

The Effect of Paroxetine on Ouabain-Induced Toxicity in Isolated Guinea Pig Atria

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Abstract- It has been reported that selective serotonin reuptake inhibitors (SSRIs) possess some cardiac effects. In the present study we have investigated the effect of paroxetine (PX), a potent SSRI agent, on spontaneously as well as ouabain-induced arrhythmia beating isolated guinea-pig atria. The Guinea-pig heart was rapidly removed; the auricles were dissected out in oxygenated modified Krebs solution. The rate and force of spontaneous contractions were recorded isometrically with a photosensitive transducer. PX (1-16 µg/ml) caused a dose-dependent decrease in the rate of contractions (14-70%) and contractile force (8-16%). Ouabain alone (1.2 µg/ml) produced arrhythmia at 7.2 ± 1.5 min and asystole at 20.1 ± 3.1 min. Pretreatment with PX (4 µg/ml) significantly increased the time of arrhythmia onset to 19.8 min. In addition, PX prolonged the duration of action beating from 20.1 ± 3.1 min to 43.1 ± 2.6 and delayed the occurrence of asystole. The pattern of contractile force by PX + ouabain treatment was more regular than that observed after administration of ouabain alone. The above findings may be probably be due to the inhibition of cardiac Na^+ and Ca^{2+} channels or autonomic nervous system. Results also suggest that PX may reduce the membrane conductance through inhibition of ionic channels to prevent ouabain-induced arrhythmia.

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Introduction

Paroxetine (PX) is a phenylpiperidine derivative and potent selective serotonin reuptake inhibitor (SSRI) for treatment of depression and other psychiatric disorders. Inhibition of serotonin (5-hydroxytryptamine; 5HT) transporters by PX in the brain is suggested to have implications in psychiatric condition (1). The above authors have shown that SSRIs possess cardiac effects that are not related to the inhibition of the neuronal serotonin reuptake. For example, in cardiac and vascular tissues, fluoxetine is reported to block Na^+ , Ca^{2+} and K^+ channels (2,3). The cardiac effects of SSRIs are similar to those observed by tricyclic antidepressants (TCAs) compounds, although SSRI antidepressants including fluvoxamine, citalopram and PX are considered to be less cardiotoxic (4,5). Among cardiac effects, it has been demonstrated that therapeutic use of citalopram and fluoxetine may induce mild bradycardia (6,7). In

addition, PX is proven to be efficient in the treatment of obsessive-compulsive disorder, panic disorder, social phobia, generalized anxiety disorder and post-traumatic stress disorders. Other clinical Indications of PX include the treatment of premenstrual dysphoric disorder, diabetic neuropathy, vasovagal syncope and chronic headache (8).

Recent evidence suggests that PX may decrease mental stress-induced cardiovascular side effects specifically in individuals with heart disease, even those with no psychiatric illness (9). PX has antihypertensive properties during periods of psychological stress in psychiatrically healthy subjects with a history of coronary disease, and so should be evaluated for potential cardio-protective effect (9,10).

The present study, we investigated the effect of PX on isolated guinea-pig atria. In preliminary experiments, we have found that fluoxetine, citalopram and fluvoxamine have an anti-arrhythmic effect on isolated

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atria of guinea-pig (11, 12). Moreover, we have studied the effect of PX on ouabain-induced arrhythmia as well.

Materials and Methods

Chemicals

Ouabain and paroxetine Hydrochloride were purchased from Sigma Co. (St. Louis, USA). They were dissolved in water and pH adjusted to 7.3 ± 0.1 .

Preparation of isolated atria

Guinea-pigs of either sex weighing 400-500 g were housed in the laboratory. They were anaesthetized by ether and killed by exsanguination. The heart was rapidly removed; the auricles were dissected out in oxygenated modified Krebs solution and suspended in a 50 ml bath containing the same solution kept at $36-37^\circ\text{C}$ and pH 7.4. The composition of solution was as follows (mM): NaCl 118.0, KCl 4.7, CaCl_2 2.6, MgCl_2 1.2, NaH_2PO_4 1.0, NaHCO_3 25.0, Glucose 11.1, EDTA 0.004 and ascorbic acid 0.11. After mounting atria, the preparation was allowed to stand for 30 min for equilibration. The rate and force of spontaneous contractions were recorded isometrically with a photosensitive transducer on a Beckman® RS Dynograph recorder (Quincy, MASS, USA). Seven atria were used for each experiment. Solutions of drugs were prepared so that a constant volume of 0.5 ml for each dose was added to 50 ml of the bathing fluid (12). The animals were fed with standard food and tap water until experimentation. Twelve hours before the experiment animals were kept fast, but were allowed free access to tap water. All experiments were conducted on-site at the Tehran University Medical School and were performed in accordance with the recommendations of the Medical School Ethics Committee on Animal Experimentations.

