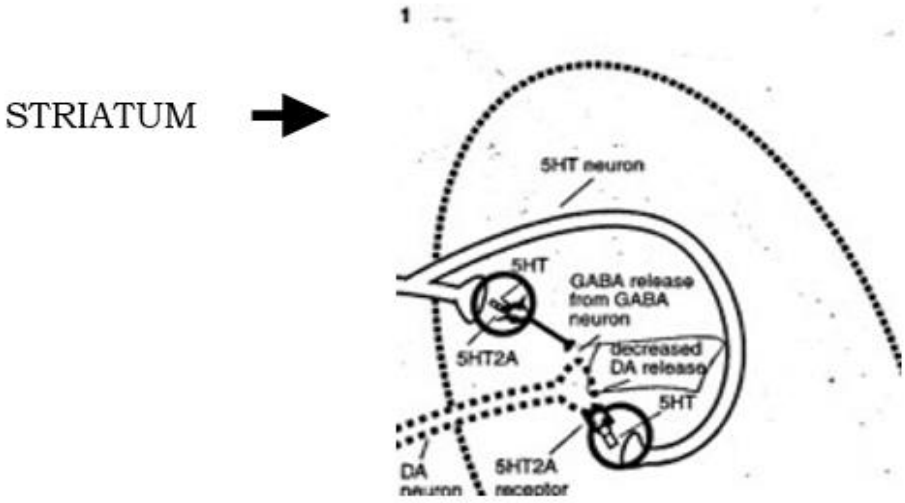
1) Serotonin is released in the cortex and binds to 5HT2A receptors on glutamatergic pyramidal neurons, causing activation of those neurons.
2) Activation of glutamatergic pyramidal neurons leads to glutamate release in the brainstem, which turn in stimulates GABA release.
3) GABA binds to dopaminergic neurons (at level of somatodendritic areas) of nigro-striatal pathway, causing inhibition of dopamine release in the striatum.







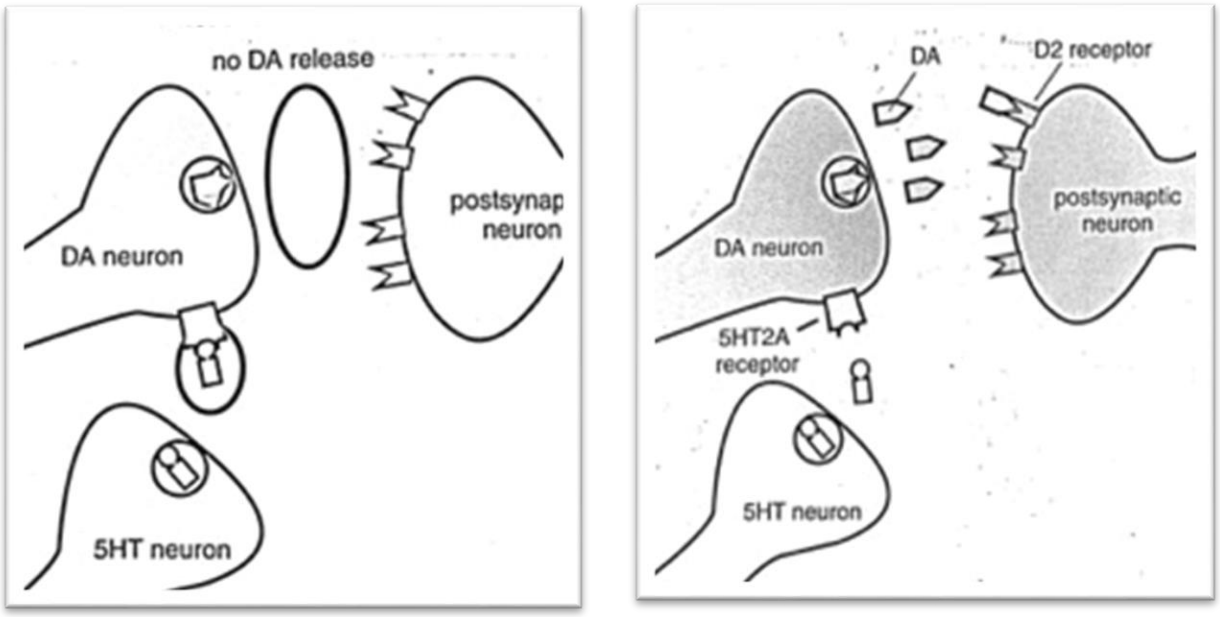
Furthermore, serotonin neurons whose cell bodies are in the midbrain raphe may innervate nigrostriatal dopamine neurons both at the level of the dopamine neutron all cell bodies in the substance nigra and at the dopamine neuronal axon terminals in the striatum. This innervation may be either via a direct connection between the serotonin neutron and the dopamine neuron, or via an indirect connection with a GABA interneuron



