Latest Advancements on Serotonin and Dopamine Transporters in Lymphocytes

Donatella Marazziti*, Giorgio Consoli, Irene Masala, Mario Catena Dell'Osso and Stefano Baroni

Dipartimento di Psichiatria, Neurobiologia, Farmacologia e Biotecnologie, University of Pisa, Pisa, Italy

Abstract: Different data show that circulating lymphocytes possess functional serotonin and dopamine transporters (SERT and DAT, respectively). This papers aims to review most of the available literature on this topic, while highlighting the possible role of SERT and DAT, as well as that of their substrates including antidepressants on the immune system.

Keywords: Serotonin, dopamine, serotonin transporter, dopamine transporter, lymphocytes, antidepressants, immune system.

INTRODUCTION

Serotonin (5-hydroxytryptamine, 5-HT) and dopamine (DA), are monoamine neurotransmitters widely represented in the central nervous system (CNS) of different animals including humans, where they modulate a variety of physiological, behavioral and endocrine functions, such as appetite, sleep, mood, sexuality, aggression/impulsivity, biological rhythms, motor control, memory, learning, and the neuronal degeneration associated with cerebral ageing [1-6]. As a consequence, therefore, monoamines have been hypothesized to be critically involved in the pathophysiology of a number of brain disorders, including Parkinson's disease, depression, anxiety, schizophrenia and drug addiction [7-10]. The availability of both 5HT and DA is strictly limited by selective, active re-uptake mechanisms performed by specific proteins, the 5-HT and the DA transporters (SERT and DAT, respectively), which play the major role of terminating the activity of the neurotransmitter, once released in the synaptic cleft and after the interaction with different receptors, ion channels and other structures present at pre- and postsynaptic level [11-13]. Not surprisingly, the transporters have attracted much interest as primary targets of compounds that might be effective in anxiety, mood and psychotic disorders. As far as the SERT is concerned, this line of thought has led to the development of selective 5-HT re-uptake inhibitors (SSRIs) which, with no doubt, are one of the most successful pharmacological achievements of the past few decades [14-20]. Furthermore, the DAT represents the main target of psychostimulants, including addictive drugs, such as cocaine and amphetamines, or mazindol and methylphenidate [21-24], but also of neurotoxins, in particular methyl-phenyl-piridinium [25]. Antidepressants, too, such as bupropion, although to a lesser extent, may bind to the DAT [26], and the same a few selective compounds that include the GBR compounds, 12909 and 12935 [27, 28].

*Address correspondence to this author at the Dipartimento di Psichiatria, Neurobiologia, Farmacologia e Biotecnologie, University of Pisa, Via Roma 67, 56100 Pisa, Italy; Tel: +39050835412; Fax: +3905021581;
E-mail: dmarazzi@psico.med.unipi.it

Since neurotransmitters are also present systemically, the transporter proteins have been described in different organs and cells. The SERT has been found in intestinal epithelial cells [29], in blood platelets [30-38] and in blood lymphocytes [39, 40]. The DAT, too, is expressed in peripheral blood cells such as platelets [41] and lymphocytes [42, 43].

Most of the available literature regarding transporters in periphery is centered on the SERT present in platelets which has been characterized pharmacologically and cloned [36, 44-49], but especially used as a reliable mirror of the same structure present in the CNS for investigating the role of 5-HT in neuropsychiatric disorders. In the past three decades, several reports have, thus, demonstrated alterations of the SERT not only in several neuropsychiatric disorders irrespective of the diagnoses [50-54], but also in physiological conditions which have been linked to dimensions or psychic states reflecting modifications of the serotonergic activity which are not always dysfunctional and might even have a strong adaptive values, when occurring in specific moments of the life [43, 55, 56]. On the contrary, the literature concerning the SERT and DAT in lymphocytes is just at its dawn, for the technical difficulties encountered in their characterization [39, 40, 42, 43]. However, potentially, these cells are more interesting than platelets, because are nucleate and are a fundamental component of the immune system, so that, on one side, they might permit expression studies of the proteins, on the other to explore the role of neurotransmitters and their transporters within the immune network [52, 57, 58]. A literature centered on the use of lymphocytes SERT or DAT in patients with different neuropsychiatric disorders as a peripheral marker of the same brain structure is just emerging [59-65]. However, data are too meager to draw any kind of conclusion, or to highlight the possible advantages/disadvantages of lymphocyte transporters, as compared with those present in platelets.

