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Stimulation of 5-HT_{1A} receptors increases the seizure threshold for picrotoxin in mice

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Abstract

To evaluate the possible role of 5-HT_{1A} and 5-HT_{2A} receptors in the anticonvulsant effect of swim stress, mice were pre-treated with agonists and antagonists of these receptors prior to exposure to stress and the intravenous infusion of picrotoxin. 8-OH-DPAT ((±)-8-hydroxy-2-(di-*n*-propylamino) tetralin) and WAY-100635 (a selective agonist and antagonist of 5-HT_{1A} receptors), DOI (1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane) and ketanserin (a 5-$HT_{2A/2C}$ receptor agonist and antagonist) were used. Results demonstrated that 1 and 3 mg/kg of 8-OH-DPAT increased the doses of picrotoxin producing running/bouncing clonus, tonic hindlimb extension and death in stressed and unstressed mice, respectively. Pre-treatment with WAY (0.3 mg/kg) prevented the effect of 8-OH-DPAT (3 mg/kg). DOI (2.5 mg/kg) and ketanserin (1 mg/kg) failed to affect the seizure threshold for picrotoxin. The results show that stimulation of 5-HT_{1A} receptors exerts anticonvulsant actions in stressed and unstressed mice, while stimulation of 5-$HT_{2A/2C}$ receptors does not interfere with the effect of stress on picrotoxin-induced convulsions.

Keywords: Swim stress; Convulsions; (±)-8-hydroxy-2-(di-*n*-propylamino) tetralin hydrobromide (8-OH-DPAT); WAY-100635; 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI); Ketanserin

1. Introduction

Although the hypothalamic–pituitary–adrenal axis and the sympathoadrenal system are primarily involved in stress, it is known that many central neuronal systems, including serotonergic (5-hydroxytryptamine, 5-HT), are sensitive to stressors (Graeff et al., 1996; Chaouloff et al., 1999; López et al., 1999). Both serotonin and stress have been implicated in affective disorders, especially depression, and swim stress is often used as a biological stressor and as an animal model with predictive value for antidepressant drugs. 5-HT_{1A} and 5-HT_{2A} receptors appear to have special roles in serotonergic responses to stress and have been suggested to be involved in affective disorders and anxiety disorders. Jorgensen et al. (1998) concluded that these receptors, along with 5-HT_{2C} receptors, are involved in the stress-induced secretion of adrenocorticotropic hormone.

Recently, it has been demonstrated that swim stress produces a profound inhibition of 5-HT_{2A} receptor-mediated head twitch behaviour in mice. It has been suggested that this effect and the previously observed swim stress-induced anticonvulsant effect (Soubrie et al., 1980; Abel and Berman, 1993; Peričić et al., 1999, 2000, 2001a,b; Reddy and Rogawski, 2002; Galic et al., 2004) are produced by two separate and independent mechanisms (Peričić, 2003). It is well known that serotonin exerts its effects via at least 14 different receptor subtypes, but the role of only a few of them (5-HT_{1A}, 5-HT_{2C}, 5-HT_7) has been studied in relation to the control of seizures. A positive role (Wada et al., 1993; Salgado-Commissariat and Alkadhi, 1997; Clinckers et al., 2004), negative role (Löscher and Czuczwar, 1985; Gerber et al., 1998; Jakus et al., 2003), as well as a lack of effect (Löscher and Czuczwar, 1985; Watanabe et al., 1998) of 5-HT_{1A} receptors have been described. On the other hand, a positive role of 5-HT_{2C} (Applegate and Tecott, 1998; Jakus et al., 2003) and a negative role of 5-HT_7 receptors (Graf et al., 2004) in the control of brain excitability have been suggested.

The aim of this study was to explore whether agonists and antagonists of 5-HT_{1A} and 5-HT_2 receptors are able to modify the anticonvulsant effect of swim stress in mice. To this end, we treated non-stressed and swim-stressed animals with

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8-OH-DPAT ((±)-8-hydroxy-2-(di-*n*-propylamino) tetralin) and DOI (1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane), selective agonists, or with WAY-100635 and ketanserin, antagonists of 5-HT_{1A} and 5-$HT_{2A/2C}$ receptors, respectively.

