Effects of GABA$_B$ receptor ligands in animal tests of depression and anxiety

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Abstract:

Preclinical evidence strongly implicates GABA$_B$ receptors in the pathophysiology of several psychiatric disorders including anxiety and depression. In the present study, we investigated the effects of the selective GABA$_B$ receptor agonists baclofen and SKF 97541, the GABA$_B$ receptor positive allosteric modulator CGP 7930 and the GABA$_B$ receptor antagonist SCH 50911 in the modified forced swimming test (FST) and in the elevated zero maze test (EZM), i.e. in animal models predictive of antidepressant and antianxiety activities, respectively. The classical antidepressant imipramine and the anxiolytic diazepam were employed as control drugs in the FST and in the EZM, respectively.

In the FST, baclofen (0.25 mg/kg), SKF 97541 (0.01–0.05 mg/kg) or CGP 7930 (1–3 mg/kg) and SCH 50911 (1–3 mg/kg) showed antidepressant-like activity, significantly decreasing immobility time; these effects were not related to changes in locomotor activity. The antidepressant effects produced by the GABA$_B$ receptor ligands were compared with that of imipramine (30 mg/kg). In the EZM, CGP 7930 (1 mg/kg) and SCH 50911 (1–3 mg/kg) produced anxiolytic-like effects, significantly increasing time spent in the open areas of the maze; those effects were comparable with the effects of diazepam (1–2 mg/kg).

Our results indicate that differential manipulation of GABA$_B$ receptors can modify behaviors relevant to depression and anxiety. The GABA$_B$ receptor positive allosteric modulator CGP 7930 and the antagonist SCH 50911 show both antidepressant and anxiolytic profile, while the GABA$_B$ receptor agonists (baclofen and SKF 97541) produce effects that are characteristic of antidepressant drugs.

Key words:
GABA$_B$ receptor ligands, elevated zero maze, forced swim test, rats

Introduction

γ-Aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the mammalian central nervous system, where it acts on two receptor classes: ionotropic (GABA$_A$ and GABA$_C$) and metabotropic GABA$_B$ receptors. The GABA$_A$ and GABA$_C$ receptors, located mostly postsynaptically, are coupled with Cl$^-$ channels and mediate fast synaptic inhibition [4]. The GABA$_B$ receptors are coupled to G proteins and form a heterodimer of GABA$_{B1}$ – existing in two N-termi-nal splice variants (1a and 1b) – and GABA$_{B2}$ sub-units, both necessary for GABA$_B$ receptors to be functionally active [5, 9, 18, 22]. The GABA$_B$ receptors modulate neurotransmitter release by presynaptic depressing Ca^{2+} influx *via* voltage-activated Ca^{2+} channels and by postsynaptic increasing K$^+$ conductance, engaged in slow synaptic inhibition [8].

Preclinical evidence strongly implicates GABA$_B$ receptors in the pathophysiology of several psychiatric disorders including anxiety and depression [32]. For example, in animal models GABA$_{B1}$ and GABA$_{B2}$ receptor knockout mice exhibit more anxious beha-

vior and altered depression-related activity [23, 24]. In line with the above observations, antidepressant-like effects in a number of experimental models including forced swimming test (FST), learned helplessness, olfactory bulbectomy or chronic mild stress, have been demonstrated after several GABA$_B$ receptor antagonists [28, 30, 37], but not after its agonists [25, 26, 30] or positive modulators [37]. On the other hand, a positive modulator of GABA$_B$ receptors has been shown to produce anxiolytic activity [11].

In the present study, we investigated the effects of GABA$_B$ receptor ligands in animal models predictive of antidepressant and antianxiety activities. We examined the effects of the selective GABA$_B$ receptor agonists baclofen and SKF 97541 [8, 17, 34], the GABA$_B$ receptor allosteric positive modulator CGP 7930 [38] and the GABA$_B$ receptor antagonist SCH 50911 [6] in the modified FST and in the elevated zero maze test (EZM), respectively. The classical antidepressant imipramine and the anxiolytic diazepam were employed as control drugs in the FST and in the EZM, respectively.

Materials and Methods

Animals

The experiment was performed on male Wistar rats (280–300 g). They were housed in groups of six to eight per cage in standard plastic rodent cages (57 × 35 × 20 cm), at a room temperature of $20 \pm 1°C$ and 12-h light/dark cycle (light on 06:00–18:00 h). The rats had free access to food (Labofeed pellets) and water. All the experiments were approved by the Local Committee for the Welfare of Laboratory Animals and Ethics and met the international guidelines for the care and use of laboratory animals.

