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INFLUENCE OF SERTRALINE ON THE ANTINOCICEPTIVE EFFECT OF MORPHINE, METAMIZOL AND INDOMETHACIN IN MICE

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Abstract: Interaction between analgesic and various psychotropic drugs constitute a subject of many research investigations. Literature data considering this issue are often inconsistent. Sertraline is one of the most potent drugs in the family of selective serotonine reuptake inhibitors (SSRIs). The influence of sertraline (5 mg/kg) on antinociceptive effect of morphine (10 mg/kg), metamizol (500 mg/kg) and indomethacin (10 mg/kg or 1.4 mg/kg) was investigated in a mouse model using the tail–flick and hot–plate tests. All drugs were injected intraperitoneally. Sertraline was administered to mice 30 min before applying the analgesic drugs. Measurement of nociception was performed within 2 h after sertraline administration. The research studies were futher conducted with multiple (14 days) drug dosage. Sertraline after single dose increased the antinociceptive effect of morphine (in the hot–plate test) and metamizol and indomethacin (only in the tail–flick test). Sertraline after 14 day administration decreased analgesic effect of morphine (only in the hot–plate test). Sertraline applied for 14 days increased the antinociceptive effect of indomethacin. Sertraline alone after multiple doses increased pain reaction time. The results of experiments suggest the role of sertraline in nociception and possibility of interaction between sertraline and analgesic drugs.

Keywords: sertraline; morphine; metamizol; indomethacin; interaction

Antidepressive drugs are applied in the treatment of pain both in patients without and with depression. Among the most often used are tricyclic antidepressants (TCAs). Amitryptylline, imipramine, doxepine and opipramol are indicated in case of cancer pain, arthritis, diabetic polyneuropathy, trigeminal neuralgia, atypical facial pains, migraine, tension headaches and psychogenic pain (1,2,3). Moreover, atypical antidepressive drugs are also applied in the treatment of pain, e.g. mianserin (4). It is likely that selective serotonine reuptake inhibitors (SSRIs) could replace TCAs in selected disease entities, especially considering fewer side effects in comparison to TCAs.

In the studies on the involvement of SSRIs drugs in antinociception it was shown that fluoxetine, citalopram and fluvoxamine increase pain perception threshold in mice and rats in a dose–dependent fashion (5,6,7). It was also shown that fluoxetine was more effective analgesic in comparison to amitryptylline in the treatment of rheumatic pain. Also side effects were seen less frequently after treatment with fluoxetine (8).

The opinion on antinociceptive activity of SSRIs administered alone or on interaction with other analgesics is far from being settled. The observation of patients treated prophylactically because of tension headache showed that amitryptylline significantly reduced the frequency and duration of headache, and also analgesic drug consumption while the administration of citalopram had no effect on these end–points (9). It was also shown that fluoxetine administered together with morphine in postoperative tooth pain decreased the analgesic activity of morphine (10).

Sertraline is a relatively new drug in the SSRIs family.

In preliminary studies, the possibility of sertraline administration in the treatment of diabetic neuropathy was shown (11). Akaoka and Astn–Jones have found that sertraline (and also fluoxetine) applied in morphine abstinence significantly decreased opioid discontinuation effect (12). Onal and Tuglular showed analgesic activity of sertraline in mice, but the results of the experiment were no dose–dependent and their interpretation was difficult (13).

The aim of the present study was to investigate in a mouse model the influence of sertraline on antinociceptive activity of analgesic drugs such as morphine, metamizol and indomethacin which are characterized by different mechanism of action, kinetics and influence on various levels of pain transmission pathways in the nervous system.

Morphine is a strong agonist of opioid μ receptors, and a weaker agonist of κ and δ receptors.

Morphine exerts its analgesic effect on various levels of the CNS:

– increases the pain threshold in the cerebral cortex;

– inhibits pain transmission in the thalamus;

– inhibits presynaptic release of substance P by the first neurone of nociceptive pathway in posterior horns of the spinal cord;

– activates serotoninergic neurones in descending pathways.