Experimental design

Each atrium was examined 30 min after equilibration. For each experiment one dose of drug was added in the bath. The duration of exposure of drug with atria was approximately 45 min. Experiment were performed in 3 groups of atria as follow:

Group I: PX was added to the bath in doses of 1, 2, 4, 8 and 16 $\mu\text{g/ml}$. Only one dose of paroxetine was added to each atrium. For each dose 7 atria was used.

Group II: Seven atria were treated with ouabain (1.2 $\mu\text{g/ml}$).

Group III: Seven atria were pretreated with 4 $\mu\text{g/ml}$ of PX for 10 min. Ouabain (1.2 $\mu\text{g/ml}$) was then added to the bath without washing PX.

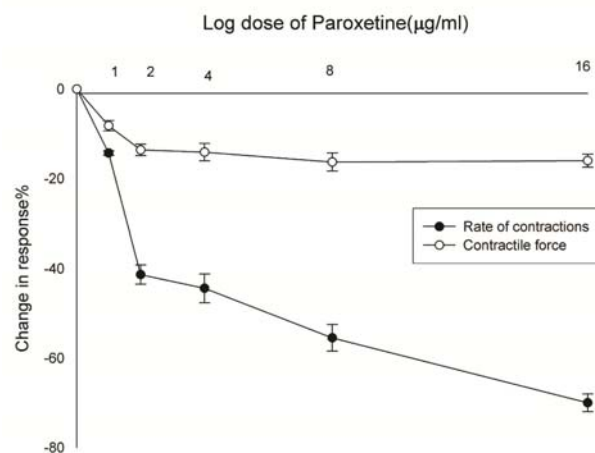


Figure 1. The effect of paroxetine (1-16 $\mu\text{g/ml}$) on rate of contractions ($P < 0.001$) and contractile force ($P > 0.05$) in isolated guinea-pig atria. Results are mean \pm SE ($n=7$).

Statistical analysis

The values obtained are expressed as the mean \pm SE of seven guinea-pig atria. Statistical analysis of differences between groups was carried out by using student's *t*-test for paired data. A probability of 0.05 was taken as the level of statistical significance.

Results

Paroxetine at a concentration of 1, 2, 4, 8 and 16 $\mu\text{g/ml}$ caused a significant decrease in heart rate, in a dose-dependent manner (14-70%) ($P < 0.001$, Figure 1). Regarding the contractile force, although its amplitude was reduced (8-16%), the reduction was not significant (Figure 1).

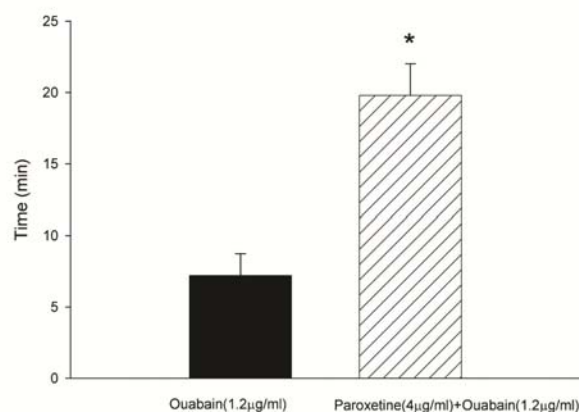


Figure 2. The mean time of onset of arrhythmia. * indicates a significant increase in the mean time of onset of arrhythmia ($n=7$, $P < 0.001$).

