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ORIGINAL PAPER

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Long-term use of sertraline leads to alterations in contractility of rat isolated vas deferens

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Abstract Previous experiments with rat isolated vas deferens have shown that sertraline pretreatment inhibits its contractile responses to noradrenaline, KCl, serotonin and electrical field stimulation. In the present study, the aim was to investigate the effects of long-term use of sertraline on contractile responses of rat isolated vas deferens. Fifteen Sprague-Dawley rats were given long-term (21 days) sertraline treatment, while another 15 were used as control. Both vas deferens were excised. Epididymal and prostatic segments of each underwent electrical field and chemical stimulation (noradrenaline, serotonin, acetylcholine, adenosine-triphosphate). Epididymal and prostatic segments had different contraction characteristics. Long-term sertraline treatment inhibited contractile responses of vas deferens segments to electrical field stimulation. The responses to noradrenaline were amplified with a left shift on both segments. Responses to serotonin had only a left shift on epididymal segments, while no contractile responses were observed on prostatic segments of the groups. Long-term treatment with sertraline had peripheral effects on rat vas deferens contractility, and some of the effects may be through mechanisms other than the inhibition of serotonin re-uptake.

Keywords Calcium channels · Ejaculation · Norepinephrine · Serotonin · Sertraline · Vas deferens

Introduction

Selective serotonin re-uptake inhibitors (SSRIs), with fewer overall side effects than tricyclic antidepressants, are used in the treatment of depression [9]. But like other antidepressant drugs, treatment with SSRIs may be accompanied by sexual dysfunction [3, 7, 9]. The use of sertraline, an SSRI, was shown to delay ejaculation time and to cause anejaculation [6, 13]. The alterations in the central serotonergic re-uptake are suggested to be involved [9, 13]. On the other hand, it was shown that sertraline inhibited the contractile responses to noradrenaline, KCl and electrical field stimulation on rat isolated vas deferens [5]. The current study was designed to investigate the effects of the drug's long-term use on isolated vas deferens strips from rats.

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Methods

This study was undertaken on 30 Sprague-Dawley rats weighing between 220 and 300 g. Fifteen rats in the treatment group were given sertraline (Pfizer, Istanbul, Turkey; 10 mg/kg/day, once daily intraperitoneally) for 21 days. The other 15 rats were given physiological fluid in the same manner and were used as controls. Under urethane anesthesia, both vas deferens were excised, excluding epididymis. The middle one-third of vas deferens samples was discarded, and the remaining segments were saved as epididymal and prostatic segments. The samples were stored at 4ºC in Tyrode solution (composition in mmol/l: NaCl, 137; KCl, 2.68; $CaCl_2$, 1.8; $NaHCO_3$, 11.9; NaH_2PO_4, 0.42; $MgCl_2$, 1.03; D-glucose, 5.55). Vas deferens segments were dissected and 10-mm strips were suspended in 10 ml jacketed organ baths containing Tyrode solution at 37ºC, bubbled with 95% O_2 and 5% CO_2. The upper end of the strip was anchored to the force-displacement transducer (MAY FDT 10-A) while the lower end was anchored to the organ bath. A tension of 10 mN was applied and an equilibration period of 60 min was allowed. Isometric contractions were recorded on a transducer data acquisition system (MAY TDA 97 Polygraphy), connected to a personal computer running Polwin 97 software (MAY PWS97) under the MS Windows 95 operating system.

Electrical field stimulation (EFS) was produced by bipolar platinum electrodes. Four square pulses of 10 V with 5 ms duration every 60 s with increasing frequencies (5, 10, 20, 40, 80, 160 Hz) were generated by MAY ST95PT Stimulator.

Noradrenaline (NA; 10^{-8}-10^{-4} M; Sigma, St.Louis, MO, USA), serotonin (10^{-8}–10^{-4} M; Sigma, St.Louis, MO, USA), acetylcholine (10^{-8}–10^{-4} M; Sigma,), adenosine-triphosphate (ATP; 10^{-8}–10^{-4} M;

Sigma,) was added to the organ bath and concentration-response curves were obtained. In each curve, the maximum response was established as 100% and each response was calculated as a percentage of the maximum contraction.

