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Short review

Selective serotonin reuptake inhibitors as a novel class of immunosuppressants

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ABSTRACT

In the past decades, selective serotonin reuptake inhibitors (SSRIs) have been shown to exert several immunological effects, such as reduced lymphocyte proliferation, alteration of cytokine secretion and induction of apoptosis. Based on these effects, SSRIs were proposed as drugs for the treatment of autoimmune pathologies and graft-versus-host disease. This review summarizes preclinical and clinical evidence supporting a role for SSRIs in autoimmune diseases and graft-versus-host disease, and discusses what is known about the mechanism underlying these effects.

Contents

1. Introduction

Selective serotonin reuptake inhibitors (SSRIs) are amongst the most prescribed drugs worldwide [1]. Indications for these drugs are broad and comprise major depression, panic disorder, obsessive–

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compulsive disorder and other less well-established indications such as obesity, eating disorders, post-traumatic stress disorder, social phobia and premenstrual disorder [2]. In comparison to other types of antidepressants, SSRIs have a more beneficial adverse effect profile with nausea, diarrhea, sexual dysfunction, headache, dizziness, agitation, insomnia and under certain circumstances increased suicide risk [2,3]. In addition to these well described side effects, there are indications from animal studies [4], *in vitro* studies [5], and some clinical observations in patients with depression [6] that SSRI treatment may affect the cellular immune response.

Abnormalities in the proliferation, cytokine secretion and viability of peripheral blood lymphocytes have been observed when these cells were exposed to SSRIs. Moreover, the replication and viability of cancer cells are also affected by SSRIs. Several groups have attempted to reveal the underlying mechanism by which these effects are executed. An overview of the immunological effects of SSRIs on immune cells is provided, both in *in vitro* and *in vivo* situations, and special attention is paid to the role of serotonin (5HT) and its transporter in this effect.

The majority of research reports immunosuppressive effects of SSRIs such as decreased lymphocyte proliferation and reduced pro-inflammatory cytokine secretion [5,7]. Therefore, SSRIs have already been tested in several animal models of autoimmune disorders and graft-versus-host disease [8–14]. However, for fluoxetine an immunosuppressive as well as an immunostimulatory effect was described, depending on the concentration used and the degree of lymphocyte activation *in vitro* [15,16]. Similarly, the beneficial effect of fluoxetine in the treatment of lymphoma [17,18] was attributed to both a direct suppressive effect on the malignant cells and a stimulatory effect on anti-cancer immunity. Thus, it appears that under specific *in vitro* and *in vivo* conditions, fluoxetine can exert immunostimulatory effects, which seem applicable in the treatment of lymphoma. The potential applications of SSRIs in cancer were recently reviewed by Frick and Rapanelli [19]. As the doses of fluoxetine used in animal models of lymphoma and autoimmune disorders were in the same range (10–25 mg/kg) [11,12,18,20], the difference between immunostimulation and immunosuppression *in vivo* does not rely on the different dose used. Instead, the investigated disease and its underlying immunological mechanism appear to determine whether fluoxetine exerts either a stimulatory or a suppressive effect. For other SSRIs such as paroxetine and sertraline, only immunosuppressive effects have been described [5,8,13]. In this review we will focus on the immunosuppressive effect of SSRIs.

Based on the observed immunosuppressive effects, the application of SSRIs in autoimmune disorders and graft-versus-host disease was examined. Although several research groups have shown improvement in clinical scores in animal models of autoimmune diseases, discussion remains about the feasibility of using SSRIs as immunosuppressants in men, as the doses applied in animal studies are generally higher than the ones currently used in humans for the treatment of depression. Nevertheless, limited clinical evidence is available demonstrating the usefulness of SSRIs in autoimmune disorders.

2. Effects of SSRIs on immune cell functioning

SSRIs have been shown to alter several aspects of immune cell functioning. Not only the proliferation, but also cytokine secretion and viability of lymphocytes are affected when exposed to SSRIs. In addition to lymphocytes, cancer cells also seem to undergo changes when they are incubated with SSRIs [21–23]. Finally, recent evidence showed an effect of fluoxetine on neutrophil adhesion and recruitment to inflammatory sites, demonstrating that not only cellular but also innate immunity is impacted by SSRIs [24].

