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Baclofen, a Selective $GABA_B$ Receptor Agonist, Dose-Dependently Impairs Spatial Learning in Rats

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McNAMARA, R. K. AND R. W. SKELTON. *Baclofen, a selective $GABA_B$ receptor agonist, dose-dependently impairs spatial learning in rats.* PHARMACOL BIOCHEM BEHAV 53(2) 303–308, 1996.—The present investigation assessed the effects of the selective $GABA_B$ receptor agonist baclofen (1, 3, and 6 mg/kg) on spatial learning in the Morris water maze, an aversively motivated spatial learning task. Potential anxiolytic and sedative effects of baclofen were also assessed in an open field. Baclofen dose-dependently reduced locomotion in the open field but had little effect on thigmotaxia (anxiety). In the water maze, baclofen dose-dependently impaired spatial learning and reduced swim speed. During the probe trial given after training, only rats treated with the highest dose of baclofen (6 mg/kg) failed to show a bias for the correct quadrant. Following four additional retraining trials, a second drug-reversal probe trial was given and it was found that rats switched from saline to the highest dose of baclofen (6 mg/kg) showed a bias for the correct quadrant, as did rats switched from the two lowest doses of baclofen (1 and 3 mg/kg) to saline. Rats switched from the highest dose of baclofen (6 mg/kg) to saline failed to show a quadrant bias. Performance on a visible platform task was not impaired by baclofen at any dose. Together these results suggest that baclofen resembles $GABA_A$ agonists/positive modulators in that it impairs spatial learning, but not performance of a previously acquired escape response, but differs in that it does not reduce thigmotaxia (anxiety). Potential mechanisms by which baclofen impairs mnemonic processes are discussed.

Baclofen $GABA_B$ Spatial learning Cue learning Thigmotaxia Activity Open field Morris water maze

PHARMACOLOGICAL and anatomical evidence indicate that GABA receptors can be dissociated into at least two subtypes: $GABA_A$ and $GABA_B$ [(18), reviewed in (22)]. The pharmacological profile of the $GABA_B$ receptor is distinct from that of the $GABA_A$ receptor, with $GABA_B$ receptors being insensitive to bicuculline, a competitive $GABA_A$ receptor antagonist, and to conventional $GABA_A$ receptor agonists (18). Conversely, baclofen [β-(*p*-chlorophenyl)-GABA], binds stereospecifically to the $GABA_B$ receptors but not to $GABA_A$ receptors (2). $GABA_A$ receptors are coupled to Cl^- ionophores whereas $GABA_B$ receptors are coupled indirectly to Ca^{2+} or K^+ channels via G-proteins [reviewed in (1)]. Moreover, $GABA_A$ and $GABA_B$ receptors are differentially distributed throughout the mammalian CNS, with $GABA_B$ receptors accounting for 20–30% of total GABA receptors, though $GABA_B$ receptors do predominate in some regions (3,7). At the cellular level, $GABA_A$ receptors are thought to be localized primarily to postsynaptic sites whereas $GABA_B$ receptors are located both pre- and postsynapticially (11,17). Activation of presynaptic $GABA_B$ receptors inhibits neurotransmitter release at GABAergic and glutamatergic synapses (9,16,33) whereas activation of postsynaptic $GABA_B$ receptors mediates late inhibitory postsynaptic potentials (30).

The net effect of $GABA_B$ receptor activation in the hippocampus, an essential structure for spatial learning (31), is disinhibition. Baclofen disinhibits neurons (4,20), enhances paired-pulse facilitation (29), and facilitates the induction of long-term potentiation (4,28,32), a persistent form of synaptic plasticity thought to model information storage processes. Consistent with its disinhibitory action, baclofen also induces

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epileptiform activity in the hippocampus (4,27,32), which, when induced by kindling stimulation, impairs spatial learning in the Morris water maze (23).