Convulsions were produced by an i.v. infusion of picrotoxin, a non-competitive γ-aminobutyric $acid_A$ ($GABA_A$) receptor antagonist. This convulsant has been used extensively to manipulate the GABA system and to investigate its involvement in epileptic activity. Picrotoxin-induced seizures represent a model of generalised convulsive epilepsy (Mackenzie et al., 2002). As shown previously (Peričić et al., 2001a), of the GABA-related convulsants, swim stress was most effective against convulsions produced by this convulsant. We measured drug and swim stress-induced changes in doses of picrotoxin needed to produce running/bouncing clonus and tonic hindlimb extension, two convulsant signs whose onset in mice can be determined precisely. The latency to death was also registered.

2. Materials and methods

2.1. Animals

Male CBA mice (25–30 g) bred in our institute, three months old, were used. They were housed at a constant temperature (22 °C) and under a light cycle of 12-h light/12-h darkness (lights on at 7.00 a.m.). They were caged in groups of ten. Food and water were freely available. Prior to the experiment, the animals were not habituated to i.v. drug administration. The procedures used in the study were in compliance with the European Communities Council Directive of 24 November 1986 (86/609/EEC).

2.2. Stress procedure

Mice were subjected to swim stress (10-min swimming) at 18–19 °C, as previously described (Wilson and Biscardi, 1994). After swimming, the animals were dried with a towel and placed near a heater. The i.v. injection of picrotoxin started 15 min after the termination of stress. Control non-stressed animals were used for comparison.

2.3. Drugs

1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI), (±)-8-hydroxy-2-(di-*n*-propylamino) tetralin hydrobromide (8-OH-DPAT), ketanserin tartrate, WAY-100635 maleate and picrotoxin, all from Sigma (St. Louis, MO), were used. Ketanserin was dissolved in 0.1 N HCl and then diluted with distilled water. The pH was adjusted with 1 N NaOH. Picrotoxin was dissolved in warm saline, while the other drugs were dissolved in distilled water. Picrotoxin was given by constant intravenous (i.v.) infusion into a tail vein, WAY-100635 was given subcutaneously (s.c.) and the other drugs were administered intraperitoneally (i.p.) in a volume 1 ml per 100 g body weight. Depending on the experiment, 8-OH-DPAT, 1 or 3 mg/kg, was administered 65 or 30 min, respectively, before picrotoxin. Ketanserin (1 mg/kg), WAY-100635 (0.3 mg/kg), or DOI (2.5 mg/kg) was injected 65, 45, or 25 min, respectively, before picrotoxin. The dose of DOI and the time of its administration were based on the reports of Darmani (1993) and Chaouloff et al. (1994). The dose and timing of WAY-100635 administration were according to Castro et al. (2003) and Forster et al. (1995), while the timing and doses of 8-OH-DPAT administered were chosen from the study of Schreiber and De Vry (1993). While studying the anti-immobility effects of this drug in the rat forced swimming test, the authors observed that 8-OH-DPAT was four times more potent when tested 30 min (compared with 60 min) after the last (second) application. Therefore, we presumed that this time point of 8-OH-DPAT administration would be suitable for the experiment in which we planned to give the antagonist of 5-HT_{1A} receptors (WAY-100635) prior to the agonist (8-OH-DPAT). The same drug pre-treatment period (as in one of the experiments with 8-OH-DPAT) was used for ketanserin, so as not to change the experimental protocol.

Both doses of 8-OH-DPAT decreased locomotor activity. The symptom was most pronounced approximately 20 min after drug injection. Later on, the animals showed hindlimb abduction, raised or rigid Straub tail, forepaw padding, circling behaviour and tremor of the head. Ptosis was also present. All symptoms were more pronounced following the administration of 3 mg/kg than 1 mg/kg. Ketanserin decreased spontaneous activity, and the change was equally pronounced 20 and 60 min following drug injection. Following injection of WAY-100635, the animals showed grooming behaviour, rearing and sniffing. Decreased locomotor activity was observed later on. The mice injected with DOI developed characteristic head twitch behaviour.

2.4. Convulsive activity

For determination of convulsive activity, the animal was taken from its home cage and placed in a glass cylinder (20×7 cm^2) with numerous holes for ventilation. The tail of the animal was drawn through a hole of the plastic cover and warmed for 1 min under a tensor lamp. A butterfly infusion needle (length 20 mm, gage 27) was inserted into the tail vein and correct placement was verified by the appearance of blood in the infusion tubing. During the infusion, the animal was held lightly by the tip of the tail to allow free movement. The concentration of picrotoxin was 0.75 mg/ml and the infusion rate, controlled by a microinfusion pump, was 1.1 ml/min. The animal was observed throughout the infusion, and the time between the start of infusion and the onset of convulsive signs was recorded, mainly as described by Kosobud and Crabbe (1990), by an observer unaware of the treatment.