Paroxetine and ouabain arrhythmia

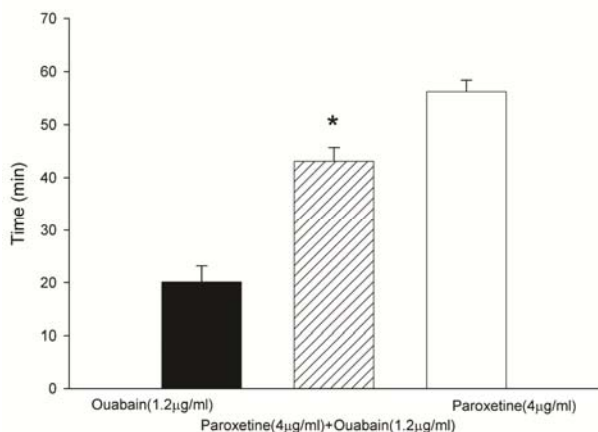


Figure 3. The mean Time of complete atrial block

* Indicates a significant increase the mean time of asystole (n=7, $P < 0.001$).

The baseline of the heart rate and amplitude of contractile force before adding the drugs were $180 \pm 4 \text{ min}^{-1}$ and $35 \pm 2.1 \text{ mm}^{-1}$, respectively. Ouabain alone (1.2 µg/ml) produced arrhythmia after $7.2 \pm 1.5 \text{ min}$ and asystole at $20.1 \pm 3.1 \text{ min}$ (Figures 2, 3).

When a single dose of ouabain (1.2 µg/ml) was added to the bath 10 min after the addition of PX (4 µg/ml, n=7), it was observed that the onset of arrhythmia induction was delayed and equal to $19.8 \pm 2.2 \text{ min}$ instead of $7.2 \pm 1.5 \text{ min}$ (Figure 2). Asystole was also delayed at $43 \text{ min} \pm 2.6$ ($P < 0.001$, Figure 3). The pattern of contractile force by PX+ouabain was more regular than by ouabain alone. It was also observed that lower concentrations of PX were ineffective against intoxication induced by 1.2 µg/ml of ouabain.

Discussion

The cardiovascular toxicity of old generation of anti-depressants well established. These drugs inhibit cardiovascular Na^+ , Ca^{2+} and K^+ channels often leading to life-threatening arrhythmia. SSRIs have fewer and more benign side effects profile than predecessors (3, 13, 14). PX is a potent inhibitor of serotonin and a very weak inhibitor of norepinephrine reuptake (15). In the present experiments PX produced a significant decrease in the rate of contractions and dose-dependent of in vitro guinea-pig atria (Figure 1). These effects are similar to those of fluvoxamine, citalopram and sertraline (11,12,16), The drug showed non-significant changes in the force of contractions ($P > 0.05$, Figure 1). It has been reported that PX produces a direct cardiac action

probably due the inhibition of cardiac and vascular Na^+ , Ca^{2+} and K^+ channels in the heart (14). It has also been reported that PX increased cardiac vagal activity and heart rate variability in patient with panic disorders (17). High concentration of PX alone has an inhibitory action on KCL or ATP induced contractile response of isolated vas deference that is attributed to its blocking effect on calcium channels (18). It has been demonstrated that some antidepressant such as PX and sertraline have Na^+ channels blocking activity (19). The decrease of heart rate by PX may also be due to a prolonged atrio-ventricular conduction time or a decrease in relative cardiac sympathetic activity (20,21). These observations support the idea that PX may acts through an inhibition of cardiac ionic channel and partly by Vagal and sympathetic tone in isolated atria.

Cardiac glycosides act by inhibition of $\text{Na}^+\text{-K}^+$ pump, thus, increasing $[\text{Na}]_i$ and causing more Ca^{2+} to enter the cardiac myocytes. Digitalis toxicity appears to be caused by excessive Ca^{2+} influx into cardiac cells. Both therapeutic and toxic effects of digitalis are due to myocardial Ca^{2+} loading (22). A beneficial effect of a number of TCAs drugs (e.g. amitriptyline and imipramine) in arrhythmia associated with ouabain administration in the dog was observed (23). PX at high concentration has lipophilic properties (8,24). This effect may result depolarization block by direct partition into cell membrane which alters the transport. PX at doses sufficiently to produce serotonin blockade has a weak quinidine-like effects too (8). This stabilizing action of PX may explain its preventive effect on ouabain-induced arrhythmia. Another possible explanation for PX to prevent ouabain-induced arrhythmia may be inhibition of Na^+ and Ca^{2+} channels.

Therefore, PX prevents or delay ouabain-induced arrhythmia in isolated guinea-pig atria in a dose dependent manner. This appears to be through quinidine-like effects on membrane permeability which corrects the ionic disturbance induced by ouabain.

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