

THE EFFECTS OF SELECTIVE SEROTONIN REUPTAKE INHIBITORS ON MOTILITY OF PERIPHERAL SMOOTH MUSCLES

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ABSTRACT

Selective serotonin reuptake inhibitors are chemically heterogeneous antidepressant drugs with small affinity for adrenergic, muscarinic and histaminergic receptors. This fact makes them one of the safest drugs among all antidepressants. However, the results of some experimental studies suggest that these antidepressants can modulate tone and spontaneous contractions of smooth muscle peripheral cells primarily by affecting the voltage-dependent ion channels. Fluoxetine causes relaxation of intestinal smooth muscle cells, contraction of gastric smooth muscle cells, and inhibition of muscular and neuronal nicotinic receptors, neuronal sodium channels, and voltage-dependent potassium channels on animal's models. Paroxetine exhibits concentration-dependent stimulating effect on the spontaneous contractions of the isolated isthmus of human Fallopian tube. Citalopram induces contractions of the gastric fundus and the antrum, intestinal smooth muscle cell relaxation and has proarrhythmic effects due to blockage of Kv potassium channels. Escitalopram also blocks Kv channels of vascular smooth muscle cells of coronary arteries, as well as the hERG channels in the heart of rabbits, but it also shows concentration-dependent stimulating effect on the spontaneous contractions of the isolated ampulla of human Fallopian tube. Sertraline inhibits a wide range of heart ion channels including Kv channels on the vascular smooth muscles of rabbit coronary arteries. Fluvoxamine and dapoxetine also inhibit Kv channels of coronary arteries of rabbits, while at present there is no data on the effect of vilazodone and vortioxetine on peripheral smooth muscle cells. Knowledge of these peripheral effects of selective serotonin reuptake inhibitors could be of great importance in making treatment decisions for patients, such as in the case with paroxetine and escitalopram, which should be avoided in women of reproductive age due to the stimulating effect they have shown on spontaneous smooth muscle contractions of the human Fallopian tube.

Keywords: Selective serotonin reuptake inhibitors, fluoxetine, paroxetine, citalopram, escitalopram, sertraline, fluvoxamine, dapoxetine, smooth muscle cells.



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INTRODUCTION

Selective serotonin reuptake inhibitors (SSRIs) are chemically heterogeneous antidepressant drugs introduced into clinical practice in the 1980s (1). Due to their safety profile, over time they have become the first-line therapy for the treatment of mood and anxiety disorders. These drugs exert their effect by inhibiting the transport protein at the presynaptic terminal, thereby inhibiting the reuptake of serotonin into the presynaptic nerve endings. As a result of this inhibition, the concentration of serotonin in the synaptic cleft increases, leading to increased activation of postsynaptic serotonin receptors and enhancement of serotonergic transmission in the central nervous system (2). SSRIs includes older medicines such as fluoxetine, fluvoxamine, paroxetine, citalopram, escitalopram and sertraline, as well as a group of newer drugs such as dapoxetine, vortioxetine and vilazodone (3,4). As mentioned previously, except for the treatment of depression and all forms of anxiety disorders, SSRIs are used to treat some eating disorders (bulimia nervosa), premenstrual dysphoric disorder and premature ejaculation; they could also be effective in treating irritable bowel syndrome, various forms of addiction and fibromyalgia (4,5).

SSRIs are 20-1500 times more selective for serotonin transporters over noradrenaline-carrying proteins across the membrane of presynaptic nerve endings. In addition, compared to tricyclic and other older antidepressants, their affinity for adrenergic, muscarinic, and histaminergic receptors is almost insignificant (2). This is one of the main reasons for their favorable safety profile, which, as noted earlier, favors their use over other antidepressants (6). However, although SSRIs are generally safer to use than other groups of antidepressants, their use is also often accompanied by the occurrence of serious adverse effects, primarily metabolic (7) and sexual adverse effects (8). The relatively common occurrence of sexual side effects (decreased libido, impaired erection, delayed ejaculation, anorgasmia) during the administration of these antidepressants indirectly indicates that these drugs also have some peripheral effects, primarily on smooth muscle cells. Besides, the results of a large number of experimental studies (9-12) show that SSRIs also influence voltage-dependent sodium, potassium, and calcium channels and thus modulate smooth muscle cell contractility. The effect of SSRIs on peripheral smooth muscle is specific with respect to type and tissues, with significant differences between individual representatives of this group of antidepressants.

