JPP JOURNAL OF Pharmacy and Pharmacology
ROYAL PHARMACEUTICAL SOCIETY
JPP Journal of Pharmacy And Pharmacology
Review

Understanding the molecular pharmacology of the serotonergic system: using fluoxetine as a model

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Keywords
molecular and clinical pharmacology; molecular and receptor pharmacology; pharmacokinetics and drug disposition

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Received June 21, 2011
Accepted September 22, 2011

doi: 10.1111/j.2042-7158.2011.01384.x

Abstract

Objectives Serotonin is a monoamine neurotransmitter that is widely distributed in the body and plays an important role in a variety of psychological and other body functions such as mood, sexual desire and function, appetite, sleep, memory and learning, temperature regulation and social behaviour. This review will assess the use of fluoxetine, one of the most commonly used selective serotonin reuptake inhibitors, as a model for understanding the molecular pharmacology of the serotoninergic system.

Key findings Seven serotonin receptor families have been discovered to date. All serotonin receptors, except 5-HT_3, are G-protein coupled, seven transmembrane receptors that activate an intracellular second messenger cascade. The 5-HT_3 receptor is a ligand-gated ion channel. Furthermore, 5-HT_{1A} receptors are known as autoreceptors since their stimulation inhibits the release serotonin in nerve terminals. A transporter protein found in the plasma membrane of serotonergic neurones is responsible for the reuptake of this neurotransmitter. Selective serotonin reuptake inhibitors, such as fluoxetine, act primarily at the serotonin transporter protein and have limited, if any, reaction with other neurotransmitter systems. Selective serotonin reuptake inhibitors appear to bind with the serotonin transporter with different rates of occupancy, duration and potency.

Summary The following review focuses on the interaction of serotonin with this membrane transporter in the body and assesses the use of fluoxetine as a reference drug in the understanding of this interaction.

Introduction

The selective serotonin reuptake inhibitor (SSRI) fluoxetine is one of the most widely used drugs in its class, and it is used in the treatment of depression, obsessive-compulsive disorder, bulimia and panic disorder.[1] It is considered to be the reference drug for the treatment of depression. The other commercially available SSRIs include citalopram, escitalopram, fluvoxamine, paroxetine and sertraline. Despite the fact that SSRIs have very different molecular structures, they all have similar mechanisms of action, albeit with slightly different pharmacokinetic properties, which may lead to small differences in some pharmacokinetic parameters such as half-life, and differences in clinical and adverse and drug interactions.[2] Fluoxetine was the first drug of its class that was approved by the regulatory authorities in Europe and the USA. It is well absorbed from the gastrointestinal tract and its bioavailability is about 72%. Peak plasma concentrations are observed after 6 to 8 h.[3] Food does not appear to affect the systemic bioavailability of fluoxetine, although it may delay its absorption by 1 to 2 h, which is probably not clinically significant.[4] Fluoxetine is a chiral molecule that is commercially available as a racemic mixture, i.e. a 50 : 50 mixture of its enantiomers (*R*)-fluoxetine and (*S*)-fluoxetine.

Fluoxetine, similar to other SSRIs, has been shown to exert its antidepressant effect by interacting with a membrane protein. The following review focuses on the interaction of serotonin with this membrane protein in the body and how fluoxetine, as the reference drug in this class, interferes with this interaction in order to carry out its pharmacological effects. The developments with respect to the molecular understanding of these interactions are key to the development of more targeted drug molecules acting on this important system. Table 1 gives an overview of the mode of action, adverse effects and pharmacokinetic parameters of fluoxetine and other SSRIs. Newer SSRIs have fewer adverse effects than fluoxetine, i.e. fewer activating side effects (e.g. insomnia, agitation, tremor and anxiety) and fewer gastrointestinal adverse events (e.g. nausea, vomiting, diarrhoea, weight loss and anorexia). These side effects had lead to non-adherence issues

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Table 1 Comparison of properties of SSRIs[2,5]