Drugs

The following drugs were used (in parentheses: full chemical names and suppliers): (R)-baclofen (Tocris Cookson, Bristol, UK), CGP 7930 (3,5-*bis*(1,1-dimethylethyl)-4-hydroxy-β,β-dimethyl-benzenepropanol; Tocris Cookson, Bristol, UK), diazepam hydrochloride (Polfa, Warszawa, Poland), imipramine hydrochloride, (Pliva, Kraków, Poland), SKF 97541 (3-aminopropyl(methyl)phosphinic acid; Tocris Cookson,

Bristol, UK) and SCH 50911 ((+)-5,5-dimethyl-2-morpholineacetic acid hydrochloride; Tocris Cookson, Bristol, UK). The drugs were dissolved in saline, except for CGP 7930 which was dissolved in 2 drops of ethanol and diluted as required in a 1% aqueous solution of Tween 80 (Sigma-Aldrich, USA) and diazepam which was dissolved in a 1% aqueous solution of Tween 80. All the drugs were injected in a volume of 1 ml/kg *ip* at a single dose. (R)-baclofen, CGP 7930, diazepam and SKF 97541 were given 30 min, SCH 50911 was given 45 min, and imipramine was given 60 min before behavioral tests.

The forced swimming test (FST)

On the 1st day of the FST, the rats placed individually in a cylinder (50 cm high × 23 cm in diameter) filled to a 30-cm depth with water ($25 \pm 1°C$) for 15 min and then were removed from the water, dried with towels and placed in a warmer enclosure for 15 min then returned back to their home cages, as described previously [13, 14]. The cylinders were emptied and cleaned between rats. At 24 h after the forced swim (the 2nd day of the FST) rats were retested for 5 min (300 s) under identical conditions. Retest sessions were scored by two observers unaware of the treatment condition, and the following behavioral parameters were measured: immobility, swimming or climbing. A rat was rated to be immobile if it was making only movements necessary to keep its head above water; swimming behavior was recorded if a rat was actively making swimming movements that caused it to move within the centre of cylinder and swim below the surface of water (diving); climbing behavior was recorded if a rat was making forceful thrashing movements with its forelimbs against the walls of cylinder. All parameters were measured manually. The data are expressed as the mean time ($\pm$ SEM) of behavior under study within the 300-s observation period. The one-way analysis of variance (ANOVA), followed by *post-hoc* Dunnett's test, was applied to evaluate statistical significance of differences between the treatment and control group. Six to eight animals were used per group.

The elevated zero-maze (EZM)

The EZM as originally described by Shepherd et al. [36]. The maze comprised a black annular platform (105 cm in diameter, 10 cm wide) elevated to 65 cm above the ground level, divided equally into four
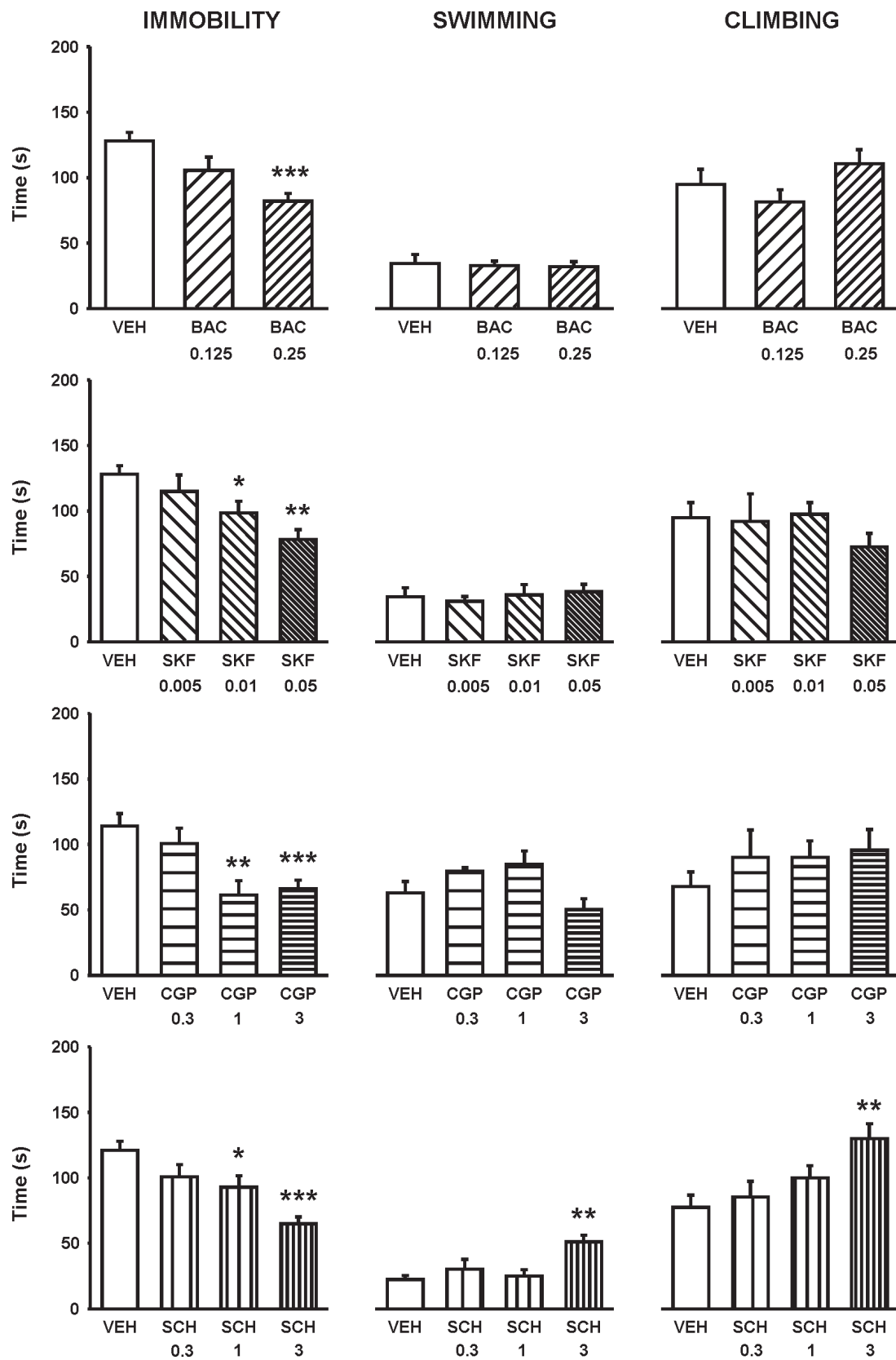
Fig. 1. Effects of baclofen (BAC), SKF 97541 (SKF), CGP 7930 (CGP) and SCH 50911 (SCH) on the immobility, swimming and climbing in the FST. * p < 0.05, ** p < 0.01, *** p < 0.001 *vs.* vehicle (VEH). N = 6–8 rats/group