The aim of this paper is to review the literature on the SERT and DAT in lymphocytes with a special focus on future developments and applications. MEDLINE and PubMed (1975-2009) databases were searched for English language articles using the keywords 5-HT, DA, lymphocytes, SERT,

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DAT, immune system, antidepressants, neuropsychiatric disorders. We reviewed papers that addressed the following aspects: the basic structure of SERT and DAT, their characterization in lymphocytes, the role of 5-HT and DA within the immune system, the effects of antidepressants at their levels, and, finally, some hypotheses on the role of SERT and DAT in lymphocytes.

STRUCTURE OF THE SERT

Structurally, the SERT is a 70 kDa glycoprotein with a sequence of a 630 amino acids with molecular weights of 70 kDA, characterized by 12 hydrophobic membrane-spanning domains, with cytoplasmatic amino- and carboxy-termini, showing a certain degree of similarity with the DAT and norepinephrine, glicine, and GABA transporters [66-69] (Fig. **1**). The SERT uses transmembrane ion gradients of Na+, Cl- and K+ and an internal negative membrane potential for the transport of their substrate [70-72], a mechanism which requires energy, is temperature-dependent, and is potently inhibited by tricyclic antidepressants (TCAs) and SSRls [36, 73] (Fig. **2**). In addition to drugs that specifically target SERT, this transporter is also affected by cocaine, amphetamines, and ecstasy (3,4-methylendioxymethamphetamine) drugs that are widely abused [74].

The rapid modifications of the activity and surface density of the SERT have been linked to changes in its phosphorylation state, as it presents three phosphorylation sites for protein kinase of type C (PKC) and three sites for protein kinase of type A (PKA) [12]. PKCs are phosphorylases activated by diacylglycerol derived from the hydrolysis of membrane phosphatidylinositol-4,5-bisphosphate, while PKA is stimulated by cyclic adenosine-monophosphate (cAMP). Phorbol esthers, which activate PKC, provoke a decrease in 5-HT re-uptake, while choleric toxin or compounds which increase cAMP concentrations and therefore PKA, increase 5-HT re-uptake: it can be concluded that PKC inhibits and PKA activates 5-HT re-uptake [75].

STRUCTURE OF THE DAT

The DAT belongs to the large transporter family just mentioned for SERT. It is a 80-kDa glycoprotein with a sequence of a 620 amino acids, which has been cloned and characterized [76-84]. As with other members of the family, molecular modeling of the amino-acid sequence of the DAT [85] predicts a topology of 12 transmembrane segments connected by alternating extracellular and intracellular loops, with the N- and C- termini located in the cytosol, a large extracellular loop between transmembrane domains 3 and 4 containing numerous consensus sequences for N-linked glycosylation, and potential sites for phosphorilation by PKA and PKC within putative intracellular domains and in the N- and C- termini [86]. A study using cysteine/lysine-modifying reagents and biotinylated probe scanning has agreed with the proposed topology on predicting extracellular domains of the SERT [87]. The DAT display highest amino acid homology with the norepinephrine transporter (67%), SERT (49%), and GABA transporter (45%) [88].