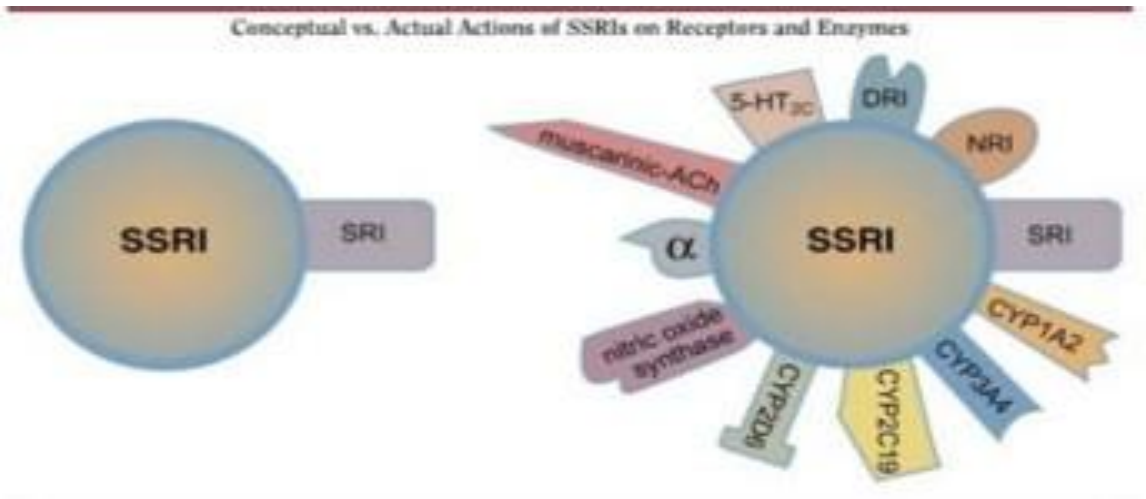
5-HT2A receptor stimulation by serotonin at either end of substantial nigra neurons hypothetically blocks dopamine release in the striatum.

As a matter of fact, 5HT2A receptor antagonism carried out by an atypical antipsychotic at these same sites hypothetically stimulates downstream dopamine release in the striatum. Such release

of dopamine in the striatum should mitigate EPS, which is potentially why antipsychotics with 5HT2A antagonist properties are atypical.



SSRI Antidepressants: pharmacodynamics and metabolism



Despite the fact that SSRI antidepressants are expected to act upon SERT (presynaptic serotonin transporter), as have been properly designed to bind exclusively to this molecular target, almost all SSRI may variably bind to several receptors or enzymes on neurons, such as DAT, NET,

muscarinic receptors, 5-HT2c serotonin receptors, alfa-1 or alfa-2 receptors and many others. A a consequence, the amount of all that unexpected activity exerting by SSRI on several targets might play a crucial role either in carrying out antidepressant and anxyiolitic effects but also provoking in some case side effects, among these extrapyramidal symptoms such as rest-postural tremor and mild bradykinesia.