Metamizol is a non–narcotic analgesic. The mechanism of its effect is different than that of non–steroid antiinflammatory drugs (NSAIDs). It inhibits the activity of cyclooxygenase (COX) in the central nervous system. Metamizol does not show peripheral activity. There is evidence suggesting that metamizol plays a role in the activation of opioid system by affecting the periaqueduct grey matter.

Indomethacin is a strong inhibitor of COX–1. Unlike metamizol, analgesic effect of indomethacin is not based on β–endorphins.

EXPERIMENTAL

Materials

The experiments were carried out on Swiss male mice (19–25 g). The mice were housed in group cages under normal laboratory conditions at a temperature of 20–21°C, and natural day/night cycle and they had free access to commercial chow food and water. All experiments were performed between 9.00 a.m. and 2.00 p.m. The drugs were injected intraperitoneally (*i.p.*) in 0.9% NaCl. Sertraline (Sertraline hydrochloride „Pfizer", Belgium) at a dose of 5 mg/kg was given 30 min before the analgesic drugs: morphine (Morphinum hydrochloricum „Polfa", Warsaw, Poland) was given at a dose of 10 mg/kg, metamizol (Pyralgin „Polpharma" S.A., Starogard, Poland) at 500 mg/kg, indomethacin (Metindol „Polfa" S.A., Kraków, Poland) at doses of 10 and 1.4 mg/kg. In prolonged administration study all drugs were administered for 14 days.

All procedures used in these studies were approved by the Ethical Committee of Medical University Łódź, Poland (licence115, permission 119).

Methods

Nociception tests

The tail–flick test of D'Amour and Smith modified for mice were used (14). Mice were placed in retention boxes. The latency of tail withdrawal was determined by focusing a radiant heat source on the tail at about 3 cm from the tip of the tail. The temperature of heat source was 70 ± 0.2°C and maximum time of exposure was 60 s. This noxious stimulation did not cause tissue damage. The latency was measured 30, 60 and 90 min after administration of analgesic drugs. Each group consisted of 8–12 mice.

The hot–plate test was derived from that of Eddy and Leimbach (15). A plastic cylinder (height: 20 cm, diameter: 14 cm) was used to confine a mouse to a heated surface of the plate. The temperature of the plate was maintained at 52 ± 0.4°C. Maximum time of exposure was 60 s. Latencies to hind paw licking were determined 30, 60 and 90 min after treatment with analgesic. The groups consisted of 8–12 mice each.