Baclofen (Lioresal®) is a first-line treatment for spasticity (19), and a number of clinical reports have provided anecdotal evidence that baclofen also perturbs mnemonic processes in some recipient patients (21,36). Systematic assessment of baclofen's amnesic actions using animal models has yielded mixed results. For example, on avoidance conditioning tasks, posttraining systemic administration of baclofen has been reported to both impair (5,6,40) and facilitate (12,35) acquisition of the conditioned response. On a successive discrimination task, baclofen dose-dependently impaired performance of an acquired response (37), suggesting that baclofen impairs sensorimotor abilities. On the radial arm maze, pretraining administration of low doses of baclofen did not affect spatial learning but exacerbated the spatial learning deficit produced by scopolamine, a muscarinic antagonist, suggesting that baclofen's amnesic action may be caused by a reduction of cholinergic activity (38). Indeed, intracranial injections of baclofen into major cholinergic cell groups [septum (39) or nucleus basalis magnocellularis (10)] impair working memory processes on maze tasks, and oxotremorine, a muscarinic agonist, attenuated the impairment produced by baclofen on a passive avoidance task (6).

The present experiment sought to characterize the effects of baclofen on acquisition and performance in the Morris water maze, an aversively motivated spatial learning task (26). Spatial learning in the water maze is impaired by positive allosteric modulators of the $GABA_A$ receptor [reviewed in (24)] but the contribution of $GABA_B$ receptors has yet to be assessed. The effects of baclofen on activity and thigmotaxia in an open field were also assessed.

METHOD

Animals

Twenty male rats of the Long–Evans strain served as subjects. They were housed in pairs in shoebox cages and maintained on a 12 L : 12 D cycle. Testing was conducted during the light phase of the cycle. The rats weighed approximately 400 g at the beginning of the experiment and food and water were continuously available.

Drugs and Group Assignment

At the beginning of the experiment, rats were randomly divided into four treatment groups. The first three groups received one of three doses of (−)-baclofen (1, 3, and 6 mg/kg; n = 5/dose; dissolved in 0.9% NaCl; Sigma) and the fourth group (n = 5) received an equivalent volume of saline (1 ml/kg; 0.9% NaCl). All injections were given IP 20 min prior to behavioral testing.

Apparatus and Procedure

Open field. Potential activity-depressant and antithigmotaxic actions of baclofen were assessed using a circular open field (diameter: 150 cm, height: 45 cm). The field was illuminated to 100 ft-c by eight 100-W bulbs and constant background noise was maintained with a stereo system. The inner surface of the field was white and featureless except for a line drawn on the floor 6 cm from the wall around the periphery. This line divided the floor of the field into a central area (85% of field) and a peripheral area (15% of field). Rats naive to the field were placed one at a time into the open field at a common point in the peripheral region and allowed to explore freely for 5 min (41). During this time the rat's path in both peripheral and central regions of the field was recorded by an overhead video-tracking system (Chromotrack; SD Instruments). Locomotion was assessed as the total distance traveled over the 5-min test period and thigmotaxia was assessed as the proportion of time spent in the peripheral region of the field. Between trials, the field was cleaned with 70% ethanol to eliminate residual odor cues.

Water maze. The Morris water maze consisted of a circular pool (diameter: 150 cm, height: 45 cm), with a featureless white inner surface. The pool was filled to a height of 25 cm with 26 ± 1°C) water, in which 1500 ml of powdered skim milk was dissolved. The hidden escape platform was a clear Plexiglas stand (13 × 13 cm) submerged 3 cm below the water surface so that it was invisible at water level. The visible platform was a black stand (13 × 13 cm) that protruded 5 cm above the surface of the water.

During initial acquisition, which began 2 days after open field testing, the submerged escape platform was maintained in the center of the northwest quadrant. Groups of five rats were given four trials each day for 6 consecutive days followed by a probe trial (see below) as the last trial of the sixth day. For each trial the rat was placed in the water facing the pool wall at one of four randomly determined starting locations (north, south, east, or west pole). During each trial, the rat's swim path and escape latency were recorded with an overhead video-tracking system (Chromotrack; SD Instruments). Swim speed was calculated as the distance divided by the escape latency (cm/s) obtained for each trial. Once the rat located the platform, it was permitted to remain on it for 15 s. If the rat did not locate the platform within 60 s, it was placed on the platform for 15 s. After each trial, the rat was returned to a holding cage positioned 90 cm under a 250-W brooding lamp (for warmth) and allowed to remain there for the intertrial interval (approximately 4 min).