The convulsive signs were running/bouncing clonus (RB clonus, violent whole-body clonus, including running and explosive jumps) and tonic hindlimb extension (THE, characterised by extreme rigidity, with forelimbs and hindlimbs extended caudally). The onset of the two convulsant signs was easily recognised, and the experiments were highly reproducible. Sometimes after the onset of running/bouncing clonus or tonic hindlimb extension, the needle was pulled out from the vein. In such cases, we could not measure all three parameters.

Therefore, degrees of freedom in the ANOVA for the two convulsant signs and death were not always equal within one experiment.

For each animal, the dose of convulsant (milligram per kilogram of body weight) required to elicit a particular convulsant sign was calculated from the time of infusion, the infusion rate, the concentration of picrotoxin and the body weight. The time to death was also recorded. All experiments were carried out between 9 and 13 h.

2.5. Statistical analysis

Results are expressed as mean values ± standard error of the mean (S.E.M.). Statistical analysis of results was by one-way analysis of variance (ANOVA), followed by the Newman–Keuls multiple comparison test, and by two-way ANOVA, when the effects of two different treatments (stress, drug) were studied in the same experiment. *P*-values of <0.05 were considered significant.

3. Results

3.1. The effect of 8-OH-DPAT and WAY-100635 on picrotoxin-induced convulsions in unstressed and swim-stressed mice

As shown in Fig. 1A, and indicated by two-way ANOVA, in accordance with our results published previously (Peričić et al., 2000), swim stress increased the doses of picrotoxin needed to produce running/bouncing clonus [$F(1,27)=495,18$], tonic hindlimb extension [$F(1,24)=85.71$] and death [$F(1,24)=88.76$; $P<0.0001$ for all symptoms]. 8-OH-DPAT, a selective 5-HT_{1A} receptor agonist, administered in a dose of 1 mg/kg i.p. 65 min prior to picrotoxin produced significant effects: running/bouncing clonus [$F(1,27)=10.51$; $P<0.003$], tonic hindlimb extension [$F(1,24)=4.81$; $P<0.04$] and death [$F(1,24)=6.74$; $P<0.02$]. As revealed by two-way ANOVA, the interaction stress × drug was insignificant ($P>0.05$): running/bouncing clonus [$F(1,27)=3.02$], tonic hindlimb extension [$F(1,24)=2.46$] and death [$F(1,24)=3.16$]. Post hoc analysis by Newman–Keuls test indicated that 8-OH-DPAT increased significantly ($P<0.05$ or $P<0.01$) the doses of picrotoxin needed to produce convulsive symptoms and death in swim-stressed but not in unstressed animals. In comparison with the vehicle-treated stressed animals, the threshold doses of picrotoxin needed to produce the two convulsive signs and death were 11.4%, 26.6% and 33.8% greater, respectively, in 8-OH-DPAT-treated, stressed mice.

In order to find out whether blockade of 5-HT_{1A} receptors affected picrotoxin-induced seizures in a way opposite from that induced by 5-HT_{1A} receptor stimulation, we gave WAY-100635, a selective antagonist of 5-HT_{1A} receptors. This drug, administered in a dose of 0.3 mg/kg s.c., failed to produce significant changes in the doses of picrotoxin needed to produce convulsive symptoms and death (Fig. 1B), as indicated by two-way ANOVA [running/bouncing clonus: $[F(1,28)=0.174]$, tonic hindlimb extension: $[F(1,28)=0.31]$ and death: $[F(1,28)=0.00]$. The effects of stress in this experiment (running/bouncing clonus: $[F(1,28)=119.03]$, tonic hindlimb extension: $[F(1,28)=151.60]$ and death: $[F(1,28)=125.39]$) were highly significant ($P<0.0001$), as they were in the other experiments. As indicated by two-way ANOVA, the interaction drug × stress was for all symptoms insignificant (running/bouncing clonus: $[F(1,28)=0.00]$, tonic hindlimb extension: $[F(1,28)=0.26]$ and death: $[F(1,28)=0.24]$).

