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Selective Serotonin Reuptake Inhibitors (SSRI) Pathway

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Serotonin (5-hydroxytryptamine, 5-HT) is a neurotransmitter that influences multiple processes, including autonomic function, motor activity, hormone secretion, cognition, and complex processes associated with affection, emotion, and reward [1].

In the terminal axon of the serotonergic neuron, free tryptophan (TRP) is converted to 5-HT [2]. 5-HT synthesis is a two-step process catalyzed by tryptophan hydroxylase (TPH) and aromatic decarboxylase (DDC). TPH is the rate-limiting enzyme and exists in two isoforms TPH1 and TPH2. The TPH2 isoform is the predominant form in neuronal tissue [3], [4]. The 5-HT uptake into presynaptic storage vesicles is mediated by the vesicular monoamine transporter (SLC18A2). The transporter accumulates serotonin into synaptic vesicles using a proton gradient across the vesicular membrane [5]. 5-HT that is not stored in vesicles is degraded by monoamine oxidase A (MAOA) to 5-hydroxyindoleacetic acid (5-HIAA).

An action potential stimulates a calcium-dependent exocytotic release of serotonin from presynaptic vesicles into the synaptic cleft, where it interacts with both post- and presynaptic receptors. At the presynaptic side, 5-HT activates 5-hydroxytryptamine (serotonin) receptor 1A (HTR1A), B (HTR1B), and D (HTR1D), which results in an attenuation of the 5-HT exocytosis [2]. This feedback loop regulates the 5-HT concentration in the synaptic cleft and therefore, the extent of stimulation of various HTR receptor subclasses at the postsynaptic membrane [6]. Prolonged administration of selective serotonin reuptake inhibitors (SSRI) desensitizes these feedback loops. Thus, their regulatory effects on the serotonergic neurotransmission are weakened [7]. Postsynaptic HTR1 receptors (HTR1A, HTR1B, HTR1D, HTR1E, HTR1F) work together with HTR2 receptor subtypes (HTR2A, HTR2C) in mediating effector signals via activation of second messenger cascades [2]. Postsynaptic, the main signaling pathway for HTR1 receptor subtypes is via coupling of Gi/o protein alpha subunit (GNAI). This interaction decreases cyclic AMP formation by inhibiting adenylate cyclases (ADCY) [8]. After interaction with 5-HT, the main signaling linkage for the HTR2 receptor subpopulation is to activate phospholipase C (PLCB) through coupling of Gq/11 protein alpha (GNAQ) [8]. PLCB catalyzes the formation of myoinositol- 1, 4, 5-trisphosphate (IP3) and diacylglycerol (DAG) [9].The postsynaptic, ionotropic HTR3 receptor is a cation-specific ligand-gated ion channel, which does not activate a second messenger system [10]. The binding of 5-HT to this receptor depolarizes the postsynaptic membrane by sodium influx and potassium efflux, which is assumed to influence the activation of HTR2 receptors. HTR4, HTR6, and HTR7 primarily couple Gs protein alpha (GNAS), which results in an activation of adenylate cyclase, and consequently in an increase of cyclic AMP levels [9]. Further operational diversity is supported by the existence of a great number of splice and editing variants for several HTRs, their possible modulation by accessory proteins and chaperones, as well as their potential to form homo or heteromers both at the GPCR and at the ligand-gated channel level [11].

The amplification of all those second messenger signals in further downstream reactions leads to the mediation of neurotransmitter release from central serotonergic, noradrenergic, and dopaminergic neurons in the brain by regulating potassium channels, several protein kinases, and other calcium dependent signals. Chronic administration of antidepressant treatments have been reported to commonly increase the expression of brain-derived neurotrophic factor (BDNF), an activity-dependent secreted protein that is critical to organization of neuronal networks and synaptic plasticity [12], [13].

The solute carrier family 6 (neurotransmitter transporter, serotonin), member 4 (SCL6A4) is responsible for terminating the action of 5-HT in the synaptic cleft. Released serotonin is transported back into the presynaptic terminals via this integral membrane protein. SCL6A4 is a member of the Na+/Cl−-dependent transporter family [14].

Four major classes of antidepressant drugs exist: monoamine oxidase inhibitors, selective serotonin reuptake inhibitors (SSRI), tricyclic compounds, and atypical antidepressant drugs [7]. To date, no comprehensive hypothesis concerning the antidepressant action for those therapies has been established [15]. Nonetheless, those drugs have one or more primary molecular targets in order to act. The molecular target for SSRI is SCL6A4, resulting in an inhibition of 5-HT reuptake in the presynapse from the synaptic cleft. The five SSRI fluoxetine, fluoxamine, paroxetine, sertraline, and citalopram vary in their pharmacological profile resulting in differential efficacy or side-effect profile for particular patients [16], [17], [18]. SSRI have a high affinity for 5-HT uptake transporters, low affinity for noradrenaline uptake transporters, and very low affinity for neurotransmitter receptors.