As well as the SERT, the DAT is functionally dependent on the presence of external Na+ and Cl- ions, although some investigations revealed that its interactions with ions is considerably more complex than the simple picture of two Na+ ions and one Cl- ion being co-transported with one DA molecule [89-93]. In this case also, modification of the transport velocity of the DAT has been reported following activation/inhibition of second messenger system pathways, through the modulation of PKA and PKC**.** The PKC-mediated phosphorylation [94, 95] provoke the sequestration

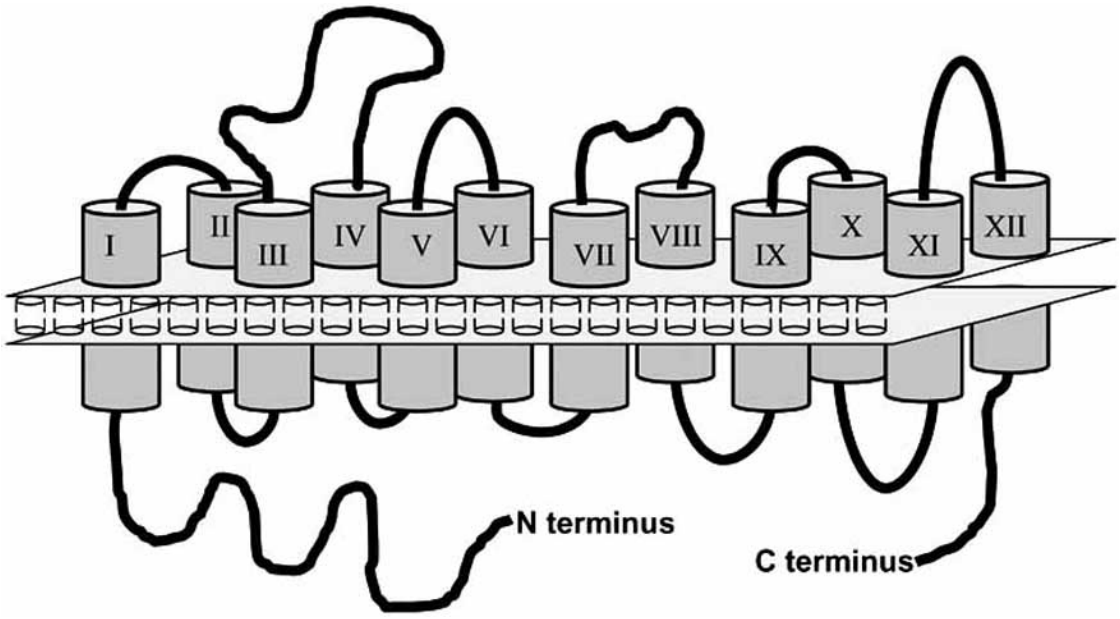

Fig. (1). General structure of SERT and DAT.