Statistical analysis

Results were presented as mean ± SEM. The Mann-Whitney U test was used to assess the differences and a p value smaller than 0.05 was considered to be significant.

Results

Epididymal and prostatic segments had different contraction characteristics. The epididymal segment was responsive to NA, serotonin, acetylcholine, and ATP. The prostatic segment was responsive to NA and ATP but was irresponsive to serotonin and acetylcholine.

Epididymal segment

Responses to EFS

In the treatment group, the responses were smaller in amplitude for the frequencies between 10 and 80 Hz (Fig. 1a).

Responses to NA

In the treatment group, the contractile responses were greater in amplitude and concentration-response curve showed a left shift (Fig. 1b).

Responses to serotonin

The maximum amplitude of the contractions were similar in both groups, but a left shift in responses was significant (Fig. 2a).

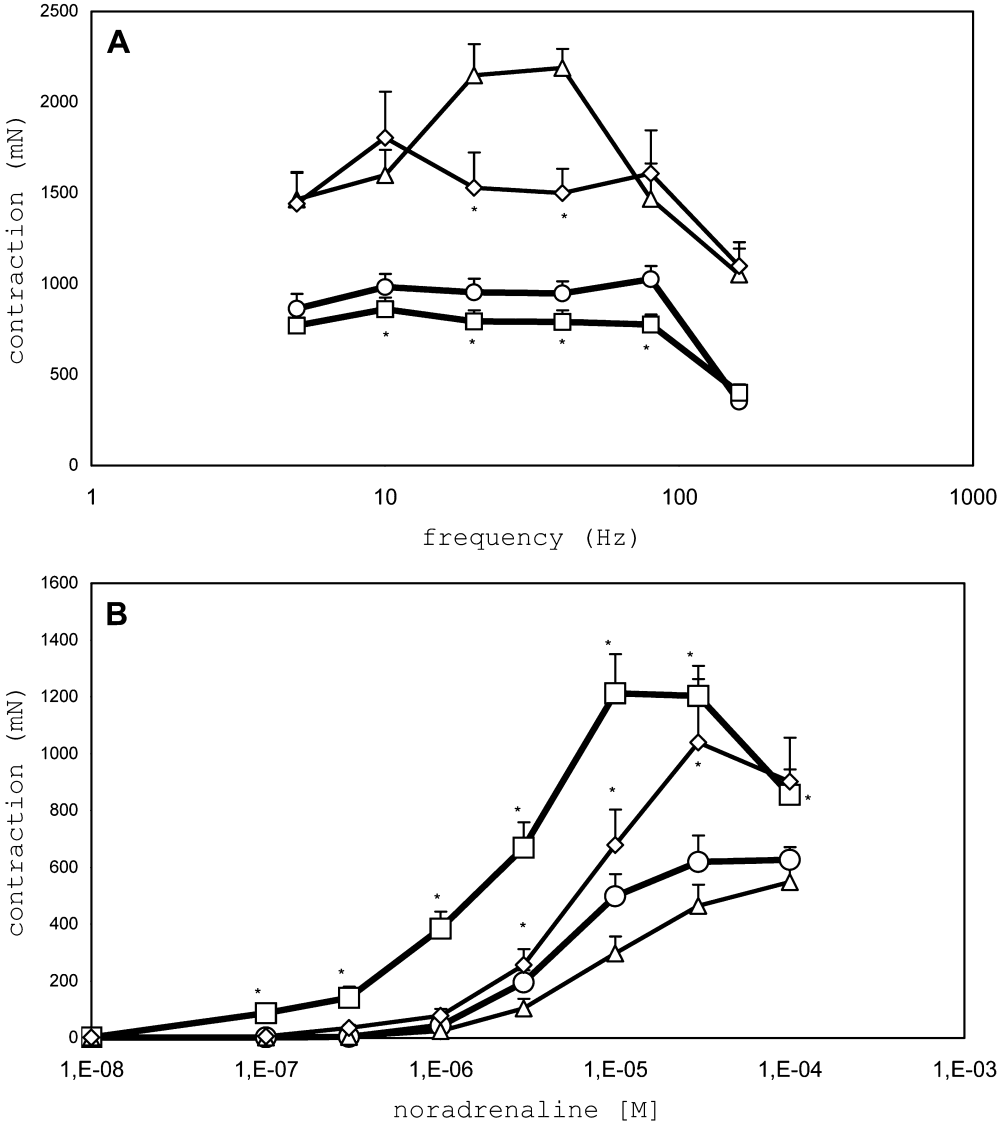

Fig. 1A, B The contractile responses of the epididymal and prostatic segments of vas deferens to electrical field stimulation (**A**), and to increasing concentrations of noradrenaline (**B**).● : control, epididymal segment; ■ : treatment group, epididymal segment; ▲ : control, prostatic segment; ♦ : treatment group, prostatic segment; ($n = 6$; mean ± SEM); *: $p < 0.05$, compared to its control, Mann-Whitney U test