Statistical analysis

The normality of the distribution was checked

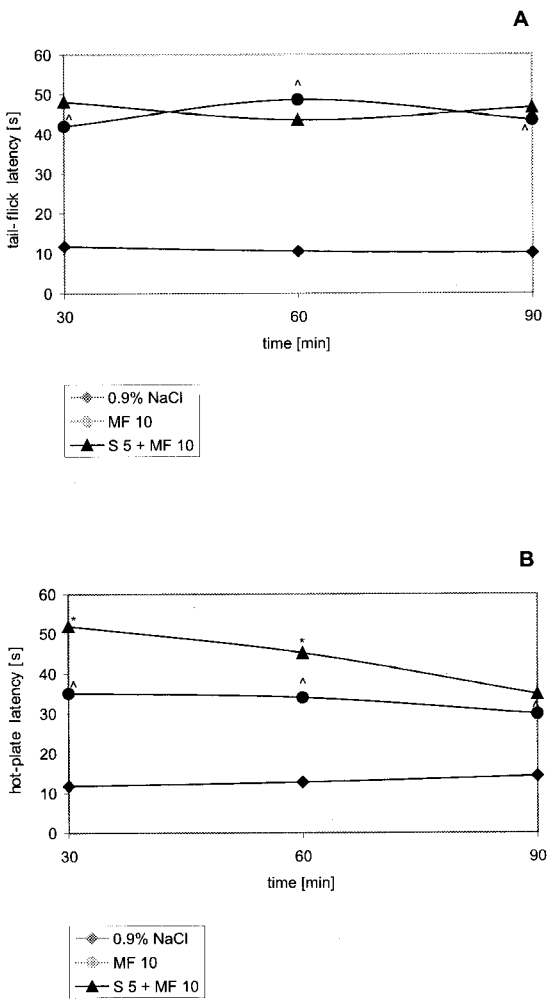

Figure 1. The antinociceptive effect on (**A**) tail–flick and (**B**) hot–plate tests after *i.p.* administration of saline (0.9% NaCl), morphine 10 mg/kg (MF 10), sertraline 5 mg/kg + morphine (S 5 + MF 10).

^ significantly different from the saline control group, $p < 0.05$

* significantly different from the morphine group, $p < 0.05$

with the Kolmogorow–Smirnow test with the Lilieforse correction and then variance equality was tested by Kruskal–Wallis (ANOVA) test. The statistical evaluation was performed by means of Mann–Whitney U–test or Wilcoxon matched pair test, by use of Statistica for Windows 4.0 programme.

RESULTS

Sertraline administered in a single dose 30 min prior to morphine administration significantly prolonged the time to pain reaction occurrence in comparison to animals in which only morphine was applied. This effect was noted in hot–plate test (Figure 1B), but was not observed in tail–flick test (Figure 1A). The administration of sertraline in a single dose together with metamizol did not significantly change the reaction of animals to pain stimulus in hot–plate test (Figure 2B), but increased antinociceptive effect of metamizol in tail–flick test (only at 60 min of observation it was statistically significant, Figure 2A). Single dose of sertraline administered together with indomethacin significantly prolonged the time to pain reaction in mice in comparison to animals in which only indomethacin alone was administered. This effect was visible only in tail–flick test (Figure 3A).

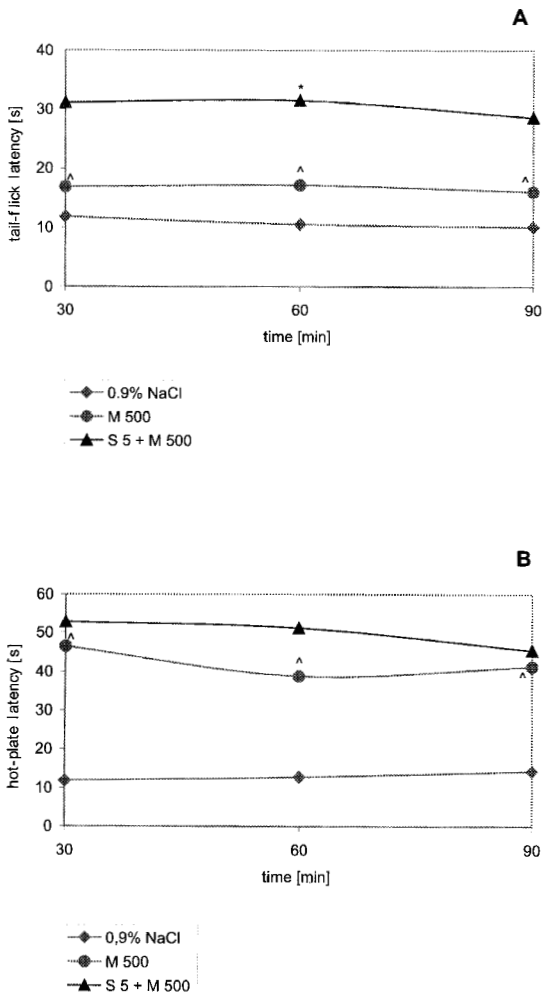

Figure 2. The antinociceptive effect on **(A)** tail–flick and **(B)** hot–plate tests after *i.p.* administration of saline (0.9% NaCl), metamizol 500 mg/kg (M 500), sertraline 5 mg/kg + metamizol (S 5 + M 500).
^ significantly different from the saline control group, $p < 0.05$
* significantly different from the metamizol group, $p < 0.05$