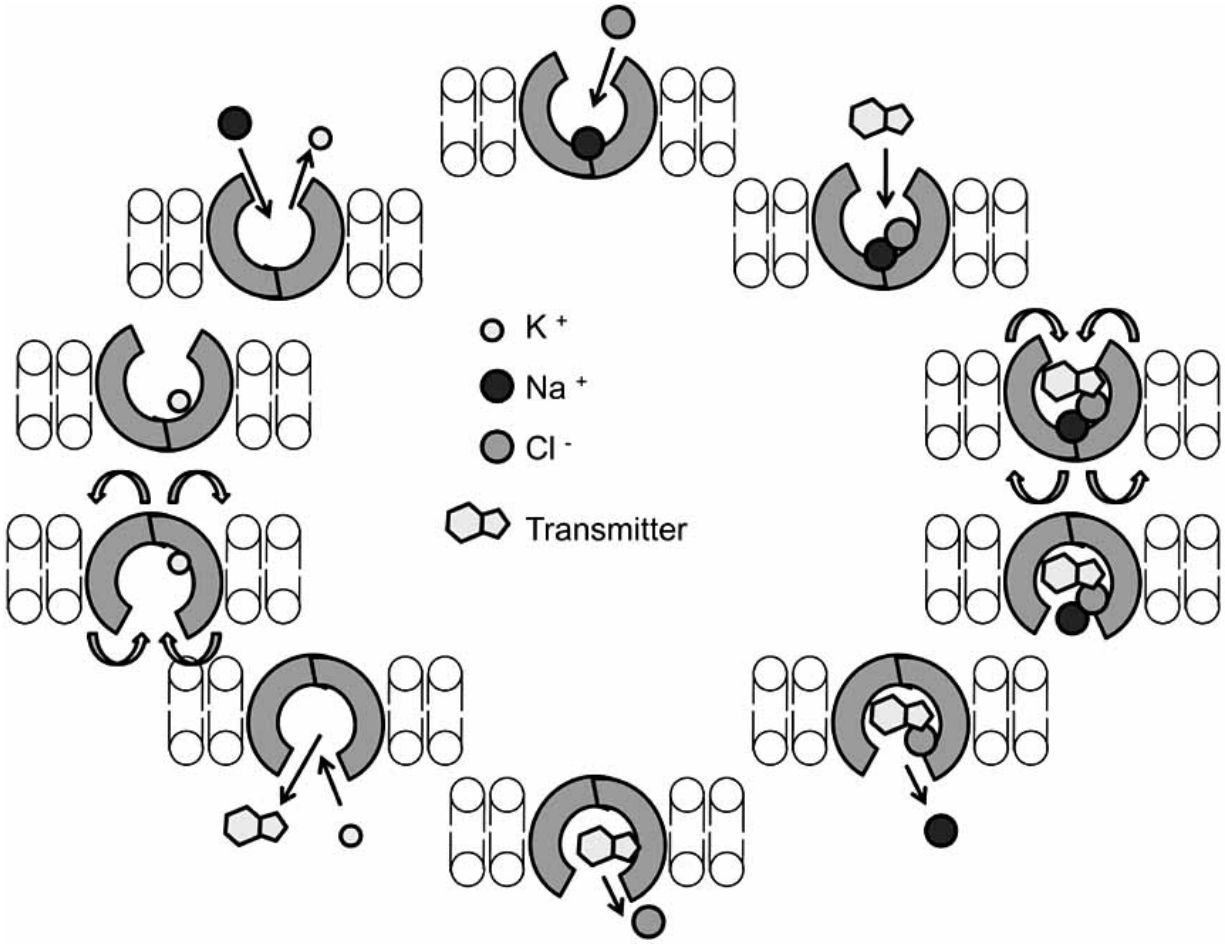

Fig. (2). General mode of functioning of SERT.

of the transport protein [96-98] and down-regulation of transport activity [99, 100].

SERT IN LYMPHOCYTES

An active 5-HT transport with specific pharmacological characteristics was described in human resting lymphocytes in 1994 [39]. The re-uptake was temperature, Na+ and Cl^- dependent and potently inhibited by the antidepressants clomipramine, imipramine, fluoxetine and fluvoxamine, which are specific for the SERT, while compounds that are more selective for norepinephrine and DAT, such as mazindol, desipramine and GBR 19209, had a lower inhibitory effect. A few years later, another study showed the presence of a high-affinity, specific and saturable ^{3}H-paroxetine binding in membranes obtained from human lymphocytes in resting conditions [40]. Different parameters indicated that ^{3}H-paroxetine labeled one site only which corresponded to the SERT and had the same affinity of that described in the CNS and platelets [101-103]. In addition, pharmacological displacement studies revealed a profile overlapping with that obtained in the brain and platelets, since all the tested compounds showed a similar rank of potency in the two tissues [40, 73]. A functional SERT was described also in lymphoblastoid cell lines, as well as in Burkitt lymphoma lines, where it seemed to provoke apoptosis reversed by SSRIs [104].