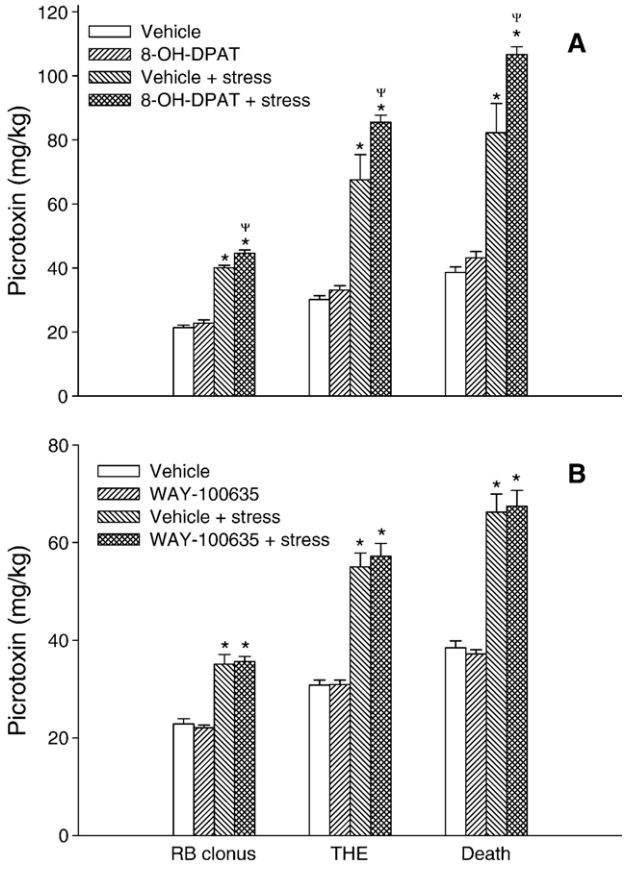

Fig. 1. Effect of 8-OH-DPAT (A) and WAY-100635 (B) on the dose of picrotoxin needed to produce convulsive signs and death in unstressed and swim-stressed mice. The convulsive signs were running/bouncing clonus (RB clonus) and tonic hindlimb extension (THE). 8-OH-DPAT (1 mg/kg) was administered 65 min prior to picrotoxin and 40 min prior to swim stress. WAY-100635 (0.3 mg/kg s.c.) was given 45 min before the infusion of picrotoxin was started and 20 min before stress. Swim stress (10-min swimming in water at 18–19 °C) ended 15 min before i.v. infusion of convulsant. Bars represent means ± S.E.M. from 6–8 animals per group. *$P<0.001$ versus dose of picrotoxin needed to produce the corresponding convulsive sign in unstressed groups; $^{\Psi}P<0.01$ versus dose of picrotoxin needed to produce the corresponding convulsive sign in the vehicle-treated stressed group (Newman–Keuls test).

3.2. The effect of combined 8-OH-DPAT and WAY-100635 treatment on picrotoxin-induced convulsions in unstressed mice

To test whether a higher dose of 8-OH-DPAT also produced a significant increase in the seizure threshold for picrotoxin in unstressed mice, and to confirm additionally the involvement of 5-HT_{1A} receptors in this effect, we treated unstressed mice with 8-OH-DPAT (3 mg/kg i.p., 30 min before picrotoxin) or with the combination of 8-OH-DPAT and the selective 5-HT_{1A} receptor blocker WAY-100635, given in a dose (0.3 mg/kg s.c.)