	Fluoxetine	Citalopram	Escitalopram	Paroxetine	Sertraline
Recommended dose (for major depressive disorder)	5–20 mg/day	20–40 mg/day	10–20 mg/day	20 mg/day	50 mg/day
Drug interaction potential	High	Relatively low	Relatively low	Moderate to high	Relatively low
Most common side effects	Nausea Headache Insomnia Nervousness Anxiety Drowsiness Anorexia Diarrhoea	Nausea Dry mouth Drowsiness Insomnia Increased sweating Diarrhoea	Nausea Insomnia Diarrhoea Headache	Nausea Drowsiness Headache Dry mouth Dizziness Weakness Fatigue Sexual dysfunction Increased sweating Diarrhoea Insomnia	Nausea Headache Insomnia Diarrhoea Dry mouth Sexual dysfunction (ejaculation failure, decreased libido) Drowsiness Dizziness Fatigue
Half-life	96–386 h	35 h	27–32 h	20 h (highly variable)	26 h
Time to steady state	30–60 days	7 days	7 days	10–14 days	7–14 days
Protein binding	94%	80%	56%	95%	98%
Metabolism	By 2D6, 2C9/10, 2C19 Active metabolites (potential for drug–drug interactions)	None; no active metabolites	None; no active metabolites	2D6; no active metabolites	None; no active metabolites
Linear kinetics	No	Yes	Yes	No	Yes
Secondary binding properties of SSRIs	Least SSRI; Norepinephrine reuptake, dopamine reuptake, serotonin-2C receptors, cytochrome P450 2D6, cytochrome P450 3A4	Most SSRI	Most SSRI	Muscarinic cholinergic receptors (most potent blocker of muscarinic receptors among the SSRIs); histamine H1 receptors; nitric oxide synthase cytochrome P450 2D6	Dopamine reuptake (more potent dopamine uptake inhibitor than other SSRIs); norepinephrine reuptake; sigma receptors

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in some patients, which undermined the efficacy of fluoxetine. However these side effects resolve in the majority of patients and become significantly less frequent with continued treatment over a 6-month period.[2]

Serotonin transporter

Serotonin (5-hydroxytryptamine, 5-HT), a monoamine neurotransmitter, plays an important role in many behaviours, including sleep, appetite, memory, sexual behaviour, neuroendocrine function and mood. In the brain, the highest level of serotonin is found in the dorsal and median raphe nuclear complex.[6] Neurones in the raphe system project beyond the raphe nucleus, most often in the lateral direction. Numerous serotonergic neurones are also found in the reticular region of the lower brain stem. Neurones in the brain stem are often divided into a caudal system and a rostral system. Nerve cells in the caudal system descend to the spinal cord along many pathways and are largely involved in sensory, motor and autonomic functioning. Serotonergic cells in the rostral system of the brainstem largely terminate in the dorsal and median raphe nuclei.

One other major serotonergic pathway in the brain is that from the cerebellum, which terminates in the cerebellar cortex and the cerebellar nuclei. Many serotonergic neurones contribute to this pathway. The presence of serotonin has also been observed in the pons, medulla, thalamus, hypothalamus, substantia nigra and locus coeruleus.[7] Serotonin is synthesised from the amino acid precursor tryptophan, packaged into vesicles in the presynaptic area and released into the synapse following an action potential. Once in the synapse, serotonin can interact with both presynaptic and postsynaptic receptors. However, immediately after interaction it is critically important for serotonin to be removed from the system.

Reuptake, the process of removing neurotransmitters from the synaptic cleft after release, determines the extent, duration and spatial domain of receptor activation.[8] Any neurotransmitter not removed from the synaptic cleft prevents further signals from passing through. Active removal reduces the level of neurotransmitter in the cleft faster than diffusion, constrains the effects of released neurotransmitter to smaller areas and allows at least part of the released chemical to be recycled for further use. Reuptake is carried out by transporter proteins that bind to the released neurotransmitter and carry it across the plasma membrane and back into the presynaptic neurone. In the case of serotonin, reuptake is carried out by the serotonin transporter (SERT).

Protein structure

The serotonin transporter is a carrier of serotonin molecules across the biological membrane.[9] Transporters undergo conformational changes and move one or more molecules per 'cycle', unlike channels, which stay open or closed, thus allowing floods of molecules to move across bilayer membranes. The serotonin transporter resembles other biogenic amine transporters structurally and functionally, such as norepinephrine and dopamine transporters.