quadrants: two opposing 'open' quadrants without walls (1 cm lip) and two opposing 'closed' quadrants (27 cm high walls). The apparatus was illuminated by a dim white light (30–50 lux). Rats were placed on a closed quadrant of the maze and a 5-min (300-s) test period was recorded. The maze was cleaned with water and dried thoroughly between test sessions. Behavioral measures comprised time spent in the open areas, frequency of head dips over the edge of the platform when animal was located in either the open or the end of the closed quadrants, and frequency of stretched attend postures from closed to open quadrants. The data are expressed as the mean time spent in the open areas ($\pm$ SEM) or mean frequency ($\pm$ SEM) of behavior under study within the 300-s observation period. The one-way ANOVA, followed by *post-hoc* Dunnett's test, was applied to evaluate statistical significance of differences between the treatment and control group. Six to eight animals were used per group.

Locomotor activity measurement

Locomotor activity was recorded individually for each animal in Opto-Varimex cages (Columbus Instruments, Columbus, USA) linked on-line to an IBM compatible PC. Each cage (43 × 44 cm) was equipped with 15 infrared emitters located on the *x* and *y* axes, 3 cm from the floor and with the same number of receivers on the opposite walls of the cage. The rats' behavior was analyzed using Auto-track software (Columbus Instruments, Columbus, USA). Locomotor activity was defined as a breakage of three consecutive photo-beams. Locomotor activity was recorded for 30 min in 5-min periods. The data are expressed as the mean distance traveled (cm) in time ($\pm$ SEM). The one-way ANOVA, followed by *post-hoc* Dunnett's test, was applied to evaluate statistical significance of differences between the treatment and control group. Six to eight animals were used per group.

Results

The FST

Effects of GABA$_B$ receptor ligands

Treatment with baclofen (0.125–0.25 mg/kg) significantly altered the time of immobility [$F_{(2, 19)} = 9.04$, $p < 0.001$], but not swimming [$F_{(2, 19)} = 0.06$] or climbing [$F_{(2, 19)} = 1.75$]. Baclofen at a dose of 0.25 mg/kg significantly decreased (by 36%) the immobility time (Fig. 1).

Treatment with SKF 97541 (0.005–0.05 mg/kg) significantly altered the time of immobility [$F_{(3, 26)} = 5.28$, $p < 0.01$], but not swimming [$F_{(3, 26)} = 0.25$] or climbing [$F_{(3, 26)} = 0.58$]. SKF 97541 at doses of 0.01 and 0.05 mg/kg significantly decreased (by 23% and 39%, respectively) the immobility time (Fig. 1).