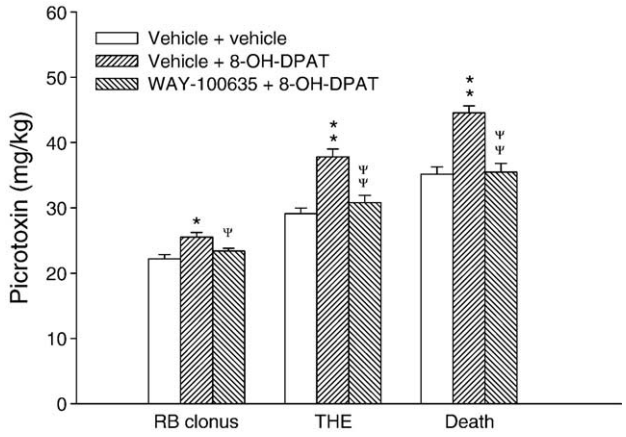

Fig. 2. The effect of combined 8-OH-DPAT and WAY-100635 treatment on picrotoxin-induced convulsions in unstressed mice. The convulsive signs were running/bouncing clonus (RB clonus) and tonic hindlimb extension (THE). 8-OH-DPAT (3 mg/kg) was administered 30 min prior to picrotoxin. WAY-100635 (0.3 mg/kg s.c.) was given 45 min before the infusion of picrotoxin was started and 20 min prior to swim stress. Swim stress (10-min swimming in water at 18–19 °C) ended 15 min before i.v. infusion of convulsant. Bars represent means ±S.E.M. from 5–6 animals per group. The results of one-way ANOVA: running/bouncing clonus [$F(2,14)=7.1$; $P<0.01$]; tonic hindlimb extension [$F(2,14)=16.68$; $P<0.0002$]; death [$F(2,14)=15.25$; $P<0.0003$]. *$P<0.01$, **$P<0.001$ versus dose of picrotoxin needed to produce the corresponding convulsive sign in control (vehicle+vehicle-treated) group; $^{\Psi}P<0.05$, $^{\Psi\Psi}P<0.001$ versus dose of picrotoxin needed to produce the corresponding convulsive sign in 8-OH-DPAT treated group (Newman–Keuls test).

which, as already mentioned, failed to alter the seizure parameters. As shown in Fig. 2 and indicated by one-way ANOVA followed by Newman–Keuls test, 8-OH-DPAT increased significantly the doses of picrotoxin needed to produce running/bouncing clonus ($P<0.01$), tonic hindlimb extension and death ($P<0.001$ for both parameters). In comparison with the threshold doses needed in control, vehicle+vehicle-treated animals, the threshold doses of picrotoxin needed to produce two convulsive signs and death were 14.9%, 29.9% and 26.7% greater, respectively, in 8-OH-DPAT-treated mice. The effect of the 5-HT_{1A} receptor agonist on running/bouncing clonus, tonic hindlimb extension and death was abolished when mice were pre-treated with the antagonist ($P<0.05$, $P<0.001$ and $P<0.001$, respectively). The seizure threshold for picrotoxin in mice subjected to combined 8-OH-DPAT and WAY-100635 treatment was not different from that observed in control animals.

3.3. The lack of effect of DOI and ketanserin on picrotoxin-induced convulsions in unstressed and swim-stressed mice

A similar stress-induced increase in the doses of picrotoxin needed to produce convulsions and death was observed in the experiment in which the possible interaction of stress with the effects of DOI, a 5-$HT_{2A/2C}$ receptor agonist, was studied. As shown in Fig. 3A, and indicated by two-way ANOVA, the effects of swim stress on threshold doses of picrotoxin needed to produce running/bouncing clonus [$F(1,21)=109.31$], tonic hindlimb extension [$F(1,21)=264.68$] and death [$F(1,20)=283.11$] were again highly significant ($P<0.0001$). DOI (2.5 mg/kg i.p.) administered immediately before stress failed to affect the doses of picrotoxin needed to produce convulsive symptoms and death: running/bouncing clonus [$F(1,21)=0.95$], tonic hindlimb extension [$F(1,21)=0.57$] and death [$F(1,20)=0.00$]. The interaction drug × stress was not significant for any of the three parameters: running/bouncing clonus [$F(1,21)=0.64$], tonic hindlimb extension [$F(1,21)=2.59$] and death [$F(1,20)=0.58$].

As shown in Fig. 3B, ketanserin (1 mg/kg i.p.), a 5-HT_2/5-HT_{2C} receptor antagonist, administered 40 min before stress and 65 min before the start of the infusion of picrotoxin, also failed to affect the doses of picrotoxin needed to induce convulsive symptoms and death in both unstressed and stressed mice. Two-way ANOVA indicated a highly significant ($P<0.0001$) anticonvulsive effect of swim stress (running/bouncing clonus [$F(1,27)=141.06$], tonic hindlimb extension [$F(1,27)=247.22$], death [$F(1,27)=330.53$]), a lack of effect of ketanserin (running/bouncing clonus [$F(1,27)=0.21$], tonic hindlimb extension [$F(1,27)=0.27$], death [F