The protein structure is composed of 12 transmembrane helices with an extracellular loop between transmembrane helices 3 and 4.[10] Both polypeptide termini are located within the cytoplasm and six putative phosphorylation sites, which are potential targets for protein kinase A and protein kinase C, exist in the same compartment. The areas important for selective serotonin affinity are localised within helices 1 to 3 and helices 8 to 12. A binding site for serotonin is believed also to be the target of selective inhibitors, such as fluoxetine (Figure 1).

Mechanism of action

Serotonin reuptake transporters are dependent on extracellular sodium (Na^+) ions and extracellular chloride (Cl^-) ions. Unlike sodium ions, choride ions can be at least partly substituted for by bicarbonate ions (HCO_3^-). Intracellular potassium ions (K^+) are also used in the process but can be replaced by other ions, most notably hydrogen (H^+) ions. The driving force for the energetically unfavourable transport of serotonin is the sodium ion influx down its concentration gradient.[12] The Na^+/K^+ ATPase pump maintains the extracellular sodium ion concentration as well as the intracellular potassium ion concentration. Na^+/K^+ ATPase pumps three sodium ions out for each two potassium ions pumped into the cell. The electrical potential produced, in addition to creating the sodium ion concentration used by the transporter protein, also leads to the loss of chloride ions from the cell.

According to the model of serotonin transporter function, the first step occurs when a sodium ion binds to the carrier protein. Serotonin, in its protonated form ($5\text{-}HT^+$), then binds to the transporter followed by a chloride ion. Chloride ions are not required for protonated serotonin binding to occur but are necessary for net transport to take place. The initial complex of serotonin, a sodium ion and a chloride ion creates a conformational change in the transporter protein.[13] The protein, which begins by facing the outside of the neurone, moves to an inward position where the neurotransmitter and ions are released into the cytoplasm of the neurone. An intracellular potassium ion then binds to the serotonin transporter to promote reorientation of the carrier for another transport cycle. The unoccupied binding site becomes, once again, exposed to the outside of the cell and the potassium ion is released outside the cell.

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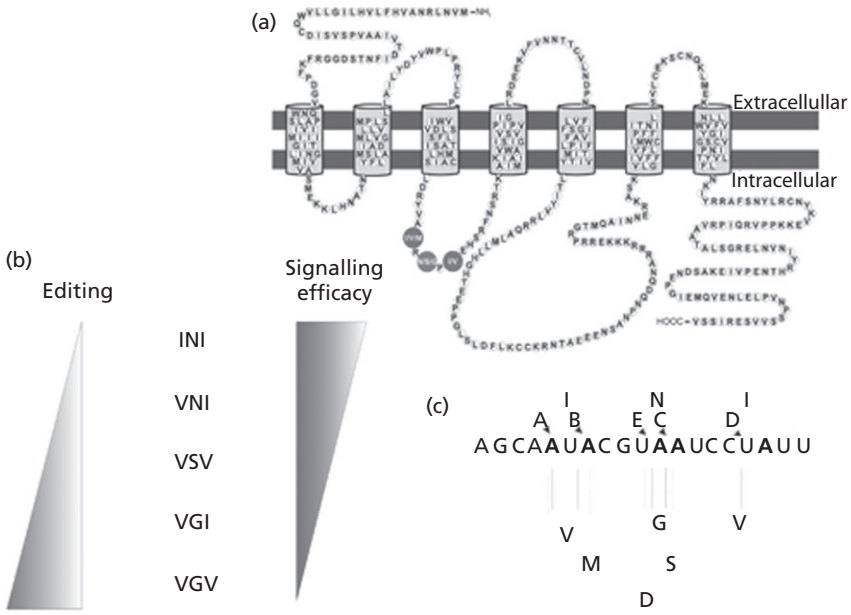

Figure 1 Serotonin 2c isoforms (reproduced with permission[11]). (a) Proposed 7TM domain structure and amino acid sequence of the serotonin 2c receptor amino acids subject to aleration by editing shown in coloured spheres. (b) Schematic representation summarising the relationship between editing and signalling efficacy of respective receptor isoforms. (c) Pre-mRNA sequence of edited region showing editing sites and assigned names designated for each site. Single-letter codes for amino acids encoded by non-edited transcript shown in black; amino acids encoded after editing at each position are indicated in blue.