Treatment with CGP 7930 (0.3–3 mg/kg) significantly altered the time of immobility [$F_{(3, 26)} = 7.19$,
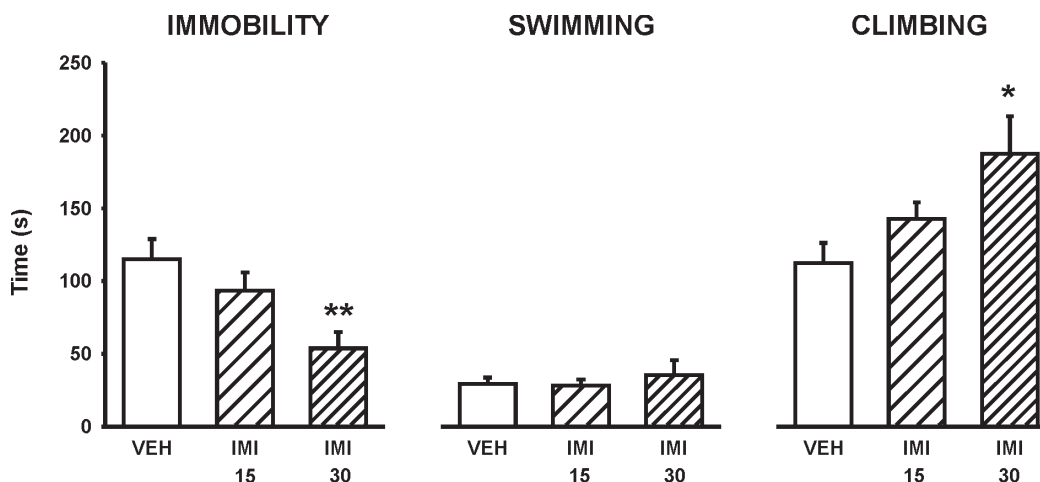

Fig. 2. Effects of imipramine (IMI) on the immobility, swimming and climbing in the FST. * $p < 0.05$, ** $p < 0.01$ *vs.* vehicle (VEH). N = 6–8 rats/group
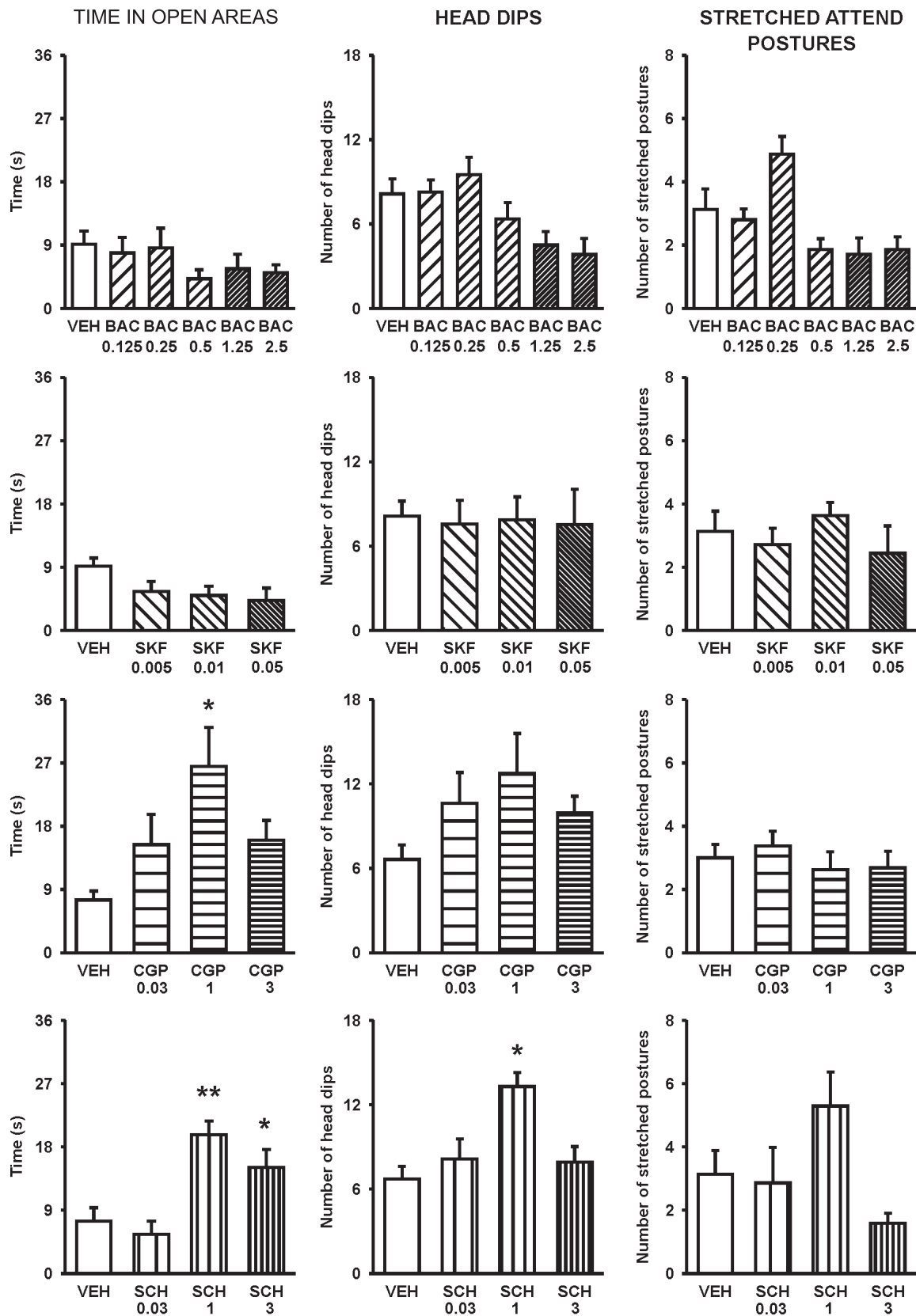
Fig. 3. Effects of baclofen (BAC), SKF 97541 (SKF), CGP 7930 (CGP) and SCH 50911 (SCH) on the time spent in the open areas, the number of head dips and the number of stretched attend postures in the EZM. * $p < 0.05$, ** $p < 0.01$ *vs.* vehicle (VEH). N = 6–8 rats/group