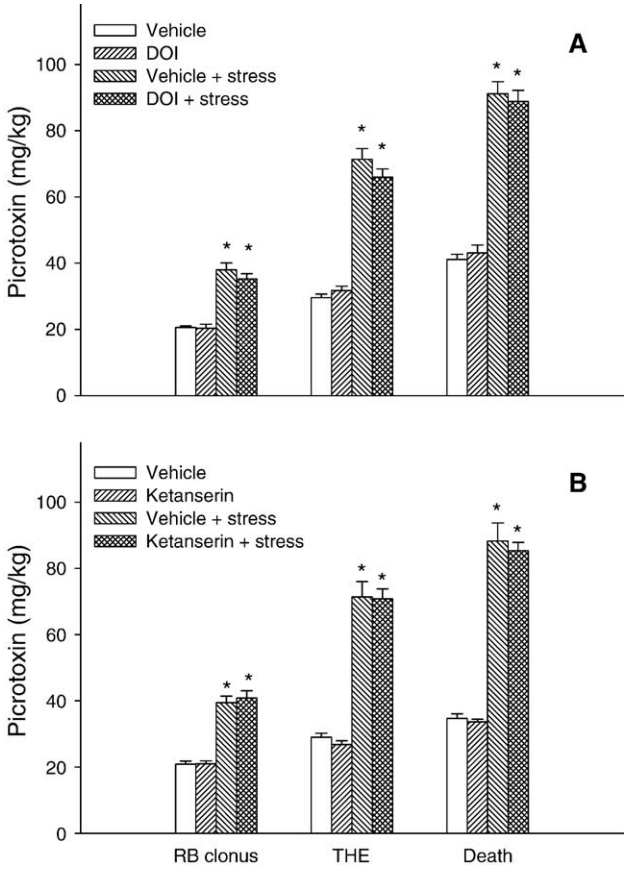

Fig. 3. The lack of effect of DOI (A) and ketanserin (B) on the dose of picrotoxin needed to produce convulsive signs and death in unstressed and swim-stressed mice. The convulsive signs were running/bouncing clonus (RB clonus) and tonic hindlimb extension (THE). DOI (2.5 mg/kg i.p.) was given immediately before stress. Ketanserin (1 mg/kg i.p.) was administered 65 min prior to picrotoxin and 40 min prior to swim stress. Swim stress (10-min swimming in water at 18–19 °C) ended 15 min before i.v. infusion of convulsant. Bars represent means±S.E.M. from 6–8 animals per group. *$P<0.001$ versus dose of picrotoxin needed to produce the corresponding convulsive sign in unstressed groups (ANOVA followed by the Newman–Keuls test).

(1,27)=0.44]), and a nonsignificant drug×stress interaction (running/bouncing clonus [$F(1,27)=0.15$], tonic hindlimb extension [$F(1,27)=0.09$], death [$F(1,27)=0.11$]).

4. Discussion

The results of the present study have confirmed and extended the data of our previous studies (Peričić et al., 2000, 2001a,b; Peričić and Švob, 2002), demonstrating a pronounced anticonvulsant effect of swim stress against convulsions induced by picrotoxin, a non-competitive $GABA_A$ receptor antagonist. Further, the study shows that 8-OH-DPAT, a selective 5-HT_{1A} receptor agonist, increased the seizure threshold for picrotoxin in unstressed and swim-stressed mice. In swim-stressed mice this effect was achieved with a lower dose of 8-OH-DPAT than in unstressed mice. WAY-100635, a selective antagonist of 5-HT_{1A} receptors, was inactive per se, but it abolished the 8-OH-DPAT-induced augmentation of the seizure threshold for picrotoxin in unstressed mice. DOI, a 5-$HT_{2A/2C}$ receptor agonist, and ketanserin, the 5-$HT_{2A/2C}$ receptor antagonist, failed to produce an effect either in stressed or in unstressed animals.

The anticonvulsant effect of swim stress has been noticed by several groups (Soubrie et al., 1980; De Lima and Rae, 1988; Abel and Berman, 1993; Reddy and Rogawski, 2002; Galic et al., 2004), as well as by ours (Peričić et al., 1999, 2000, 2001a, b). The effect is not restricted to the GABA-related convulsants used in most of these studies, since it was also observed with some GABA-unrelated convulsants (Peričić et al., 2001a; Galic et al., 2004). The anticonvulsant effect of swim stress could not be counteracted by adrenalectomy (Peričić et al., 1999) or by lesion of noradrenergic neurons (Peričić and Švob, 2002). Two groups of authors suggested the involvement of α_2-adrenoceptors (Peričić et al., 2001b; Galic et al., 2004), and one group the role of neurosteroids (Reddy and Rogawski, 2002), although the latter presumption did not find support in another study (Peričić et al., 2000).