It has been suggested that fluoxetine is more prone than other SSRI to produce adverse extrapyramidal symptoms (EPS). In fact, approx. 75% of the cases of SSRI-induced EPS have been reported among patients receiving fluoxetine (Leo, 1996). Since the first reports of fluoxetine-induced dystonic reaction (Meltzer et al., 1979) and parkinsonism (Bouchard et al., 1989), there have been several case reports and case series of SSRI- associated EPS (akathisia, dystonia, dyskinesia and parkinsonian symptoms) or worsening of existing Parkinson's disease (see Arya, 1994; Gill et al., 1997). The exact mechanisms behind SSRI-induced EPS are not known, and the relative risk of EPS during SSRI treatment is not clearly established.

Dopamine is critically involved in the regulation of movement, and therefore, the effects of SSRI-class drugs on the motor dopaminergic system are of interest. Fluoxetine- induced akathisia has been proposed to reflect 5-HT-mediated inhibition of dopaminergic neuro- transmission (Lipinski et al., 1989), which also lends support to our interpretation that sub chronic fluoxetine but not citalopram intake might reduce synaptic dopamine levels in the striatum (Tiihonen et al., 1996). It should, however, be noted that the relatively high frequency of EPS reported in fluoxetine-treated patients may be partly dependent on concomitant neuroleptic medication (Tate, 1989). Fluoxetine (Gram, 1994) but, for instance, not citalopram (Syvalahti et al., 1997), can increase the plasma levels of neuroleptic drugs by inhibiting several liver enzymes (Jeppesen et al., 1996), and this effect may be prolonged because of the possible accumulation of fluoxetine and nor fluoxetine.

Cytochrome P450 and SSRI:

Many antidepressants SSRI, are extensively metabolised in the liver through phase I oxidative reactions followed by phase II glucuronide conjugation. Most pharmacokinetic interactions with psychotropic drugs occur at the metabolic level and primarily involve the CYP mono- oxygenases. In some instances, the metabolite of the parent compound has a greater inhibitory effect on the metabolizing CYP isoenzyme(s).

The major CYP enzymes involved in drug metabolism in humans belong to families 1, 2, and 3, the specific isoforms being CYP-1A2, CYP-2C9, CYP-2C19, CYP-2D6, and CYP-3A4.

The activity of these isoenzymes is genetically determined and is greatly influenced by environmental factors, such as concomitant administration of other drugs.

Antidepressants SSRI have a wide therapeutic index, inhibition or induction of their metabolism is unlikely to be of great concern. However, SSRIs may cause a clinically relevant

Inhibitory Effect of SSRIs on CYP-450 Isoenzymes

	CYP-450 Isoenzymes				
Agent	**CYP-1A2**	**CYP-2C9**	**CYP-2C19**	**CYP-2D6**	**CYP-3A4**
Citalopram	0	0	0	+	0
Fluoxetine	+	++	+/++	+++	+/++
Fluvoxamine	+++	++	+++	+	++
Mirtazapine	0	0	0	+	0
Nefazodone	0	0	0	+	+++
Paroxetine	+	+	+	+++	+
Sertraline	+	+	+	+/++	+
Venlafaxine	0	0	0	+	+

SSRI: selective serotonin reuptake inhibitor; CYP: cytochrome P; 0: minimal/no inhibition; +: mild inhibition; ++: moderate inhibition; +++: potent inhibition.

Inhibition of CYP enzymes, and care must be exercised when an SSRI is being added to a multidrug regimen.

SSRIs differ considerably in their ability to inhibit individual CYP enzymes. This may help guide selection of an appropriate compound for the individual patient.

The inhibitory effect on CYP enzymes is concentration-dependent; the potential for drug interactions with citalopram and paroxetine is higher in the elderly because the elimination of these drugs may be affected by age. This is especially true with drugs such as fluoxetine, which exhibits nonlinear kinetics.

•**Fluoxetine:** the major metabolic pathway of fluoxetine is N-demethylation to form the active metabolite nor fluoxetine. In vivo studies have indicated that CYP-2D6 is the major isoform responsible for the N-demethylation of fluoxetine.