2.1. Proliferation

In the last decades, several research groups have demonstrated that micromolar concentrations of SSRIs are capable of altering lymphocyte proliferation. *In vitro* exposure to paroxetine, sertraline and fluoxetine has been shown to decrease the proliferation of mitogen-stimulated lymphocytes in a concentration-dependent manner [5,15,16,25–27]. An anti-proliferative effect has also been observed in Jurkat T cells [28]. Pellegrino and Bayer found that *in vivo* administration of fluoxetine to rats similarly decreased lymphocyte proliferation when induced by mitogens *ex vivo* [29,30]. The effect, however, seems to be dependent on the activation status of the cells. At suboptimal mitogenic Concanavalin A (ConA) concentrations, relatively low concentrations (0.1–1 μM) of fluoxetine have been found to stimulate T cell proliferation [15,18]. In contrast, at optimal ConA concentrations, 1 μM fluoxetine inhibited T cell proliferation and a maximal suppressive effect was reached at 10 μM [15]. Although in some situations low levels of fluoxetine seem to stimulate lymphocyte proliferation, the majority of research in general points to a negative immunoregulatory effect of SSRIs on lymphocytes. Our own data support the observation that SSRIs reduce T cell proliferation in a concentration-dependent manner at concentrations equal to or higher than 1 μM, when stimulated with anti-CD3/CD28 beads [14]. In addition to fluoxetine, other clinically available SSRIs (paroxetine, sertraline, citalopram, and fluvoxamine) also appear to induce this anti-proliferative effect [14]. Although the SSRI concentrations used in *in vitro* experiments are in the micromolar range, the anti-proliferative effect is concentration-dependent, indicating that this effect is specific and not due to general toxicity.

2.2. Cytokine secretion

Although investigated the most extensively, proliferation is not the only parameter affected by SSRIs. The functional ability of lymphocytes, under the form of cytokine secretion, is equally affected. For example, 20 μM citalopram decreased IL-2 and IFNγ secretion by mitogen-activated T cells [31]. Furthermore, paroxetine and sertraline (0–30 μM) have been demonstrated to reduce TNFα secretion by human anti-CD3 stimulated T lymphocytes [5]. Others showed that sertraline (0.01 and 1 μM) significantly decreases the IFNγ/IL-10 ratio in the supernatant of mitogen-stimulated whole blood [7,32]. Although these studies point in the same direction, showing a suppressive effect of SSRIs on the production of pro-inflammatory cytokines, it should be noted that these studies are not equal in terms of experimental setup. Whereas the first two studies used purified lymphocytes, Maes et al. used whole blood assays. In the latter model interactions between different types of blood cells are preserved, and this model is therefore believed to be more representative for the *in vivo* situation. Recently, Shenoy et al. demonstrated that not only peripheral blood lymphocyte but also thymocyte cytokine production is suppressed by citalopram [33]. Concentrations ranging from 25 to 250 μM citalopram completely suppressed anti-CD3 triggered IL2 production, severely reduced IL4 and partially suppressed IL17 production [33]. As is the case for the anti-proliferative effect of SSRIs, suppression of cytokine production is a concentration-dependent effect, confirming that it is not due to general cytotoxicity.

2.3. Apoptosis

Finally, SSRIs have been shown to induce apoptosis in lymphocytes. Whereas paroxetine and sertraline were found to decrease activated T cell viability with an IC_{50} of around 10 μM [5], other SSRIs exerted this effect only at tenfold higher concentrations. For citalopram, an IC_{50} of 180 μM was reported for pro-apoptotic action on naïve T cells [34]. According to our own research, this apoptotic effect is induced by all SSRIs used in clinical practice (paroxetine, fluoxetine, sertraline, fluvoxamine and citalopram), albeit in different concentration ranges [14].

Not only do SSRIs affect the function of healthy lymphocytes, but they also seem capable of reducing the viability of several cancerous immune cells. Amit et al. showed that paroxetine ($IC_{50} = 18$ μM) and