To assess the strength and accuracy of initial learning, a probe trial was given after the last trial on the sixth day of training. During probe trials, rats were required to swim in the pool without an escape platform for 60 s. All rats were released from the southern pole and the time spent in each quadrant was recorded with the video-tracking system. On the following day, four additional retraining trials were given, and then on the day after that, a second probe trial was given with drug conditions switched such that saline-treated rats now received the high dose of baclofen (6 mg/kg) and drug-treated rats now received saline. The latter probe was given to determine if baclofen affected performance of a previously acquired spatial bias.

On the day following the second probe trial, a visible platform task was given to determine if baclofen produced gross sensorimotor or motivational deficits. Rats were given their original (initial acquisition) drug and dose and were required to escape onto a single visible platform located in a different quadrant on each of four trials (to prevent the accurate use of spatial cues); swim path lengths and escape latencies were recorded with the video-tracking system.

Data Analysis

Group differences in total distance and percentage distance spent in the central region of the open field were analyzed using a one-way analysis of variance (ANOVA). Escape latencies, swim path lengths (distance), and swim speeds were assessed using an ANOVA procedure with repeated measures.

Post hoc comparisons were made using Tukey's test. Probe data were assessed such that the quadrant bias (percent time) spent in the goal quadrant was compared with the next highest quadrant bias using t-tests. In every case the acceptable level for statistical significance was $p < 0.05$.

RESULTS

In the open field, baclofen dose-dependently reduced activity, decreasing the overall distance traveled during the 5-min test (Fig. 1A), as confirmed by a significant group difference, $F(3, 19) = 5.65, p < 0.01$. The two higher doses of baclofen (3 and 6 mg/kg), but not the lowest dose (1 mg/kg), significantly reduced the mean total distance traveled compared to saline (all $p < 0.05$). Though there was a trend for baclofen to reduce thigmotaxia with increasing doses, none of the doses of baclofen reduced thigmotaxia significantly relative to saline controls (all $p > 0.05$) (Fig. 1B).

Baclofen dose-dependently impaired spatial learning during initial acquisition in the water maze. The mean distance and latency required by each of the treatment groups to locate the submerged platform over the 12 blocks of two trials is shown in Fig. 2A and B, respectively. Rats treated with saline rapidly acquired the platform location, reaching asymptotic levels by the fourth day of training. Rats treated with baclofen demonstrated impaired acquisition at all but the lowest dose; rats treated with the moderate dose (3 mg/kg) showed a severe impairment during the first half of training but approached control levels by the end of training. Rats given the highest dose of baclofen (6 mg/kg) demonstrated a severe impairment of spatial learning, showing slower acquisition and poorer asymptotic levels relative to controls across the entire training period (Fig. 2A,B). An overall ANOVA on distance data revealed a significant group difference, $F(3, 36) = 36.2, p < 0.001$, trial block difference, $F(11, 396) = 26.5, p < 0.001$, and a significant interaction between groups and trial block, $F(33, 396) = 1.68, p < 0.01$. Post hoc comparisons revealed that rats treated with the two highest doses of baclofen (3 and 6 mg/kg) had longer distances relative to both controls ($p < 0.01$) and rats treated with the low dose of baclofen (1 mg/kg; $p < 0.01$). Moreover, rats treated with the highest dose of baclofen (6 mg/kg) had longer distances relative to rats treated with the medium dose of baclofen (3 mg/kg; $p < 0.05$). Latency data revealed a similar pattern of deficits (Fig. 2B), with rats treated with the two highest doses showing an impairment relative to the low dose and saline controls. An overall ANOVA on latency data similarly revealed a significant group difference, $F(3, 36) = 56.9, p < 0.001$, trial block difference, $F(11, 396) = 23.8, p < 0.001$, and a significant interaction between groups and trial block, $F(33, 396) = 1.6, p < 0.05$. Post hoc comparisons revealed that rats treated with the two highest doses of baclofen (3 and 6 mg/kg) had longer escape latencies relative to both controls ($p < 0.01$) and rats treated with the low dose of baclofen (1 mg/kg; $p < 0.01$). Moreover, rats treated with the highest dose of baclofen (6 mg/kg) had longer escape latencies relative to rats treated with the medium dose of baclofen (3 mg/kg; $p < 0.01$).