Therefore, the purpose of this review article is to present the most relevant experimentally demonstrated effects of SSRI on peripheral smooth muscle, with an attempt to theoretically explain the differences in the effects of individual representatives of this group of antidepressants on contractility of peripheral smooth muscle.

FLUOXETINE

The results of experimental studies showed that fluoxetine is a potent inhibitor of muscular and neuronal nicotinic acetylcholine receptors (13), neuronal sodium channels (14), and voltage-dependent potassium channels (15). In *in vitro* experimental study conducted on cultured human corneal and lens cells by *Rae et al* (16), fluoxetine also inhibited several types of voltage-dependent potassium channels. Furthermore *Velasco et al* (17) demonstrated that fluoxetine inhibits the contractions of isolated rat uterus induced by high concentrations of potassium ions. At the level of vascular smooth muscle cells, fluoxetine interfere with the contraction induced by serotonin and/or noradrenaline. Also, fluoxetine causes significant dilatation of isolated skeletal muscle arterioles and small rat cerebral arteries, most likely by suppressing extracellular calcium influx into smooth muscle cells (18,19). It is also believed that fluoxetine at therapeutic concentrations induces relaxation of intestinal smooth muscle cells, precisely through the inhibition of calcium channels (20). There is indirect clinical evidence that fluoxetine-induced relaxation of intestinal smooth muscle cells also occurs *in vivo*. Namely, a common side effect of fluoxetine is constipation, which occurrence could be explained by this relaxation of intestinal smooth muscle cells (18). On the other hand, in the study conducted by *James et al* (21) fluoxetine showed a concentration dependent stimulating effect on the spontaneous contractions of isolated guinea pig stomach preparations. However, the intensity of these contractions, was decreased after the administration of atropine (muscarinic receptor blocker), phentolamine (alpha adrenergic blocker) and 5-HT receptor antagonist. This indicates that the contractile effect induced by fluoxetine at the level of gastric smooth muscle cells is at least in part caused by the interaction with muscarinic, alpha-adrenergic, and serotonergic receptors. While the occurrence of constipation that often accompanies fluoxetine administration may be explained by relaxation of intestinal smooth muscle cells, the stimulatory effects of fluoxetine on gastric smooth muscle contractions could be a theoretical explanation for the opposite gastrointestinal adverse effect of fluoxetine, i.e.- diarrhea.

PAROXETINE

In addition to fluoxetine, paroxetine is also known to affect the contractility of intestinal smooth muscle. However, available data on the effects of paroxetine on the motility of the gastrointestinal tract are controversial. Thus, the results of clinical studies (22,23) indicate that paroxetine increases motility in the small intestine without affecting the gastric emptying or to the transit of the colon. On the other hand, in the experimental *in vitro* study carried out by *Afzal et al* (24), paroxetine exhibited an inhibitory effect on rabbit ileum smooth muscle cell contractions. This relaxation was dose-dependent and resulted in extension of ileal transit time. Paroxetine also affects gastric smooth muscle cells by increasing gastric accommodation in healthy volunteers (25). Because of the aforementioned effects of paroxetine in the gastrointestinal tract, previous studies have been conducted to

investigate its possible efficacy for the treatment of irritable bowel syndrome, but at present the clinical benefit of this potential application has not been confirmed (26). In study conducted by *Milosavljevic et al* (27), paroxetine showed concentration-dependent stimulating effect on the contractions of the isolated isthmus of human Fallopian tube, while the other SSRIs tested in this study (fluoxetine, citalopram, escitalopram, sertraline) did not show statistically significant effect on spontaneous contractions of human isthmus. A possible explanation for this effect that distinguishes paroxetine from other SSRIs lies in the fact that paroxetine is a potent inhibitor of NO synthase (28), since *Perez Martinez et al* (29) have demonstrated that inhibitors of NO synthase accelerates motility of the Fallopian tubes of rats. In relation to other representatives of SSRIs, paroxetine shows the greatest potential for inhibition of noradrenaline reuptake (30) and the strongest anticholinergic effect (31). Paroxetine also differs from other SSRIs in that it does not have a significant effect on the contractility of rabbit coronary smooth muscle cells (9,11,12).