As in our previous studies, the anticonvulsant effect of swim stress observed in the present study was very pronounced, e.g. swim stress more than doubled the dose of picrotoxin needed to produce tonic hindlimb extension and death.

As shown in Fig. 1A, stimulation of 5-HT_{1A} receptors by 8-OH-DPAT (1 mg/kg) produced a significant anticonvulsant effect only in stressed animals. In unstressed mice, the observed smaller increase in the seizure threshold failed to reach the level of statistical significance. The fact that swim stress is able to induce changes in the effect of 5-HT_{1A} agonists has already been reported (Briones-Aranda et al., 2002), although the results appear to be in contradiction with our results. However, Briones-Aranda et al. used substantially lower doses of 8-OH-DPAT, and behavioural testing was performed 24 h and not 15 min after swim stress, which also differed from our model. Bearing in mind that swim stress produces profound changes in the brain 5-HT system (Kirby et al., 1995; Adell et al., 1997; Tan et al., 2004), a different effect of drugs affecting serotonergic transmission, following swim stress, should not be surprising.

As shown in Fig. 2, a higher dose of 8-OH-DPAT increased the seizure threshold for picrotoxin in unstressed mice as well, and this effect was abolished following pre-treatment with WAY-100635, a 5-HT_{1A} receptor antagonist, suggesting that stimulation of 5-HT_{1A} receptors decreases the susceptibility to seizures. At variance with these conclusions are the conclusions of Löscher and Czuczwar (1985), who reported that 8-OH-DPAT was either without effect (rats) or that it even decreased the seizure threshold for pentylenetetrazol (mice). However, the latter experiments were performed only in unstressed animals and with a lower dose of 8-OH-DPAT (0.5 mg/kg). Most other studies suggested a positive role of 5-HT_{1A} receptors in the control of brain excitability (Wada et al., 1993; Gariboldi et al., 1996; Salgado-Commissariat and Alkadhi, 1997; Watanabe et al., 2000; Tokarski et al., 2002). Moreover, Lu and Gean (1998) suggested the involvement of 5-HT_{1A} receptors in the effects of the antidepressant drug fluoxetine, since a 5-HT_{1A} receptor antagonist blocked the inhibition of epileptiform activity induced by this drug. In contrast, another group of authors (Gerber et al., 1998; Jakus et al., 2003) obtained different results when using the same drugs but a different experimental model. Hence, although most experimental data in animals suggest that serotonin acting via 5-HT_{1A} receptors mediates an antiepileptic and anticonvulsant effect, there are studies that show the opposite (Löscher and Czuczwar, 1985; Gerber et al., 1998; Jakus et al., 2003) or no effect (Löscher and Czuczwar, 1985; Watanabe et al., 1998).

As shown in Results, both 8-OH-DPAT and stress had a greater effect on picrotoxin-induced tonic hindlimb extension than on running/bouncing clonus, which is in accordance with the suggestion that the convulsive responses which appear following the administration of convulsants represent qualitatively distinct seizure components mediated by separable and independent anatomical circuits located in the forebrain and hindbrain (Gale, 1988).

Although it has been shown that swim stress produces a very profound inhibition of 5-HT_{2A} receptor-mediated behaviour (Peričić, 2003), neither DOI, an agonist, nor ketanserin, an antagonist of 5-HT_{2A} receptors, affected the convulsions produced by picrotoxin infusion, confirming our previous suggestion that swim stress-induced inhibition of head twitch behaviour does not appear to be related to the swim stress-induced anticonvulsant effect. However, Wada et al. (1997) reported that DOI facilitated the development of amygdala kindling in rats.

In conclusion, our results show that 8-OH-DPAT, a selective 5-HT_{1A} receptor agonist, increases the seizure threshold for picrotoxin in unstressed and swim-stressed mice. Additionally, the results suggest that swim stress-induced anticonvulsant activity, observed in this and many other studies, and the swim stress-induced inhibition of 5-HT_{2A} receptor-mediated behaviour observed in our previous study (Peričić, 2003) are not directly linked.

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