Mode of action of selective serotonin reuptake inhibitors

The synaptic reuptake of serotonin is susceptible to drug manipulation. By blocking the action of serotonin tranporters, the amount of serotonin in the synaptic cleft increases. SSRIs act primarily at the serotonin transporter protein and have limited, if any, reaction with other neurotransmitter systems. Such agents bind to the transporter protein directly and block the reuptake process.[14] Consequently, more serotonin remains in the cleft, where it is free to travel to more distant receptors as well as to continue to react with nearby receptors. Like the binding of substrates, antagonist binding to serotonin transporters is also dependent on extracellular sodium ions although ion dependency is different for each antagonist. It is unclear whether these inhibitors bind to the same serotonin transporter domain as serotonin does or operate through more indirect mechanisms.

The binding of SSRIs to serotonin transporters may occur at the same site as serotonin binding, as these agents have a similar structure to the neurotransmitter in question.[15] These inhibitors have a selective effect on the serotonin reuptake pump, so that an initial increase in serotonin occurs only at the cell body and the dendrites, not at axon terminals.[2] Consequently, the rate of firing of serotonergic neurones is inhibited and serotonin is released by an action at 5-HT_{1A} somatodendritic autoreceptors.

Longer-term exposure to serotonin eventually causes downregulation of these 5-HT_{1A} autoreceptors and disinhibition of serotonin release at axon terminals.[16] The delay in producing the increase in serotonin at the terminals is usually taken as the reason for the delayed onset of action of such agents. The increased release of serotinin at the terminals, in the presence of an inhibited serotonin reuptake pump, increases the availability of serotonin to postsynaptic serotonin receptors. Such receptors may eventually downregulate, but this is a very complex process. Some models have shown that when extracellular serotonin goes up, its synthesis and release from vesicles will be inhibited. On the other hand, when extracellular serotonin goes down, its synthesis and release from the vesicles will be facilitated.[17] These complex processes occur because serotonergic systems must respond rapidly to signals, while ensuring homeostasis.

A 'short' repeat length genetic variation in the promoter region or exon of the gene that codes for this transporter has been shown to affect the rate of serotonin uptake and may play a role in sudden infant death syndrome, aggressive behaviour in Alzheimer disease patients, post-traumatic stress disorder and depression susceptibility in people experiencing emotional trauma.[18] Recent structural discoveries regarding the transporter, together with the location, type of organism in which they were found and a reference, are found in Table 2.

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Table 2 Recent discoveries in serotonin transporter structure

Discovery	Position and type	Reference
Alpha helices	Residues 386–421, rat	[10]
Downregulation	Whole structure, human	[19]
Extracellular loop 4	Residues 386–423, rat	[10]
G56A mutation	Exon 2, human	[20]
'Hinge' structure	Residues 402–405, rat	[10]
Inward current	Whole structure, xenopus	[21]
I425V mutation	Exon 9, human	[22]
Length variation mutation	5-HTTLPR, human	[23]
Oligomeric structure	Whole structure, human	[24]
Rs-25531 mutation	5-HTTLPR, human	[25]
Rs-25532 mutation	5-HTTLPR, human	[26]
SCAMP2 regulation	Subcellular, human	[27]
SNARE regulation	Subcellular, human	[28]
Tandem repeats	Intron 2, human	[29]
Tight regulation	Whole structure, human	[30]

Genetic variation

The gene that encodes the serotonin transporter is called Solute Carrier Family 6 neurotransmitter transporter, serotonin, member 4 (SLC6A4). The solute carrier (SLC) group of membrane transport proteins includes over 300 members organised into 47 families.[31] Solutes that are transported by the various solute carrier group members are extraordinarily diverse and include both charged and uncharged organic molecules as well as inorganic ions. Depending on the solute carrier, these transporters are functional as either monomers or obligate homo- or hetero-oligomers. By convention of the nomenclature system classifying them, members within an individual solute carrier family have greater than 20% sequence homology to each other.[16]

In humans, this gene is found on chromosome 17 on location 17q11.1-q12 and is organised into 14 exons. Mutations associated with this gene may result in changes in serotonin transporter function and in fact more the 50 different phenotypic changes have been discovered as a result of genetic variation.[26,32]