The effects of baclofen on swim speed during acquisition

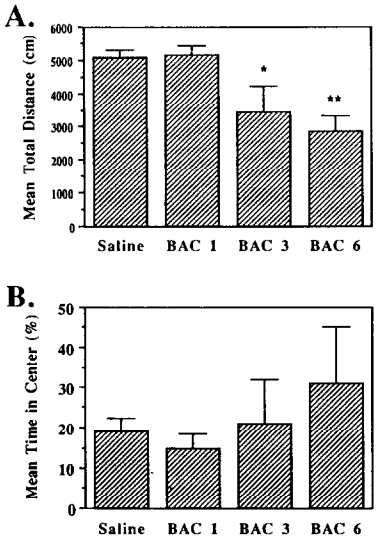

FIG. 1. Effects of three different doses of baclofen (BAC) on (A) the mean total distance traveled and (B) the percent time spent in the central region in the open field during the 5-min test session (thigmotaxia). Note that baclofen dose-dependently reduced activity but had little effect on thigmotaxia. *$p < 0.05$, **$p < 0.01$ compared to saline group (BAC numbers give dose in mg/kg).

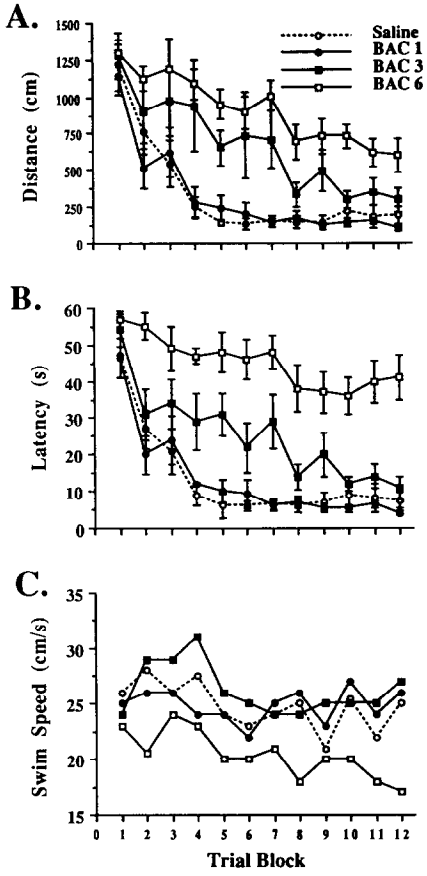

FIG. 2. Effects of baclofen (BAC) on (A) the distance taken to reach the submerged platform, (B) latency to reach the submerged platform, and (C) swim speed (cm/s) over the 6 days (four trials/day broken down into 12 blocks of two trials) of training. Note that baclofen dose-dependently increased the distance and latency taken to reach the submerged platform and reduced swim speed.

are shown in Fig. 2C. Controls tended to swim at approximately the same rate over the course of training. Only rats treated with the highest dose of baclofen (6 mg/kg) swam at a slowed rate, with rats treated with the low and moderate doses of baclofen swimming at control rates. An overall ANOVA on swim speed data revealed a significant group difference, $F(3, 36) = 16.8, p < 0.001$, trial block difference, $F(11, 396) = 3.2$, $p < 0.001$, and a significant interaction between groups and trial block, $F(33, 396) = 1.45$, $p < 0.05$. Post hoc comparisons revealed that only those rats treated with the highest dose of baclofen (6 mg/kg) had slower swim speeds relative to controls ($p < 0.01$) and compared to rats treated with the low (1 mg/kg) and medium (3 mg/kg) doses of baclofen (all $p < 0.01$).

Results from the first probe trial are illustrated in Fig. 3A. Control rats showed a robust bias for the goal quadrant, as did rats treated with the two lowest doses of baclofen (1 and 3 mg/kg; all $p < 0.05$ compared with the next highest quadrant bias). In contrast, rats treated with the highest dose of baclofen (6 mg/kg) distributed the majority of their swim time between the correct quadrant and the quadrant diagonally opposite. In fact, they showed a robust bias for the opposite quadrant.