CITALOPRAM

Experimental studies have shown that the effects of citalopram on smooth muscle cells are similar to the effects of fluoxetine. At concentrations of 0.1-10 μM , citalopram induces vascular and intestinal smooth muscle cell relaxation through the inhibition of voltage-dependent sodium, potassium, and calcium channels. The inhibition of the ion channels of the heart produced by citalopram could result in its proarrhythmic adverse effects (20). Similar to fluoxetine, citalopram induces contractions of the fundus and the antrum of the stomach, which could be inhibited by atropine (21). Moreover, the results of recent experimental *in vitro* studies show that citalopram blocks Kv 1.3 and Kv 1.5 potassium channel subtypes (32), as well as delayed potassium rectifier current in mouse cortical neurons, predominantly through inhibition of Kv 2.2 potassium channel subtypes (33).

ESCITALOPRAM

Certain effects of escitalopram on smooth muscle cells are also well-known. It seems that escitalopram blocks the *hERG* channels in the heart, which could explain the adverse effect of this antidepressant related to QT interval prolongation and its proarrhythmic potential (34). Also, a group of authors from South Korea recently showed that escitalopram blocks Kv channels in the membranes of vascular smooth muscle cells of rabbit coronary arteries (9). The inhibitory effect of escitalopram was dose-dependent and was not associated with a primary effect of escitalopram that is achieved through the inhibition of serotonin reuptake. Escitalopram differs from other SSRIs in its effect on spontaneous contractions of the ampoule of the human Fallopian tube.

Milosavljevic et al (27) showed that only escitalopram produced a stimulating effect on smooth muscle cells of the ampulla of the human Fallopian tube, while fluoxetine, paroxetine, citalopram, and sertraline did not show a statistically significant effect on this portion of the human Fallopian tube. This effect of escitalopram could have a negative impact on the possibility of conception in female patients undergoing treatment with this antidepressant. It is believed that the fertilization process of the ovum occurs precisely in the ampullary segment of the Fallopian tube, so acceleration of the Fallopian tubes physiological motility would reduce the time required for fertilization (35).

SERTRALINE

Sertraline inhibits a wide range of heart ion channels (10). Similar to escitalopram, sertraline induces dose-dependent inhibition of Kv channels on the vascular smooth muscle cells of rabbit coronary arteries. The exact mechanism behind the blockage of Kv ion channels by sertraline is unknown, but it is obvious that the inhibition of these channels is not due to the primary mechanism of action of sertraline. Sertraline inhibits Kv channels in the closed state (11). On the other hand, it seems that sertraline has no effect on the sensitivity and propulsive function of the stomach, so there is no evidence to support the potential use of sertraline in order to alleviate the symptoms of dyspepsia (36). Sertraline also showed neither a stimulatory nor an inhibitory effect on spontaneous contractions of the isthmus and ampulla of human Fallopian tube (27).

OTHER REPRESENTATIVES OF SSRIS

In vitro studies have shown that fluvoxamine inhibits Kv 1.5 subtype of voltage-dependent potassium channels in Chinese hamster ovary cells (37) and *hERG* channels in human embryonic kidney 293 T cells (38). Similarly to escitalopram and sertraline, fluvoxamine also produces a dose-dependent inhibition of voltage-dependent Kv channels in the inactive state on the smooth muscles of the coronary arteries of rabbits (12).

Dapoxetine also causes dose-dependent inhibition of Kv 1.5 channels on cell lines (39) as well as dose-dependent inhibition of Kv channels of rabbit coronary arteries, but unlike fluvoxamine, escitalopram and sertraline, dapoxetine inhibits Kv channels while they are in the open state (40).

The effects of vilazodone and vortioxetine have not yet been tested on peripheral smooth muscle cells.

A summary of the effects of the representative of the SSRIs on the smooth muscle cells and ion channels of different tissues is shown in Table 1.

Table 1. Summary of the effects of SSRIs on the smooth muscle cells and ion channels[illegible]

CONCLUSION

Selective serotonin reuptake inhibitors produce significant effects on peripheral smooth muscle cells and ion channels in the heart, which are species and tissue specific. Knowledge of these peripheral effects of SSRIs could be of great importance in making treatment decisions for patients, such as in the case with paroxetine and escitalopram, which should be avoided in women of reproductive age due to the stimulating effect they have shown on spontaneous smooth muscle contractions of the human Fallopian tube. Therefore, there is a real need to conduct new experimental studies that will examine the potential effects of SSRIs on the smooth muscle cells of those tissues that have not been studied so far.

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