I425V on chromosome 17 m is found in unrelated families with obsessive compulsive disorder and it leads to faulty transporter function and regulation.[33] The presence of rs-25531 in the same gene of some patients with this variation suggests a genetic 'double hit', resulting in greater biochemical effects and more severe symptoms. A variable number of tandem repeat mutations may occur in the second intron (STin2). This variation is found with allele repeat numbers 9, 10 and 12. The 12 repeat allele of the STin2 VNTR polymorphism has a statistically significant association with autism.[20] The promoter region of the SLC6A4 gene may contain a polymorphism with 'short' and 'long' repeats in a region. This region is termed the serotonin transporter-linked polymorphic region or 5-HTTLPR.[34] The short variation leads to decreased transcription of the gene and may partly account for anxiety-related personality traits. At least 14 allelic variants of the serotonin transporter-linked polymorphic region are known. The low-expression variant of this type of polymorphism, i.e. the short version, leads to an increased risk of major depression.

In addition to the alteration of the expression of serotonin transporter protein and concentrations of extracellular serotonin in the brain, the variation in serotonin transporter-linked polymorphic region is associated with changes in brain structure.[35] Enlargement of the thalamus and reduced cortical volume provide an anatomical basis for explaining why subjects who inherit such a short–short genotype are more vulnerable to major depression and suicide.

The short 'S' allele of the serotonin transporter gene-linked polymorphic region has been associated with poorer antidepressant response in major depressive disorder and with antidepressant-induced mania. In about 80% of subjects homozygous for the 'S' allele, fluoxetine treatment develops new or worsening insomnia ($P < 0.005$).[36] Also, in around 70% of subjects homozygous for the 'S' allele, fluoxetine treatment develops agitation ($P < 0.001$). Therefore, the 'S' allele of the serotonin transporter gene-linked polymorphic region may identify patients at risk of developing insomnia or agitation following fluoxetine treatment. The short variant allele restricts transcriptional activity of the serotonin transporter promoter, leading to low functional expression of the serotonin transporter.

Binding of selective serotonin reuptake inhibitors

SSRIs appear to bind to the serotonin transporter with similar rates of occupancy but different duration and potency. The rate of occupancy of the serotonin transporter exceeds 80% for sertraline, paroxetine and fluoxetine at minimum therapeutic doses.[37] However, the duration of occupancy of the transporter is significantly shorter for sertraline and paroxetine, which is approximately 10 h less than for fluoxetine, which is approximately 50 h. The rate of occupancy and the duration of occupancy tend to indicate a longer-term influence of fluoxetine on the serotonin transporter.

The most potent reuptake inhibitor in humans is paroxetine, followed by clomipramine, a noradrenaline reuptake inhibitor, citalopram, fluoxetine and imipramine, another noradrenaline reuptake inhibitor, with no differences between male and female subjects. All agents, except paroxetine and clomipramine, show significantly lower binding affinities in elderly subjects of both sexes. It seems that although the pharmacological profile of the serotonin transporter is not modified qualitatively by age, quantitative changes in its affinity do perhaps occur. Recent evidence suggests that at tolerable doses SSRIs have increasing occupancy with increasing plasma concentration.[38]

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The relationship between *in vivo* brain serotonin transporter binding, plasma concentration and the pharmacological effect of SSRIs in mice is of particular clinical interest.[39] Oral administration of fluvoxamine, fluoxetine, paroxetine and sertraline at pharmacologically relevant doses exerts a dose- and time-dependent binding activity of brain serotonin transporter and the *in vivo* serotonin transporter-binding potency is stronger for paroxetine than for fluoxetine and stronger for sertraline than for fluvoxamine.

The time courses of brain serotonin transporter binding by SSRIs in mice are mostly in parallel to those of their plasma concentrations.[40] Also, norfluoxetine has been suggested to contribute largely to the long-lasting binding activity of brain serotonin transporter following fluoxetine administration. Oral administration of SSRIs significantly suppress a 'marble-burying behaviour' in mice, with no change in locomotor activity and the extent and time course of suppression agree well with that of brain serotonin transporter binding.