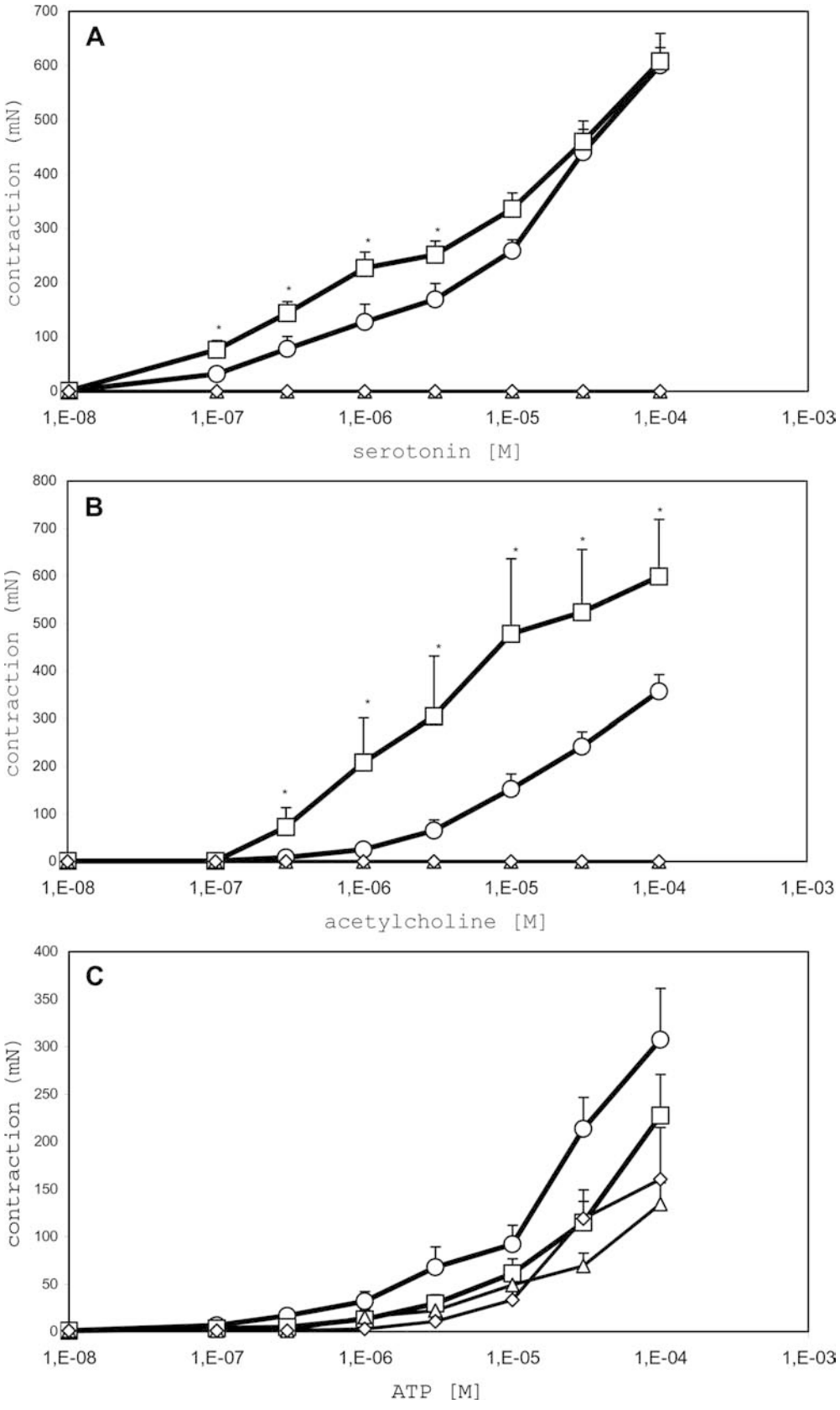

Fig. 2A–C In epididymal and prostatic segments of vas deferens, the concentration-response curves for serotonin (**A**), for acetylcholine (**B**), and for ATP (**C**).● : control, epididymal segment; ■ : treatment group, epididymal segment; ▲ : control, prostatic segment; ♦ : treatment group, prostatic segment; ($n = 6$; mean ± SEM); *: $p < 0.05$, compared to its control, Mann-Whitney U test

Responses to acetylcholine

Similar to the responses to NA, the contractile responses were greater in amplitude in the treatment group with a left shift (Fig. 2b).

Responses to ATP

The concentration-response curves were not different in control and treatment groups (Fig. 2c).

Prostatic segment

Responses to EFS

In the treatment group, the responses were smaller in amplitude for the frequencies of 20 and 40 Hz (Fig. 1a).

Responses to NA

Prostatic segments of the treatment group generated contractions with higher amplitude and a left shift was significant (Fig. 1b).

Responses to serotonin

Prostatic segments did not respond to serotonin (Fig. 2a).

Responses to acetylcholine

Prostatic segments did not respond to acetylcholine (Fig. 2b).

Responses to ATP

The concentration-response curves for ATP were not different in control and treatment groups (Fig. 2c).

Discussion

Sertraline, like other SSRIs, is used in the treatment of depression [9]. Sexual dysfunction, observed during the treatment, is thought to be central in origin [9, 13]. Other than its central nervous system-related effects, in vitro studies showed that sertraline alters the contractile responses to NA and EFS on isolated vas deferens in which the contractile system is mainly adrenergic [5, 8, 10, 12]. In lower concentrations, a potentiation of NA responses and in higher concentrations a clear inhibition of NA responses as well as EFS responses was obvious