Fluoxetine follows nonlinear kinetics, and its plasma concentrations increase to a greater extent than the increase in drug dosages would predict. When fluoxetine is taken routinely, it takes about one month for it to reach a steady-state level in the blood and cause a drug interaction. Due to the long elimination half-lives of fluoxetine (one to four days) and norfluoxetine (seven to five days), inhibition of CYP enzymes may persist for up to six weeks after discontinuation of the antidepressant.

•**Fluvoxamine:** interacts with several CYP isoenzymes. It is a potent inhibitor of CYP-1A2 and CYP-2C19 and a moderate inhibitor of CYP-2C9 and CYP-3A4.

• **Sertraline:** the major metabolic pathway of sertraline is N-demethylation to form N - desmethylsertraline, which is less potent than the parent drug as a serotonin reuptake blocker. CYP-3A4 is the major isoform responsible for this reaction. Sertraline is a mild to moderate inhibitor of CYP-2D6 and a weak inhibitor of the other CYP isoenzymes; this accounts for its favorable interaction profile.

•**Paroxetine:** Among the SSRIs, paroxetine is the most potent in vitro inhibitor of

CYP-2D6, although it affects other CYP isoforms only minimally. Paroxetine therefore has the potential to cause clinically significant drug interactions when co-administered with CYP-2D6 substrates.

•**Citalopram:** is a racemic mixture, with its antidepressant effects attributed exclusively to the S (+)-enantiomer (Escitalopram). Citalopram is a weak in vitro inhibitor of CYP-2D6, that make that Citalopram as well as Escitalopram has an optimal profile in terms of safety.

Discussion:

A variety of movement disorders have been reported with the use of SSRI antidepressants (Meltzer et al., 1979; Bouchard et al.,1989; Brod, 1989; Reccoppa et al., 1990; Klee et al., 1993; Jimenez et al., 1994; Caley, 1997; Lane, 1998; Dixit et al., 2015; Kumar et al., 2018). These are attributed to the interaction of serotonergic and dopaminergic mechanisms in the midbrain, basal ganglia and cerebral cortex, which are complex and not fully defined. It is proposed that the effect of serotonin on dopamine metabolism varies in relation to the state of the dopaminergic system activity and differs in various areas of the brain. Indeed, one of the hypotheses which has been considered is that SSRIs may interfere with DA reuptake, which could lead to increase

synaptic DA levels. This could stimulate striatal DA presynaptic autoreceptors D2-type, leading to further inhibition of dopamine release and metabolism.

Besides, it also seems quite consistent, from previous studies, the hypothesis that serotonergic 5-HT1 and 5HT2 class receptors are involved in playing a pivotal role in regulating synaptic dopamine levels especially in the striatum and, therefore, causing EPS. The overall effect of the decreased dopaminergic tone in the striatum may produce parkinsonism, particularly in susceptible individuals. Such could well be the case in those with a nigrostriatal system already compromised and at risk of developing Parkinson's disease at a later date but provoked at present by the use of an SSRI. Furthermore, several other risk factors might contribute leading to Parkinsonism, such as advanced age, chronic cerebrovascular disease, concomitant medications which entail anti-dopaminergic and serotonergic effects, and deficient hepatic cytochrome P450 (CYP) isoenzyme status.

Conclusions:

SSRI drugs, may cause extrapyramidal side effects in susceptible individuals. Extrapyramidal symptoms may arise in response to a certain SSRI because of a resultant imbalance between serotonin and dopamine activity in basal ganglia. Patients vulnerable to this imbalance include those whose capacity for metabolism is decreased (e.g., the elderly or those with reduced hepatic functioning). Additionally, those on high doses of SSRI, or those treated with concurrent medications that slow the metabolism of SSRI, may be vulnerable to extrapyramidal symptoms. Although further experience as well more accurate molecular investigations will be necessary to confirm the cause-and-effect relationship between SSRIs with drugs acting on the hepatic P450 system.

Hence, these agents should be used judiciously with due regards for the development of such symptoms.

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