Updates on transporter function

The plasma membrane serotonin transporter is the major protagonist in regulating extracellular serotonin concentration and constitutes the target of drugs used to treat a host of metabolic and psychiatric disorders. The exact mechanisms sustaining SERT function still remains elusive. It appears that external 5-HT reduces both serotonin transport and serotonin transporter antidepressant binding. In this regard, 5-HT_{2B} receptors are thought to be key players in controlling the overall serotonin transport system.[41]

In the absence of external 5-HT, 5-HT_{2B} receptor coupling to nitrous oxide production ensures serotonin transporter phosphorylation to basal level and maximal serotonin uptake. In the presence of 5-HT, 5-HT_{2B} receptor-protein kinase C coupling promotes additional phosphorylations of both serotonin transporter and Na^+, K^+-ATPase α-subunit, impairing the electrochemical gradient necessary for serotonin uptake. Serotonin transporter hyperphosphorylation also affects antidepressant recognition. Finally, such 5-HT_{2B} receptor-mediated control of serotonin transporter activity operates in primary neurones from raphe nuclei.[42]

The serotonin transporter plays a critical role in the maintenance of normal neurotransmission by serotonin. Recent evidence suggests that serotonin transporter and other neurotransmitter transporters are tightly regulated.[43] Activation of protein kinase C results in a decrease in serotonin transporter-mediated 5-HT uptake, which is due to an internalisation of the transporter. However, little is known about the mechanism and proteins involved in the downregulation of the transporter.

One candidate serotonin transporter-regulatory protein is the SNARE, i.e. soluble N-ethylmaleimide-sensitive factor-attachment protein receptor, syntaxin 1A (Syn1A), which has recently been implicated in the regulation of ion channels as well as the serotonin transporter-related gamma-aminobutyric acid and glycine transporters. Syntaxin 1A appears to interact with the serotonin transporter and alters the subcellular localisation of the transporter, resulting in a reduction of serotonin transport. The secretory carrier membrane protein 2 (SCAMP2) has also been found to play a role in the regulation of subcellular distribution of serotonin transporter.[44]

Residues 386–423 of the rat brain serotonin transporter are thought to form a hydrophilic loop connecting transmembrane regions 7 and 8, known as extracellular loop 4 (EL4). This extracellular loop has been hypothesised to play a role in conformational changes associated with substrate translocation.[10] Extracellular loop 4 variants, such as M386C, appear to show very low transport activities and low cell surface expression, indicating high structural and functional importance. It seems that in some variants, certain amino acid residues in this extracellular loop are situated in positions highly exposed to the aqueous environment.

However, in other variants, other amino acid residues are situated in positions that are either buried in the extracellular loop or functionally unimportant. Positions 386–399 and 409–421 of the rat brain serotonin transporter are proposed to form α-helices, connected by amino acid residues, within which four positions, 402–405, may form a turn or hinge. The presence of serotonin alters the accessibility of the loop to high affinity reagents. Serotonin-induced accessibility changes require both sodium ions and chloride ions since these are associated with active substrate translocation. Evidence supports the role of extracellular loops in conformational changes within the serotonin transporter.[45]

In major depression, in humans and in animal models of depression, the defect in serotonergic neurotransmission may originate presynaptically.[46] Such a pathologic state may be caused by excessive presynaptic autoreceptor activity in serotonergic neurones and because antidepressants downregulate the number of these inhibitory receptors, allowing more normal serotonin release to occur. In fact, it appears that fluoxetine reduces serotonin transporter mRNA briefly, but this influence is sustained after several days of treatment. However, fluoxetine reduces dorsal raphe 5-HT_{1B} mRNA levels in a time-dependent and washout-reversible manner.[47]

Such a reduction in 5-HT_{1B} mRNA is specific to the dorsal raphe nucleus and is not found in several postsynaptic, non-serotonergic regions.[47] Thus, chronic fluoxetine may be involved in elevating serotonin release from axonal terminals by downregulating mRNA coding for presynaptic 5-HT_{1B} autoreceptors while causing only transient effects on

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serotonin transporter mRNA. Evidence suggests that the human serotonin transporter has two binding sites, an orthosteric high-affinity site and a low-affinity allosteric site.[13] Activation of the allosteric site may increase the dissociation half-life for serotonin.