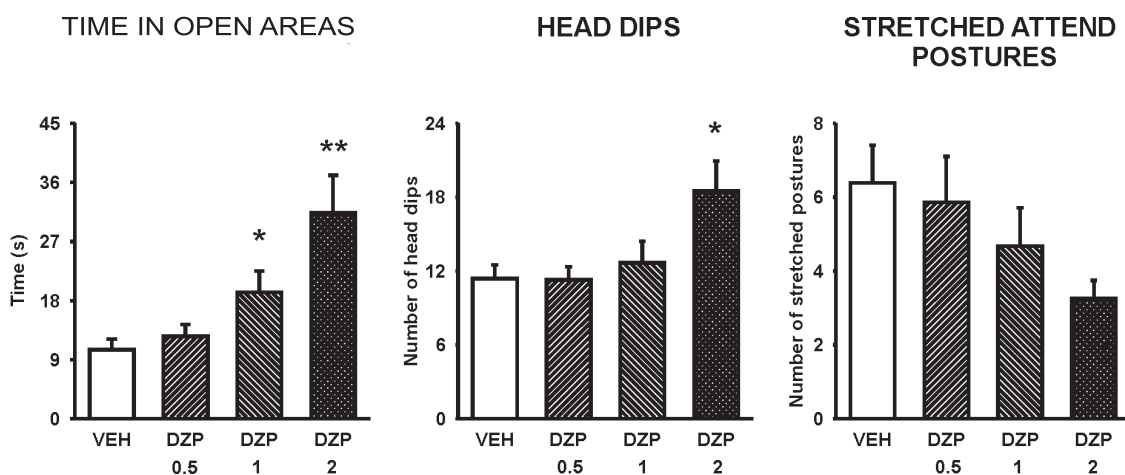**TIME IN OPEN AREAS**   **HEAD DIPS**   **STRETCHED ATTEND POSTURES**

Fig. 4. Effects of diazepam (DZP) on the time spent in the open areas, the number of head dips and the number of stretched attend postures in the EZM. * $p < 0.05$, ** $p < 0.01$ *vs.* vehicle (VEH). N = 6–8 rats/group

$p < 0.001$], but not swimming [$F(3, 26) = 3.38$] or climbing [$F(3, 26) = 0.71$]. CGP 7930 at doses of 1 and 3 mg/kg significantly decreased (by 46% and 42%, respectively) the immobility time (Fig. 1).

Treatment with SCH 50911 (0.3–3 mg/kg) significantly altered the time of immobility [$F(3, 25) = 9.29$, $p < 0.001$], swimming [$F(3, 25) = 6.32$, $p < 0.01$] and climbing [$F(3, 25) = 4.88$, $p < 0.01$]. SCH 50911 at doses of 1 and 3 mg/kg significantly decreased (by 23% and 46%, respectively) the immobility time, while its dose of 3 mg/kg significantly increased swimming and climbing (Fig. 1).

