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Invited review

Immunomodulatory effects of fluoxetine: A new potential pharmacological action for a classic antidepressant drug?

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ABSTRACT

Selective serotonin reuptake inhibitors are frequently used antidepressants. In particular, fluoxetine is usually chosen for the treatment of the symptoms of depression, obsessive–compulsive, panic attack and *bulimia nervosa*. Antidepressant therapy has been associated with immune dysfunction. However, there is contradictory evidence about the effect of fluoxetine on the immune system. Experimental findings indicate that lymphocytes express the serotonin transporter. Moreover it has been shown that fluoxetine is able to modulate the immune function through a serotonin-dependent pathway and through a novel independent mechanism. In addition, several studies have shown that fluoxetine can alter tumor cell viability. Thus, it was recently demonstrated *in vivo* that chronic fluoxetine treatment inhibits tumor growth by increasing antitumor T-cell activity.

Here we briefly review some of the literature referring to how fluoxetine is able to modify, for better or worse, the functionality of the immune system. These results of our analysis point to the relevance of the novel pharmacological action of this drug as an immunomodulator helping to treat several pathologies in which immune deficiency and/or deregulation is present.

Contents

1. Introduction

Serotonin [5-hydroxytryptamine (5-HT)] and catecholamines are primitive biogenic amines essential to the regulation of central processes, like food and sexual appetite, mood, sleep, body temperature and breathing. Their bioavailability is exquisitely regulated through diverse mechanisms, such as vesicular sequestration mediated by selective transporters. In addition, these neurotransmitters and the corresponding transporter proteins are found in peripheral cells, mainly those of the immune–inflammatory axis. Also it has been described that they are able to modulate immune cell activity in an autocrine manner. These transporters have been used widely as pharmacological targets for the treatment of mood and anxiety-related disorders. Specifically, selective 5-HT reuptake inhibitors (SSRIs) have been demonstrated to be very efficient, safe and toler-

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able. In particular, fluoxetine is usually chosen for the treatment of the symptoms of depression, obsessive–compulsive disorder, panic attacks and *bulimia nervosa*. However, antidepressant therapy has been associated with alterations of the immune function.

Here we concisely review the literature pertaining to how fluoxetine is able to modify – for good or ill – the functionality of the immune system. Firstly, we describe the evidence on the presence and the role of 5-HT and of the transporters within the immune system. Secondly, we mention the findings about the alteration of 5-HT homeostasis in affective disorders and other pathologies such as cancer. Thirdly, the effect of fluoxetine on the immune response in both healthy subjects and in sickness conditions will be depicted.

2. Role of serotonin as a regulator of immune response

During the last twenty years experimental findings have indicated reciprocal communication between the immune and nervous systems, where 5-HT has been proven to have important modulatory effects [1–5]. Enterochromaffin cells of the gastrointestinal tract are the main producers of 5-HT. These cells release 5-HT, which is taken up by platelets that then act as "mobile storage units". The rapid release of platelet 5-HT is induced by inflammatory stimuli, such as C5a, platelet activating factor and IgE-containing immune complexes. Thus, at sites of inflammation, lymphocytes can be exposed to large amounts of platelet-derived 5-HT, reaching near 1 mM in the local milieu [3]. In addition, immune cells contain and synthesize 5-HT [6–9]. The content may be different between diverse subtypes of cells, in lymphocytes and monocytes, and even in subpopulations of T lymphocytes. These differences could indicate particular roles of 5-HT as an immunomodulatory factor acting as an autocrine transmitter. For example, dendritic cells are able to uptake and store 5-HT, and then release it by exocytosis, inducing proliferation and differentiation of naive T cells [10]. Therefore autocrine and paracrine interplays might take place among lymphocytes.

The neuroimmune axis constitutes one more source of 5-HT for lymphocytes. It is known that lymphoid organs are extensively innervated by the autonomic nervous system. It has been proposed that nerve fibers in close contact with lymphoid tissues might take up 5-HT and then release it on following stimulation of the nerves [3]. Several studies have shown that 5-HT is able to regulate numerous immune responses by increasing of mitogen-stimulated lymphocyte proliferation, promoting natural killer (NK) cell activation and macrophage/dendritic accessory function as well as contributing to the initiation of the delayed-type hypersensitivity response [3,11,12].

Within the immune system, 5-HT can be transformed through catabolic pathways in melatonin, a cyclooxygenase inhibitor called formyl-*N*-acetyl-5-methoxykynurenamine, formyl-5-hydroxykynurenamine, 5-hydroxyindoleacetic acid and *N*-methylserotonin. However, it is not thoroughly understood the extent by which these metabolites generated during catabolism may affect the immune system [for a review see Ref. [13]].