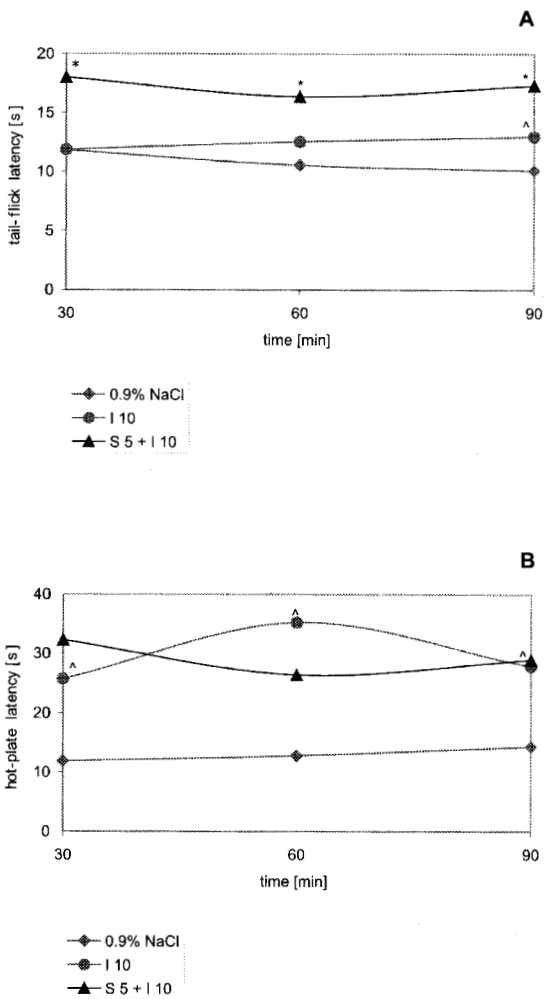

Figure 3. The antinociceptive effect on **(A)** tail–flick and **(B)** hot–plate tests after *i.p.* administration of saline (0.9% NaCl), indomethacin 10 mg/kg (I 10) , sertraline 5 mg/kg + indomethacin (S 5 + I 10).
^ significantly different from the saline control group, $p < 0.05$
* significantly different from the indomethacin group, $p < 0.05$

Sertraline with indomethacin did not change indomethacin effects in hot–plate test (Figure 3B). In mice the administration of sertraline alone in a single dose significantly prolonged the time to reaction of animals to the pain stimulus in comparison to the group which was administered 0.9% solution of NaCl. Antinociceptive activity of sertraline was observed in both tests applied (Figures 4A and 4B). Sertraline administered for 14 days together with morphine significantly shortened the time to reaction of mice to pain stimulus in comparison to the animals which were administered morphine alone. This effect was observed in hot–plate test (Figure 5B), but was not visible in tail–flick test (Figure 5A). Repeated administration of sertraline over 14 days together with metamizol did not influence the analgesic activity of metamizol in any of the tests applied (Figures 6A and 6B). Multiple administration of sertraline with indomethacin prolonged the time to reaction to the pain stimulus in mice in both tests when compared to the group receiving indomethacin alone. This effect was more pronounced in tail–flick test (Figure 7A), but in the hot–plate test a statistically significant increase of antinociceptive action was recorded only at 30 min (Figure 7B). Sertraline alone applied to mice for 14 days did not affect pain reaction time in tail–flick test (Figure 8A). In hot–plate test a decrease in pain