During the additional four retraining trials given under the same drug conditions on the following day, swim path lengths differed little from the last four trials given prior to the first probe trial: saline (186 ± 67 → 196 ± 55 cm), baclofen 1 mg/kg (129 ± 18 → 158 ± 19 cm), baclofen 3 mg/kg (325 ± 84 → 256 ± 90 cm), baclofen 6 mg/kg (610 ± 97 → 674 ± 79 cm), suggesting that the first probe trial did not extinguish the previously acquired escape response. On the second probe trial, given the following day, rats switched from saline to baclofen (6 mg/kg) still showed a significant bias for the correct quadrant, as did rats switched from the two low doses of baclofen (1 and 3 mg/kg) to saline (Fig. 3B; all $p < 0.05$). Rats switched from baclofen (6 mg/kg) to saline still failed to show a bias for the target quadrant.

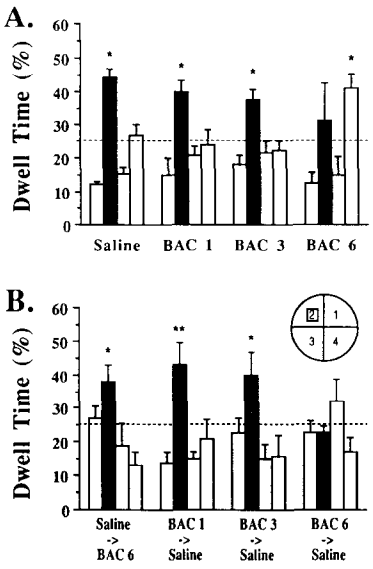

FIG. 3. The percentage of time spent in each of the four quadrants during the postacquisition probe trial (A) and "drug-switch" probe trial (B). Note: 1) the highest dose of baclofen (6 mg/kg) prevented the development of a bias for the correct quadrant during the first probe trial, and 2) rats switched from saline to the high dose of baclofen continue to show a bias for the correct quadrant whereas rats switched from the high dose of baclofen to saline continued to not show a bias for the correct quadrant. Inset indicates the four pool quadrants corresponding to graph bars from left (quadrant #1) to right (quadrant #4); (black bar = goal quadrant 2). *$p < 0.05$, **$p < 0.01$ compared to next highest quadrant bias. Dotted line represents chance levels (25%).

Baclofen did not impair performance on the visible platform task at any dose (all $p > 0.05$). Rats from each treatment group readily swam to the visible platform on the first trial, scoring the following mean distances (given as mean ± SEM): saline (159 ± 50), baclofen 1 mg/kg (168 ± 22), baclofen 3 mg/kg (150 ± 15), baclofen 6 mg/kg (184 ± 23).

DISCUSSION

In the present study baclofen dose-dependently reduced activity, decreasing the overall distance traveled in the open field, without significantly reducing thigmotaxia. Baclofen also dose-dependently impaired spatial learning in the water maze, as indicated by the longer escape latencies and distances as well as poor probe trial performance. The high dose of baclofen also reduced swim speed. However, baclofen did not impair performance of a previously acquired escape response because rats switched from saline to baclofen (6 mg/kg) showed a bias for the correct quadrant during the probe trial. None of the doses of baclofen impaired escape to the visible platform, suggesting that treated rats were: 1) motivated to escape from the pool, 2) able to escape from the pool onto a platform in a coordinated manner, and 3) able to acquire a simple association. Collectively, these data indicate that in addition to its better known activity-suppressing action, baclofen produces a dose-dependent and selective impairment of spatial learning and yet does not produce antithigmotaxia (anxiolysis).

Baclofen depressed both spontaneous (open field) and goal-directed (water maze) activity in the present study. This activity suppression is consistent with its use as an antispastic agent/muscle relaxant (19) and agrees with a previous report in which a high dose of baclofen (10 mg/kg) reduced spontaneous locomotion in an activity chamber (40), an effect thought to be mediated by reductions of forebrain dopamine activity (13). Interestingly, the moderate dose of baclofen (3 mg/kg) reduced activity in the open field but not swim speed in the water maze, suggesting that moderate activity suppression produced by baclofen can be overcome by increasing motivation. It should be noted that none of the doses of baclofen used in the present study was ataxic, as righting reflex and swimming ability were not compromised (data not shown).