Membrane receptors for 5-HT are, at present, grouped into 7 families, known as 5-HT1 to 5-HT7 [13]. In mammalian, 14 different 5-HT receptor subtypes have been found using molecular biological techniques. The 5-HT1 subgroup includes at least five subtypes: 5-HT1A, 5-HT1B, 5-HT1D, 5-HT1E and 5-HT1F. The 5-HT2 consists of three subtypes: 5-HT2A, 5-HT2B and 5-HT2C. For 5-HT5 two related receptor were identified: 5-HT5A and 5-HT5B. Excluding the 5-HT3 receptor that is a cation channel, all subtypes are G-protein-coupled receptors. 5-HT1, 5-HT4, 5-HT6, 5-HT7 subgroups are linked to adenylate cyclase and 5-HT2 to phospholipase C. The second messenger system coupled to the 5-HT5 receptors has not been identified yet; however, evidence exists indicating the functional coupling of the rat 5-HT5A receptor subtype to adenylate cyclase [14,15].

The presence of 5-HT receptors in the immune system, such as 5-HT1, 5-HT2, 5-HT3 and 5-HT7, has mostly been studied by pharmacological methods [3]. Stefulj et al. [16] investigated the mRNA expression of 5-HT receptors in rat lymphoid tissue cells and in mitogen-stimulated spleen cells by RT-PCR methods. The authors found that 5-HT1B, 5-HT1F, 5-HT2A, 5-HT2B, 5-HT6 and 5-HT7 receptor mRNAs are expressed in *ex vivo* isolated thymus, spleen, and peripheral blood lymphocytes. Mitogen-stimulated cells also expressed 5-HT3 receptor subtype mRNA. However, mRNA corresponding to 5-HT1A, 5-HT1D, 5-HT2C, 5-HT4, 5-HT5A and 5-HT5B subtypes were undetected in the examined lymphoid populations [16]. Other authors, however found 5-HT1A receptor to be expressed in lymphocytes, where it is involved in the promotion of T-cell proliferation, a property conserved between mammals and fish [8,9]. In addition 5-HT1A receptor is expressed in B lymphocytes and, as with T cells, both mRNA and protein for this receptor are up-regulated by NF-κB-dependent mechanisms [17]. Moreover, 5-HT1A receptor seems to participate in the 5-HT-augmentation of rodent splenic B cells mitogenic responses induced by lipopolysaccharide and dextran sulfate [18].

Antagonism of 5-HT1B/D receptors inhibits proliferation of human and murine T cells [19] and agonism of 5-HT1A receptors increases proliferation of rat [20], mouse [21] and human [22] lymphocytes, indicating a crucial role of 5-HT as an immunomodulator [23]. Also, the expression of 5-HTR2A in PBMC has been investigated and linked to the regulation of tumor necrosis factor (TNF)-α and interleukin (IL)-1β secretion [24]. Furthermore, it was demonstrated that 5-HT3, 5-HT4 and 5-HT7 subtypes regulate the release of IL-1β, IL-6, IL-12, IL-8 and TNF-α in monocytes and dendritic cells [12,25,26]. It was reported that 5-HT3A is expressed in naive and activated B-lymphocytes [27], T lymphocytes, and human monocytes [28]. Inhibition of the 5-HT3 receptors with antagonists, such as ondasetron and tropisentrol, disrupts TNF-α and IL-1β production, suggesting that these receptors may activate the p38/MAPK pathway [29,30]. Besides, 5-HT regulates migration, cytokine and chemokine release and T-cell priming capacity of dendritic cells [12]. Table 1 shows the different receptor subtypes and the effect of 5-HT in different cell types.

High affinity uptake of 5-HT and its inhibition by SSRIs in peripheral-blood lymphocytes has been described [31]. In addition, the expression of the 5-HT transporter (SERT) has been demonstrated by specific saturable binding of the labeled SSRI paroxetine on lymphocytes [32]. It is important to note that the capacity to accumulate 5-HT seems to be evolutionarily conserved among lymphocytes suggesting that lymphoid SERT has a relevant role, if not a crucial function, within the periphery [6,33].

Cytokine modulation of SERT mRNA expression *in vitro* has been reported [34–37]. Furthermore, TNF-α, IL-6, IL-10, IFN-γ production requires intracellular lymphocyte 5-HT, but this production may be suppressed by an increase in extracellular 5-HT concentration [38]. These observations suggest that SERT could be able to regulate the production of cytokines.

Experimental evidence shows that SERT does not act just as a transport protein but also as a substrate-dependent signal transducer [39]. In addition, SERT-delivered 5-HT has been probed to impact signal transduction directly by a novel mechanism, the "serotonylation" of small GTPases [40,41]. Thus, SERT appears equipped to modify cell's functional behavior in potentially diverse ways [15].