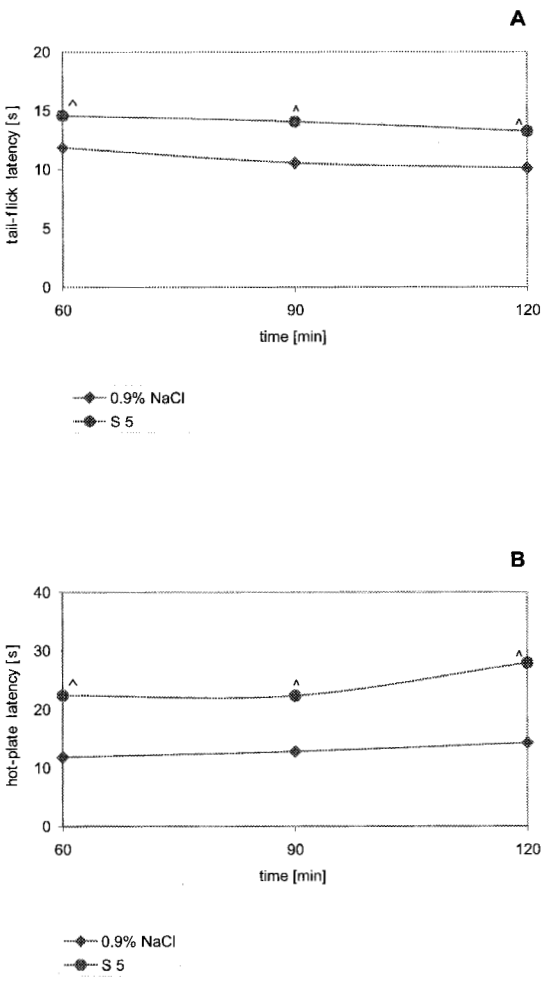

Figure 4. The antinociceptive effect on **(A)** tail–flick and **(B)** hot–plate tests after *i.p.* administration of saline (0.9% NaCl), sertraline 5 mg/kg (S 5).
^ significantly different from the saline control group, $p < 0.05$

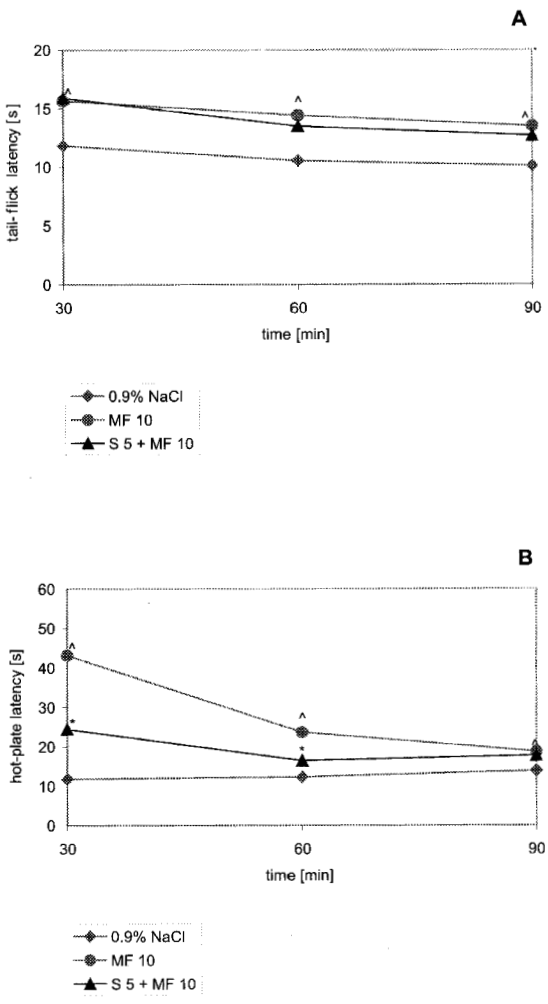

Figure 5. The antinociceptive effect on **(A)** tail–flick and **(B)** hot–plate tests after multiple *i.p.* administration of saline (0.9% NaCl), morphine 10 mg/kg (MF 10), sertraline 5 mg/kg + morphine (S 5 + MF 10).
^ significantly different from the saline control group, $p < 0.05$
* significantly different from the morphine group, $p < 0.05$

sensitivity after sertraline treatment in comparison to the group of animals which was administered 0.9% solution NaCl for 14 days was observed (Figure 8B). This effect was less pronounced after multiple than single administration of sertraline and was similar to tolerance for prolonged sertraline treatment.