Effects of imipramine

Treatment with imipramine (15–30 mg/kg) significantly altered the time of immobility [$F(2, 21) = 6.22$, $p < 0.01$] and climbing [$F(2, 21) = 4.27$, $p < 0.05$], but not swimming [$F(2, 21) = 0.31$]. Imipramine at a dose of 30 mg/kg significantly decreased (by 53%) the immobility time and increased climbing (by 67%) (Fig. 2).

The EZM

Effects of GABA_B receptor ligands

Treatment with baclofen (0.125–2.5 mg/kg) did not significantly alter the time spent in the open quadrants [$F(5, 39) = 1.03$] or the number of head dips [$F(5, 39) = 1.26$], but increased the number of stretched attend postures [$F(5, 39) = 6.29$, $p < 0.001$].

However, *post- hoc* analysis revealed that no dose of baclofen altered the number of stretched attend postures (Fig. 3).

Treatment with SKF 97541 (0.005–0.5 mg/kg) did not significantly alter the time spent in the open quadrants [$F(3, 26) = 1.84$], the number of head dips [$F(3, 26) = 0.09$] or the number of stretched attend postures [$F(3, 26) = 0.88$] (Fig. 3).

Treatment with CGP 7930 (0.03–3 mg/kg) significantly altered the time spent in the open quadrants [$F(3, 28) = 4.14$, $p < 0.05$], but not the number of head dips [$F(3, 28) = 1.68$] or the number of stretched attend postures [$F(3, 28) = 0.49$]. CGP 7930 at a dose of 1 mg/kg significantly increased the time spent in open areas (Fig. 3).

Treatment with SCH 50911 (0.03–3 mg/kg) significantly altered the time spent in the open quadrants [$F(3, 24) = 8.29$, $p < 0.001$], the number of head dips [$F(3, 24) = 5.81$, $p < 0.01$] and the number of stretched attend postures [$F(3, 24) = 3.06$, $p < 0.05$]. SCH 50911 at doses of 1 and 3 mg/kg significantly increased the time spent in the open areas, while a dose of 1 mg/kg increased the number of head dips. *Post-hoc* analysis revealed that no dose of SCH 50911 significantly altered the number of stretched attend postures (Fig. 3).

Effects of diazepam

Treatment with diazepam (0.5–2 mg/kg) significantly altered the time spent in the open quadrants [$F(3, 28) = 6.82$, $p < 0.01$] and the number of head dips
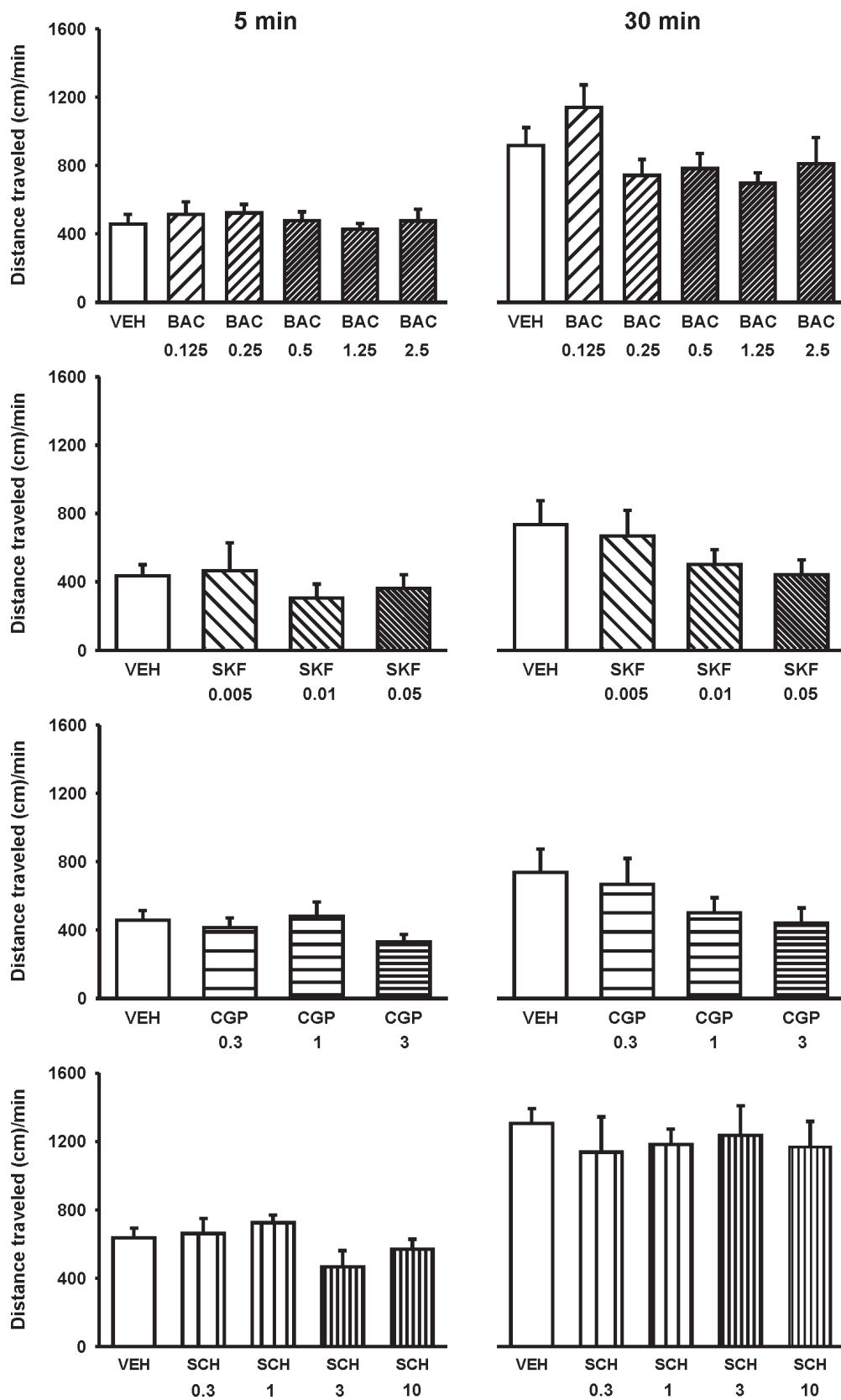
Fig. 5. Effects of baclofen (BAC), SKF 97541 (SKF), CGP 7930 (CGP) and SCH 50911 (SCH) on the basal locomotor activity in 5- and 30-min trials. N = 6–8 rats/group