DAT IN LYMPHOCYTES

Different evidences demonstrated that lymphocytes express the DAT. Faraj *et al*. [105] reported that freshly isolated lymphocytes from human blood can transport DA through a cocaine-sensitive re-uptake. This re-uptake protein shares certain characteristics with the active transport of monoamine neurotransmitters in the CNS, in particular the saturability, since the transport follows Michaelis-Menten kinetics, the dependence on a Na+ and K+ gradient across the cell membrane, the temperature dependence, and the inhibition by specific compounds acting at its level. However, these findings were put into question by the possible impact of platelet contamination during the lymphocyte preparation and, therefore, of SERT which is predominant in platelets [106]. Subsequently, the lymphocyte DAT was characterized more deeply by means of different techniques including Western immunoblotting, immunocytochemistry, ^{3}H-DA re-uptake and ^{3}H-GBR 12935 radioligand binding assay [42]. The presence of DAT in human lymphocytes was confirmed also by immunoreactivity [107] and by reverse transcriptase (RT)–PCR techniques [108]. More recently, the lymphocyte DAT protein was labeled by means of the binding of ^{3}H-WIN-35428, which is currently considered one of the most selective compounds for exploring this structure [43]. The pharmacological profile of the ^{3}H-WIN-35428 binding showed that the DA re-uptake specific inhibitors, such as

WIN-35,428 itself, GBR-12909 and BTCP, were in order of potency, the most powerful displacers of the binding. On the contrary, the SSRI fluoxetine and the tricyclic antidepressant desipramine had a negligible effect. A specific ^{3}H-DA reuptake was also measured by the same authors who reported that its pharmacological characterization was overlapping with that of the ^{3}H-WIN-35428 binding: this would suggest that the two sites correspond [43].

WHAT ARE THE MAJOR SOURCES OF 5-HT AND DA PRESENT LYMPHOCYTES?

The first problem arising from the above-mentioned evidences is that of the source of neurotransmitters, that is to say, from where lymphocytes take up 5-HT and DA.

Serotonin

Lymphocytes have been shown to store and synthesize 5HT [59, 109, 110]. Another possibility is that they "capture" 5-HT at inflammatory sites after its release from platelets, or after stimulation of noradrenergic nerve terminals in lymphoid tissues, where direct contacts between the terminals and immune cells have been described [111-113]. Again, activated T-lymphocytes, and to a lesser extent, naïve-resting T-cells, may cross the blood-brain barrier, circulate in the brain and get easily the neurotransmitters. Finally, all innervated body organs, including blood capillaries, represent "meeting points" for neurotransmitters and lymphocytes [114].

Dopamine

The major source of DA in lymphocytes are the lymphocytes themselves, which are capable of synthesizing DA, as they express the cathecolamine biosynthetic enzyme tyrosine hydroxylase [115-118]. In addition, lymphoid tissues are highly innervated by sympathetic fibers that store and release DA which can be taken up by lymphocytes [119, 120].

WHAT IS THE ROLE OF 5-HT AND DA PRESENT IN LYMPHOCYTES?

A detailed review of this topic is beyond the scope of this paper, and, therefore, only the major findings will be reported herein.

Serotonin in Lymphocytes

Besides the SERT, lymphocytes express $5HT_1$, $5HT1_A$, $5\text{-}HT1_B$, $5\text{-}HT2_A$, $5\text{-}HT_3$, $5\text{-}HT3_A$, $5\text{-}HT_7$ receptors subtypes which probably are the substrates of different activities [121-123]. During both physiological and pathological conditions, such as inflammatory processes, some specific functions of 5-HT can be recognized. Different data show that 5-HT can regulate T cell and natural killer (NK) cell function; in addition, it appears fundamental for T cell blastogenesis via 5-HT1A receptors [124]. Moreover, it seems to be involved in the initiation of delayed-type hypersensitivity reactions via 5-HT2 receptors [125, 126]. Serotonin promotes the production of various chemotactic factors, such as cytokines and interleukin-16 (IL-16), and protects NK cells from injuries, activities that appear particularly relevant during the early stages of the immune response [127, 128]. Further data suggest that 5-HT is involved in the optimal accessory function of macrophages, such as in reverting the monocyte-induced suppression of NK cell activities [121, 127, 129, 130], or the ability to provide accessory help for T-cell activation [131, 132]. Scattered data suggest that 5-HT may trigger or potentiate a variety of T-cell functions in humans, in particular, the IL-16 secretion from CD8+ T-cells [127], the IL-2 production [132], the enhancement of T-cell activation, through the PKC-dependent phospholipase-D pathway [133].