None of the doses of baclofen tested significantly reduced thigmotaxia, a defensive response selectively reduced by conventional anxiolytics (41). Though the highest dose of baclofen did tend to increase the time spent in the central region of the open field, this increase was neither significantly different from controls nor independent of activity suppression. These data are therefore consistent with previous reports in which baclofen was found to have only a weak suppressant effect on punished behavior (15,34) and suggest that baclofen lacks the "anxiolytic" properties characteristic of $GABA_A$ receptor agonists (22).

The principle finding of the present study is that baclofen dose-dependently impairs spatial learning. Although the moderate dose of baclofen (3 mg/kg) impaired acquisition over the

first nine trial blocks, rats treated with this dose did eventually acquire the location of the platform, as evidenced by the quadrant bias during the first probe trial. That this gradual improvement in performance resulted from the development of tolerance cannot be ruled out, though little tolerance was exhibited in rats treated with the highest dose (6 mg/kg), which appeared to completely prevent spatial learning. Indeed, escape latencies and distances show little reduction over the course of training and a bias for the target quadrant was not observed during the probe trial. Interestingly, these rats tended to prefer the quadrant that was closest to the experimenter (quadrant 4), suggesting that these rats may have learned that the experimenter was the best escape source when the platform could not be located. This pattern was not observed during the second probe trial when the same rats, now undrugged, avoided this quadrant. These data indicate that $GABA_B$ receptor activation by baclofen has amnesic consequences, in agreement with previous reports using avoidance conditioning (5,6,40) and maze (10,39) paradigms, and reports of memory problems in recipient patients (21,36). These data are also consistent with the finding that the $GABA_B$ receptor antagonist CGP 36742 has promnestic properties (25).

The present results indicate that the highest dose of baclofen (6 mg/kg) does not impair performance of a previously acquired escape response: rats switched from saline to the high dose of baclofen exhibited a bias for the target quadrant. This result suggests that this dose of baclofen did not impair the rat's ability to concentrate its swim in the target quadrant, use ambient cues to guide navigation, or retain and retrieve the platform's location in space. Hence, it is unlikely that the deficit observed during initial acquisition with this dose was due to performance deficits, though baclofen may be more detrimental to performance when administered prior to acquisition. The failure of baclofen (6 mg/kg) to impair performance of an acquired response contrasts with Sarter's (37) finding in which performance of a successive discrimination task was disrupted by a lesser dose of baclofen (4.69 mg/kg). It was noted, however, that baclofen-treated rats did not complete the task, making it difficult to determine whether, in fact, performance was impaired.

When rats previously treated with the high dose of baclofen during acquisition were switched to saline, a bias for the target quadrant was still not observed. Because the elimination half-life of baclofen is $\sim\sim 4$ h (14), it is unlikely that switched rats were still experiencing residual effects of baclofen during the second probe trial that was given ~ 24 h after the last injection. Moreover, the good performance of rats switched from the two lowest doses of baclofen to saline on the second probe trial indicates that a state-dependent learning effect was not a contributing factor. These results indicate that the high dose of baclofen prevented acquisition of the platform location rather than merely masking the rat's ability to express an acquired escape response.

Although the present results do not offer insight into the mechanisms by which $GABA_B$ receptor activation impairs spatial learning, three effects of baclofen on hippocampal electrophysiology are worthy of discussion. First, baclofen may have impaired spatial learning by eliciting disruptive epileptiform activity in the hippocampus (4,27,32), which we have recently shown to produce a severe spatial learning impairment in the water maze when induced by electrical stimulation (23). Although no behavioral manifestations of seizure activity were observed in rats treated with baclofen, it is possible that subconvulsant seizures did occur. Second, baclofen may have impaired spatial learning by disrupting hippocampal theta rhythm (8), which is essential for spatial learning (42). Thirdly, baclofen may have impaired spatial learning by inducing long-term potentiation in the hippocampus [e.g., (4)], thereby exhausting the availability of modifiable synapses necessary to encode new spatial information. These disinhibitory actions of baclofen contrast with those of $GABA_A$ receptor agonists/positive modulators, which also impair spatial learning (24), indicating that an intricate balance between neuronal excitation and inhibition maintained by GABAergic systems is essential for information acquisition.

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