[$F(3, 28) = 3.86$, $p < 0.05$], but not the number of stretched attend postures [$F(3, 28) = 1.99$]. Diazepam at doses of 1 and 2 mg/kg significantly increased the time spent in the open areas, while a dose of 2 mg/kg increased the number of head dips and a trend to reduce stretched attend postures was also seen (Fig. 4).

Basal locomotor activity

Neither of the $GABA_B$ receptor ligands showed significant effects on basal locomotor activity recorded during either 5- or 30-min trial (Fig. 5).

As shown in Table 1, treatment with imipramine (30 mg/kg) significantly decreased basal locomotor activity recorded in 5- or 30-min trials [$F(1, 14) = 8.05$, $p < 0.01$; $F(1, 14) = 39.3$, $p < 0.001$, respectively].

Treatment with diazepam (0.5–2 mg/kg) significantly altered the basal locomotor activity recorded in a 30-min trial [$F(3, 24) = 6.63$, $p < 0.01$], but not in a 5-min trial [$F(3, 24) = 2.19$]. *Post-hoc* analysis revealed that diazepam at a dose of 2 mg/kg significantly decreased basal locomotor activity in a 30-min trial (Tab. 1).

Tab. 1. Effects of imipramine and diazepam on the locomotor activity in 5- and 30-min trials

Treatment	Dose (mg/kg)	Time		N
		5 min	30 min	
Vehicle	–	800.3 ± 99.3	1797.6 ± 87.4	8
Imipramine	30	484.5 ± 50.6**	910.2 ± 111.3***	8
Vehicle	–	762.8 ± 53.6	1572.6 ± 144.8	7
Diazepam	0.5	905.9 ± 78.3	1565.2 ± 123.7	7
	1	614.6 ± 86.5	1136.3 ± 87.7	7
	2	759.1 ± 92.3	950.4 ± 130.5**	7

** $p < 0.01$, *** $p < 0.001$ *vs.* vehicle. N = number of rats per group

Discussion

Results of the present study demonstrate that $GABA_B$ receptor ligands, like the tricyclic antidepressant imipramine, exhibit antidepressant-like effect by reducing immobility time in the FST in rats. The effect seems to be specific as it has been demonstrated after administration of the ligands at doses which alone do not affect basal locomotor activity of the animals.