DISCUSSION

Serotonine (5–HT) is produced mainly in the neurons localized in raphe nuclei situated in median line of *mesencephalon* (midbrain), pons (brainstem) and *madulla oblongata* (bulb). The nuclei situated in the brainstem send axial fibers to the spine and take part in regulation of sensory transmission, while the nuclei situated in the midbrain (*nucleus raphe dorsalis* and *nucleus raphe medianus*) send axial fibers to the structures of the limbic system, to the nuclei of the base of the brain, *hypothalamus* and *cortex cerebri*. 5–HT activates several receptor subtypes. Through its influence on postsynaptic 5–HT1 receptors it suppresses the function of the limbic system cells; this action is important for the activity of antidepressive and anxiolytic drugs. Through its action on presynaptic receptors 5HT1A and 5–HT1B it influences the serotoninergic activity (autoreceptors) and the ac-

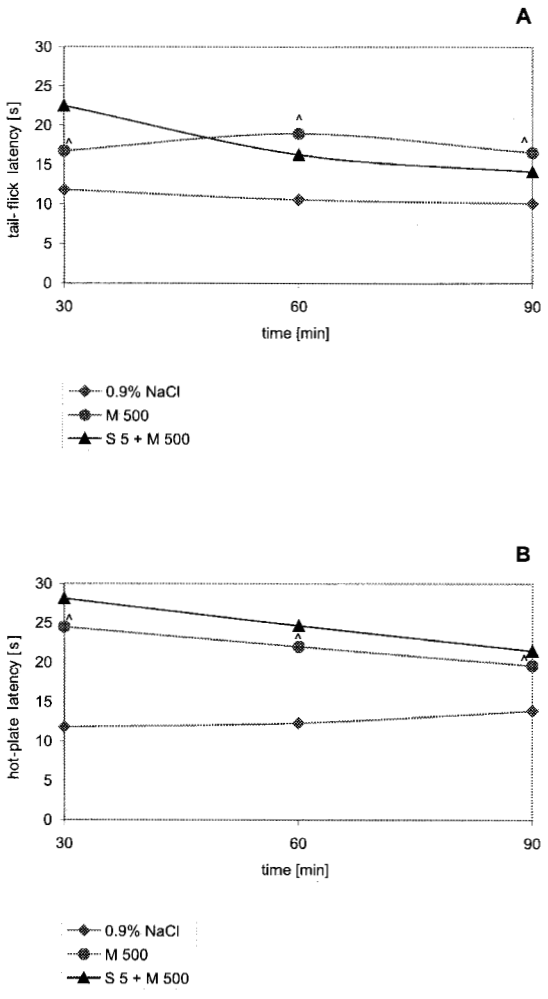

Figure 6. The antinociceptive effect on **(A)** tail–flick and **(B)** hot–plate tests after multiple *i.p.* administration of saline (0.9% NaCl), metamizol 500 mg/kg (M 500), sertraline 5 mg/kg + metamizol (S 5 + M 500)
^ significantly different from the saline control group, $p < 0.05$