The observation that current antidepressant therapies need a sustained treatment of 2–4 weeks to be effective suggests that adaptive changes in both serotonergic and noradrenergic neurotransmission and downstream neural adaptation (e.g. the BDNF receptor signaling pathway) rather than only the elevation in synaptic monoamine levels itself are responsible for the therapeutic effects [19], [20].

Several genetic polymorphisms have been associated with therapeutic SSRI response and also with adverse reaction, including genetic variants of the SCL6A4, HTR1A, HTR2A, HTR3B, TPH, BDNF, and G-protein beta3 subunit [10], [13], [21], [22].

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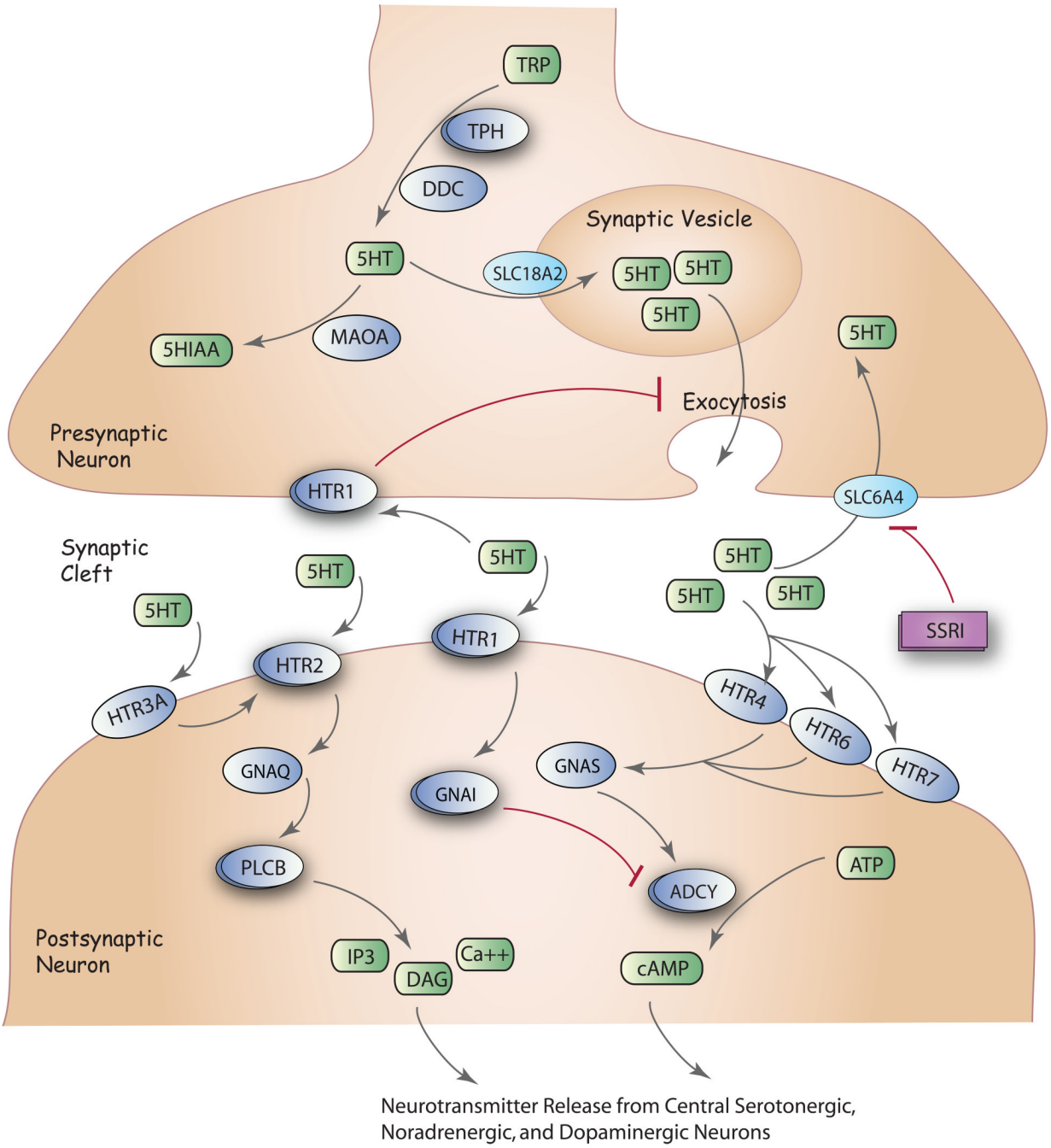

Figure 1.