While such an effect induced by SCH 50911, a $GABA_B$ receptor antagonist, is in line with several reports on other antagonists of those receptors [32], the antidepressant-like activity of the $GABA_B$ receptor agonists (baclofen, SKF 97541) and $GABA_B$ receptor positive allosteric modulator (CGP 7930) is rather unexpected. In fact, baclofen and another $GABA_B$ receptor agonist CGP 44532 as well as the $GABA_B$ receptor positive modulator GS 39783 have been described to be ineffective in the FST in mice and/or rats [7, 23, 25–27, 37]. Moreover, baclofen has been reported to antagonize anti-immobility effect of antidepressant drugs in rats [26] and when administered chronically, it has been found to be inactive in the learned helplessness paradigm and attenuated effect of desipramine in this model predictive of antidepressant activity [26]. The discrepancy between the above-mentioned and our present results comes the most probably from the dose range of the ligands. In fact, in the above-cited studies, baclofen has been administered at the relatively high doses (2.5–10 mg/kg) which were reported to produce sedative effects and no antidepressant-like actions [2, 11]. At the same time, lower doses of baclofen given to mice (0.5–1 mg/kg; [2]) or to male and female rats (0.125–0.25 mg/kg; [10, present study]) displayed anti-immobility effects in the FST.

We also observed antidepressant-like activity of the $GABA_B$ receptor antagonist SCH 50911 administrated at doses of 1–3 mg/kg, sufficient to block a number of peripheral and central effects of $GABA_B$ receptor agonist baclofen [6]. The antidepressant-like activity of SCH 50911 is supported by numerous reports indicating similar effect following the administration of other $GABA_B$ receptor antagonists, including CGP 36742, CGP 51176, CGP 56433A, CGP 55845A [32, 37]. Importantly, the above antagonists were found to be active not only in the FST but also in other models of depression, including chronic mild stress-induced anhedonia, learned helplessness paradigm and/or olfactory bulbectomy model of depression [28, 30, 37]. It is also noteworthy that up-regulation of the $GABA_B$ receptor binding has been found after repeated administration of both antidepressant drugs and the $GABA_B$ receptor antagonists [21, 30, 33]. Finally, antidepressant-like activity of the $GABA_B$ receptor

antagonist is in accord with data obtained in knockout mice, showing that the GABAB −/− animals exhibited reduced immobility in the FST [23, 24].

As far as anxiolytic-like activity is concerned, we observed such profile for CGP 7930, SCH 50911 and diazepam (the latter drug used as a positive control), but not for baclofen (even administered at a dose of 10 times higher than that producing an antidepressant effect) or SKF 97541 in the EZM. Our negative results with baclofen support an earlier observation showing its lack of effect in the elevated plus maze test in mice [12] and rats [39] as well as in the Vogel conflict test in rats [1]. On the other hand, antianxiety effects of baclofen have been observed in different models in mice and rats [3, 19, 29, 35]. Moreover, anxiolytic-like activity has been reported after the positive allosteric modulator GS 39783, though, like in the case of CGP 7930, its dose-response relationship was very poor [11, 23]. Controversial results have also been published on anxiolytic activity of the GABAB receptor antagonists. In contrast to our observation on SCH 50911, another GABAB receptor antagonist CGP 35348 has been found to be inactive in the elevated plus maze test and in the light-dark box test in mice [12, 23]. Furthermore, it has been reported that the GABAB receptor knockout mice exhibit elevated anxiety-like behavior. On the other hand, Zarrindast et al. [39] have shown antianxiety effect of CGP 35348 administered intracerebroventricularly in the elevated plus maze test in rats, while Partyka et al. [31] have reported the anxiolytic activity of the GABAB receptor antagonist CGP 3674 in several rodent tests.

In general, results of the present study do not support the recently presented concept that the GABAB receptor antagonists may be regarded as potential antidepressant drugs, while agonists of these receptors display antianxiety activity [32]. Since we observed antidepressant-like and antianxiety activities for both agonists and antagonist of GABAB receptors, the problem of psychotropic effects of the GABAB receptor ligands seems to be more complicated. Macey et al. [20], who found that both the GABAB receptor agonists and antagonists modulated in the same direction intracranical self-stimulation behavior in rats, suggested that it may results from differential effects of the GABAB receptor ligands on pre- and post-synaptic GABAB receptors. Similar suggestions were presented in recent papers from our laboratory, in which it was found that both agonists and antagonist

of GABAB receptors attenuated discriminative stimulus effect of single doses of cocaine [16] or cocaine-induced seeking behavior in self-administration procedures [15]. Interestingly, Zarrindest et al. [39], who found that anxiolytic activity CGP 35348 was antagonized by bicuculline, speculated that the former agent (*via* the blockade of presynaptic GABAB receptors) increased GABA release, which then stimulated the GABAA receptor and reduced anxiety. Whether similar mechanism(s) may be involved in the antidepressant and antianxiety effects of the GABA receptor ligands remain to be elicidated, especially when selective agonists and antagonists of pre- and post-synaptic receptors will be available.

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