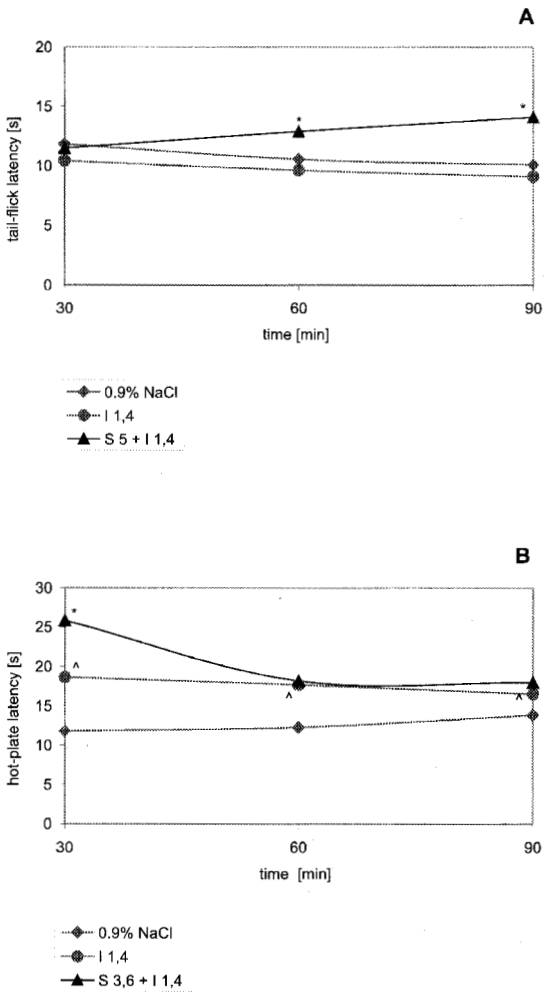

Figure 7. The antinociceptive effect on **(A)** tail–flick and **(B)** hot–plate tests after multiple *i.p.* administration of saline (0.9% NaCl), indomethacin 1.4 mg/kg (I 1.4), sertraline 5 mg/kg + indomethacin (S 5 + I 1.4).
^ significantly different from the saline control group, $p < 0.05$
* significantly different from the indomethacin group, $p < 0.05$

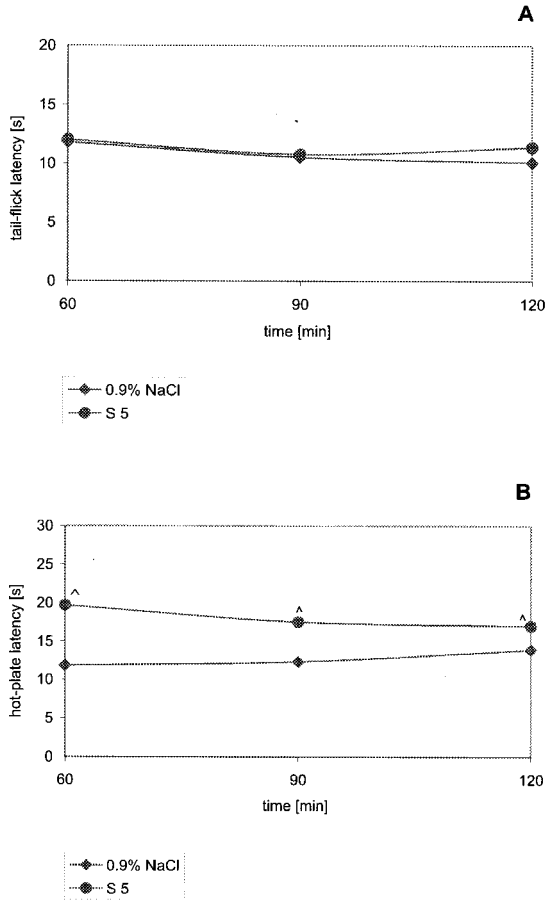

Figure 8. The antinociceptive effect on (**A**) tail–flick and (**B**) hot–plate tests after multiple *i.p.* administration of saline (0.9% NaCl), sertraline 5 mg/kg (S 5).
^ significantly different from the saline control group, $p < 0.05$

tivity of other systems (heteroreceptors). The agonists of 5–HT2 receptors lead to increased motor activity in animals while the antagonists display anxiolytic and antidepressant activity. 5–HT2 receptors are down–regulated by many antidepressive drugs. 5–HT3 receptor stimulation leads to increased release of some neurotransmitters: dopamine, noradrenaline, serotonine, γ–aminobutyric acid and neuropeptide, e.g. cholecystokinine (16).