Dopamine in Lymphocytes

Dopamine receptors of type 3 and 4 (D_3 and D_4) have been described in human peripheral blood lymphocytes through radiolabeling assays (D_3, D_4), while D_1, D_3 and D_5 receptors have been detected by means of their specific mRNAs [134-138]. The interaction of these receptors with DA or DA agonists elicit different T-cell activities. Dopamine can activate human normal naıve peripheral T-cells and trigger their adhesion to fibronectin [139]. DA can also selectively induce the chemotactic migration of naıve CD8+ T-cells [140] and T-cell cytokine secretion, in particular, the TNF-alpha and the interleukin-10 (IL-10) [138]. Dopamine can probably also activate T-cell function indirectly, by suppressing T-regulatory cells, as suggested recently [141].

IT IS POSSIBLE TO MODULATE THE IMMUNE RESPONSE THROUGH THE TRANSPORTER PROTEINS PRESENT IN LYMPHOCYTES?

As discussed above, it is now evident that functional SERT and DAT proteins are present in lymphocytes, and the same their related neurotransmitters that have been shown to elicit a variety of activities upon different components of the immune system. However, since the SERT and DAT are the targets of several drugs [74, 142-144], such as psychostimulants and antidepressants, it is conceivable that these substances also might exert certain effects at the level of the immune system. The literature on this topic is quite controversial and the different studies are not easily comparable, because reporting findings obtained in animals or humans by in-vitro or in-vivo experiments, particularly those involving d-fenfluramine, ecstasy and cocaine [145-147]. For example, the psychostimulant d-fenfluramine had a positive effect on some immune parameters in AIDS patients [148], in agreement with some data in animals [149], but in sharp contrast with others [145, 150].

Some tricyclic antidepressants and SSRIs have been shown to impair lymphocyte and monocyte survival [151], an effect perhaps depending on the doses, at least for fluoxetine [152-154]. This is at variance with the enhancement of NK-cell activity displayed by paroxetine and fluoxetine *in vitro* [155], and by the clinical evidences that antidepressant treatments may revert the low NK-cell widely described in depressed patients [156-158]. In addition, antidepressants seem to possess putative anti-inflammatory properties, while inhibiting the production of some cytokines [159], so that, recently it has been proposed that depression is "an inflammatory state" [160, 161]. These interesting properties of antidepressants may suggest their potential use in autoimmune disorders, such as experimental neuritis [162] or encephalomyelitis [163]. In any case it seems premature to conclude whether the immune system may be considered an appropriate target for antidepressant development.

CONCLUSIONS

A growing wealth of different studies has demonstrated that lymphocytes carry functional SERT and DAT proteins and that their "classical" substrates, 5-HT and DA, respectively, exert a series of effects on different components of the immune system. On one side, these evidences clearly support the perception that the division of our body in systems is quite arbitrary, on the other, they challenge the conventional functions of transporters and neurotransmitters, which appear no longer confined to the brain. In fact, neurotransmitters produced in the nerves or in lymphocytes represent the soluble messengers linking the CNS with lymphoid organs, and can modulate some immune functions through the receptors present on the surface of immune cells. The most plausible hypothesis on the role of lymphocyte transporters is that they can regulate the levels of neurotransmitters where necessary, particularly at inflammatory sites, but not only, as they can rapidly circulate everywhere and even pass rapidly the blood-brain barrier

However, lymphocyte SERT and DAT represent the targets of different compounds, such as antidepressants and psychostimulants. If we cannot disregard the "dark side" of these findings, that is to say, the possibility to affect negatively the immune system, although data in humans are quite a few, the available findings would suggest that drugs interacting with lymphocyte transporters might be beneficial particularly in severe immune disturbances, such as, perhaps, autoimmune disorders.

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