The reuptake of the neurotransmitters serotonin and noradrenaline out of the synaptic cleft is mediated by selective transporter proteins, the serotonin transporter and the noradrenaline transporter, respectively. Both transporters are integral membrane proteins that have a high degree of homology and represent members of a larger neurotransmitter transporter superfamily. The serotonin transporter appears to have an oligomeric structure. Also, it has been shown that serotonin–noradrenaline transporter fusion proteins are fully active and exhibit the pharmacological profile of both their individual components.[24] Such findings support the hypothesis that monoamine transporters are expressed and may function as oligomeric proteins composed of non-interacting monomers.

The downregulation of serotonin transporter is observed after chronic treatment with selective norepinephrine reuptake inhibitors (NRIs), such as desipramine but not following treatment with SSRIs. It appears that both the binding sites for serotonin and norepinephrine uptake are decreased in hippocampus and cortex after treatment with desipramine.[19] In contrast to this, no alteration in the binding sites for serotonin or norepinephrine uptake is observed by SSRIs. Also, norepinephrine transporter (NRT) messenger RNA levels in the locus coeruleus are unchanged by desipramine treatment. Hence, the marked decrease in norepinephrine transporter density is caused solely by a selective NRI.

As shown in the above review, a number of discoveries have been done in the last few years regarding the structure of the serotonin transporter. The main structural discoveries, together with the position in which they are found within the transporter gene/protein, type of organism producing them and a reference, are found in Table 2. Furthermore, pH affects other conducting states of the rat serotonin transporter. Acidic pH potentiates the serotonin-induced, transport-associated current and inhibits the hyperpolarisation-activated transient current. The dose–response relationships for these two effects suggest that two hydrogen-ion binding sites, with pK_a values close to 5.1 and close to 6.3, govern the potentiation of the serotonin-induced current and the inhibition of the transient current, respectively. Such a structure–function model may explain the permeation properties of neurotransmitter transporters.[48]

Conclusion

The main action of fluoxetine in the body is its interaction with the serotonin transporter. The transporter protein found in the plasma membrane of serotonergic neurones is responsible for the reuptake of serotonin. SSRIs act primarily at the serotonin transporter protein and have limited, if any, reaction with other neurotransmitter systems. The gene that encodes the serotonin transporter is called Solute Carrier Family 6 neurotransmitter transporter, serotonin, Member 4 (SLC6A4). Mutations associated with this gene may result in changes in serotonin transporter function. In fact, more than 50 different phenotypic changes have been identified to be a result of genetic variation.

SSRIs appear to bind to the serotonin transporter with different rates of occupancy, duration and potency. Research suggests that external 5-HT reduces both serotonin transport and serotonin transporter antidepressant binding. Recent evidence suggests that serotonin transporter and other neurotransmitter transporters are tightly regulated. In major depression, in humans and in animal models of depression, the defect in serotonergic neurotransmission may originate presynaptically. Finally, the human serotonin transporter has two binding sites, an orthosteric high-affinity site and a low-affinity allosteric site. Activation of the allosteric site may increase the dissociation half-life for serotonin.

Despite the benefits SSRIs have brought to patients over therapy which had been previously available, not all patients benefit from treatment. A better understanding of the pharmacogenetic mechanisms which may occur due to gene variants within the serotonin transporter and cytochrome P450 drug-metabolising enzymes may be relevant, yet studies to date have been very limited, with mixed results.[5,49,50]

The above review highlights the powerful influence of serotonin on body processes through its interaction with ligand-gated and G-protein coupled receptors around the body and through its uptake from synaptic clefts by the serotonin transporter. Consequently, the activities of both this neurotransmitter and of the structures it influences are often the target of research and development sections within large pharmaceutical industries in order to identify 'safe' lead chemicals that either mimic or suppress the actions of serotonin so that hopefully, one day, new pharmacological agents capable of treating resistant forms of somatic and psychiatric disorders can be licensed for use on an international scale.

Declarations

Conflicts of interest

The authors report no conflicts of interest related to this study.

Acknowledgements

The authors would like to thank Dr Anthony Fenech for his insightful comments on the text.

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