Xu–W et al., in their experiments on rats showed that serotonine and 5–HT1A and 5–HT1B receptor agonists displayed antinociceptive activity while the agonists of 5–HT2 and 5–HT3 receptors did not exhibit such properties (6). The antinociceptive activity of 5–HT is diminished by the 5–HT2A antagonist – spiperon and non–selective 5–HT2/ 5–HT1 receptor antagonist – mianserin. 5–HT3 receptor antagonists do not influence serotonine activity (6).

These results indicate clearly the importance of 5–HT1 receptor in antinociception.

Other experiments indicate that non–selective 5–HT receptor antagonists –dotarazine and metyzergide, antagonist 5–HT1A – NAN–190, antagonist 5–HT3 – ondansetron as well as agonists of 2–HT2 (DOI) receptors and 5–HT3 (mCPBG) receptors augment pain threshold (17)]. The agonists 5–HT1A (buspirone) and mCPP (partial agonist 5–HT2C and antagonist 5–HT2A and 5–HT3) display opposite activity; buspirone administered together with analgesics decreases their analgesic activity (17,18).

Function of serotoninergic system in noxious modulation is very complicated and related to many types and particular subtypes of 5–HT–receptors. Their activation take part in both nociceptive and antinociceptive transmission in spinal and supraspinal pathways.

Sertraline is one of the most potent drugs in the family of selective serotonine re–uptake inhibitors.

In the present study, sertraline administered as a single dose displays analgesic effect both in hot–plate and in tail–flick tests; it seems that the effect is more pronounced in hot–plate test. The results of this part of experiment is consistent with the results of Ardid et al. (5).

In this study, sertraline administered in a single dose slightly increased analgesic effect of morphine in hot–plate test; administered together with metamizol – increased analgesic activity of metamizol in tail–flick test.

In earlier studies on combined administration of another SSRI – citalopram with metamizol it was found that citalopram diminished the analgesic effect of metamizol (18). Onal and Tuglular (13) have analyzed the results of experiments in which the influence of different doses of sertraline (administered *i.v.*) on behavior of mice in hot–plate test. They have come to the conclusion that the unequivocal results might be due to different (opposing) engagement of serotonine receptors. The 5–HT1B receptor takes part in analgesic effect of serotonine released at the spinal cord level; 5–HT1A receptor facilitates the transmission of nociceptive signals (13). Most probably, also in the present experiments the influence of sertraline (different to that of citalopram) on metamizol activity is depending on the dose of the antidepressant used in the study and its prevalent effect on a particular type of the receptor. In our research sertraline increased analgesic activity of indomethacin in tail–flick test (but not in hot–plate test).

Morphine administered to mice *i.p.* for 14 days has less analgesic activity than after a single dose. This phenomenon may be explained by growing tolerance to the drug. Sertraline administered together with morphine for 14 days has transient decreasing effect on analgesic activity of morphine in hot–plate test. Repeated administration of sertraline together with metamizole does not influence the analgesic activity in any of the tests performed. Repeated administration of sertraline with indomethacin increases the analgesic properties of this drug – more distinctly in tail–flick test. Sertraline alone given to mice for 14 days displays analgesic activity only in hot–plate test and it is weaker than after a single dose. It suggests the possibility of tolerance of analgesic effect of sertraline and decrease antinociceptive effect of coadministered analgesic drugs.

CONCLUSIONS

The results of this paper suggest the possibility of interaction between sertraline and often used analgesic drugs. Sertraline itself shows analgesic effect. This effect is less pronounced or it is absent after multiple doses. Sertraline may both increase and decrease antinociceptive action of analgesic drugs. These interactions are depending on the type of applied pharmaceuticals, their dosage, mode of application and experimental model. The mechanism of sertraline interaction with analgesics is complex and probably correlated to noxious transmission both in spinal and supraspinal pathways.

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