for sertraline and fluoxetine [1, 5]. The potentiation of responses to NA in lower concentrations of sertraline is thought to be related to 5-HT_3 receptor-mediated NA release [5, 11]. The inhibition of EFS responses in in vitro studies is clear [1, 5]. Data on the inhibition of EFS and KCl responses and restoration of the responses after the use of a voltage-dependent calcium channel activator have led to the conclusion that sertraline is a calcium channel-blocking agent [5]. The interaction between calcium channels and sertraline was also observed in several studies [4, 8]. The inhibition of EFS responses, seen in the current study, was thought to be due to the same mechanism.

Both in epididymal and prostatic segments, an amplification of responses to NA was obvious. On vas deferens strips, under the influence of sertraline, blocking calcium entry, this amplification may be considered as supersensitivity. In light of in vitro studies, concluding that sertraline is a potentiator of NA responses through 5-HT_3-mediated NA release [5, 11], and concluding that sertraline is an inhibitor of NA re-uptake [2], our findings may be viewed as supersensitivity due to NA exhaustion. On vas deferens, with mainly adrenergic contractile systems, serotonin probably acts as a neuromodulator, and our findings that serotonin showed no contractile responses on prostatic segments may be another finding to direct research aims to adrenergic systems.

In conclusion, it is clear that in addition to peripheral effects of sertraline in in vitro studies, long-term use of sertraline leads to alterations in contractility of rat isolated vas deferens and some of the alterations may be through mechanisms other than the inhibition of serotonin re-uptake such as the inhibition of calcium entry or the inhibition of NA re-uptake.

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