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Research report

Effect of long term baclofen treatment on recognition memory and novelty detection

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Abstract

We studied the effect of long term baclofen treatment on recognition memory and novelty detection in rats using a habituation paradigm in an open field setting. Rats pretreated with 3 weeks' daily baclofen injection (0, 2 and 5 mg/kg) were tested in four 10 min sessions (familiarization session and three testing sessions: S_1, S_2 and S_3), with 10-min intersession intervals. During S_1, S_2 and S_3, rats were repeatedly exposed to the same two odor stimuli. During S_3, for half of the rats in each treatment group, the spatial locations of the two stimuli were switched (Change) and for the other half the stimuli were replaced in the same locations (No Change). Two habituation scores were measured for each subject: $H_1 = N_1 - N_2$; $H_2 = N_2 - N_3$ (N_i the number of contacts made during S_i). Baclofen at the highest dose (5 mg/kg) reduced the amount of habituation between S_1 and S_2 (H_1) and increased responses to novel spatial arrangement, measured as the difference between H_2 for the No-Change and Change groups. These results suggest a simultaneous impairment of recognition memory and enhancement of spatial novelty detection.

Keywords Baclofen; Recognition memory; Novelty detection; Habituation; Chronic treatment; Spatial memory; Olfaction

1. Introduction

The nervous system has not only the ability to acquire information by making new connections between previously unrelated stimuli, but also the ability to recognize something as familiar. This recognition of familiarity is often manifested in a specific type of behavioral change, namely habituation. In human infant studies, the habituation paradigm has proven to be a versatile and powerful tool for investigating the ontogeny of memory [3,22]. Habituation studies on invertebrates have contributed a great deal to our understanding of cellular and molecular mechanisms underlying learning and memory [4,5,14,19,20,39].

In other mammalian species, habituation has been relatively less studied [30], particularly with regard to the involvement of $GABA_B$ receptors. It has been shown that $GABA_B$ receptors modulate memory processes in a number of species, including rats, mice and monkeys. A number of behavioral paradigms were used based on associative learning tasks, such as passive and active avoidance learning, [7–10,26,36] classical conditioning [8,28], simple logical learning [26] and maze learning [6,13]. The only available habituation study was on social learning. In this study, exposure to a familiar juvenile partner led to habituation of an approach response to that partner and the $GABA_B$ receptor antagonist CGP 36742 increased the amount of habituation [26].

The study presented here focused on the effect of long term/low dose baclofen treatment on habituation to odor stimuli and dishabituation to changes in their spatial arrangement. Long term treatment was chosen in order to deal with the detrimental effect of baclofen on the normal functioning of the motor system by allowing the animals to develop a tolerance to the drug effect on the motor system. This study also allows us to determine whether the drug effect on memory is resistant to the development of tolerance. The choice of relatively low doses reflects our concerns over how much one can generalize from pharmacological studies using high doses, to smaller changes due to clinical treatment or

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changes of endogenous concentration during normal function.

Clinically, the effect of long term baclofen treatment on habituation may provide an animal model for possible drug effects on recognition memory in human patients who use baclofen chronically (months or years) for spasticity. First of all, long term baclofen administration used in this study created a pharmacological condition similar to that among patients under chronic baclofen treatment. Secondly, the relatively low doses used in this study, compared with those used in previous baclofen studies, are closer to the dose range used by human patients. Finally, the learning situation in a habituation paradigm resembles more closely the way people learn and recognize their sensory environment in their daily life, in which no explicit immediate reward or punishment is necessarily involved.

In this study, we adopted and modified a habituation–dishabituation procedure used by Tomlinson and Johnston [38]. This procedure provides an efficient tool for studying two related phenomena, habituation to familiarity and dishabituation to novelty, with no explicit training involved (see Materials and Methods section). Combining this procedure with long term baclofen treatment, we wish to answer the following questions. How does chronic baclofen treatment affect habituation to odor stimuli? How does such treatment affect dishabituation to a novel spatial arrangement? Does the detection of novelty correlate with detection of familiarity? Finally, we report two main findings. First, chronic baclofen treatment, even at the rather low dosages used in our study, impaired habituation in rats. Secondly, the impairment of habituation and facilitation of novelty detection were both found in the group treated with highest dose of baclofen (5 mg/kg). Our results suggest a simultaneous impairment of recognition memory and enhancement of novelty detection.

2. Materials and Methods

2.1. Subjects

A total of 54 albino Sprague–Dawley rats, 30 female and 24 males, (purchased from the Charles River Laboratories, Wilmington, MA) were used. At the onset of the drug treatment, they were aged between 4 and 5 weeks. They were housed in pairs in translucent plastic cages (20 × 20 × 40 cm), with food and water available ad lib. The light cycle began at 07.00 h and ended at 21.00 h.

2.2. Apparatus

Two connected circular chambers (Fig. 1) were used in the following open field study. Although a single circular chamber worked in the hamster study [38], our pilot study indicated that rats develop a fear for the open field, approximately after 5 weeks of age. This emotional state can lead to a cessation of exploratory behavior and refusal to approach target objects placed away from the wall. Two circular areas connected by a narrow opening increased the baseline activity level, which is critical for avoiding floor effects and allowing for a separate measure of motor activity. This environment was presumably more interesting to the rats than a single circular open field.

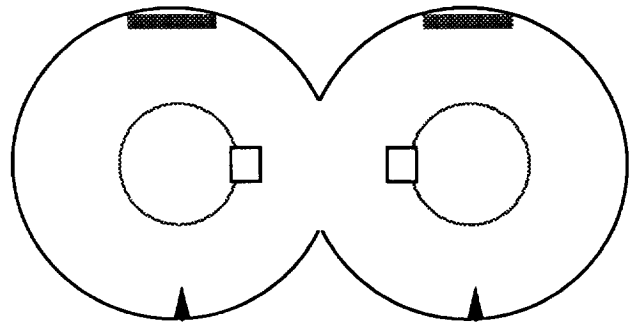

Fig. 1. The testing arena had two circular areas connected by a small opening, in which the rats were allowed free exploration of the environment. The two smaller inner circles were not marked on the floor but only used in data analysis for measurement of fear of open field. The two odor containers (marked as squares) were placed along the line connecting the two centers of the circles, off the edge of the two inner circles. The arrangement maximizes contact frequency because the rats consistently ran from one circular area to the other and the two odor containers were placed sufficiently close to the opening. The shaded bars indicate the location of grating markers on the chamber wall and the entry place of the rat was on the opposite side of the circles, marked with arrows.

The diameters of the two connected circles were 90 cm and the width of the opening was 18 cm. The height of the chamber wall was 62 cm. The wall of the chamber was made of white plastic and was directly placed on a water resistant floor which allowed easy cleaning. To provide visual cues for spatial orientation, two distinct grating patterns (4 cm width) were used for each circular area: four equally spaced black horizontal strips (90 cm in length) were attached to the walls opposing the animals' direction of entry. The bottom of the patterns were 26 cm above the floor.

Two identical glass cheese shakers, 6 cm in height and 4 cm in width served as carriers of two odor stimuli: the honeysuckle (O1) and gardenia (O2) oil purchased from Nature's Elements. An extremely small amount of oil (approximately one-tenth of a drop) was applied directly under the perforated stainless steel caps, prior to each experiment.

The test was conducted in an air conditioned dark room, with temperature set at 22 °C. The light source was provided by a 40-W bulb suspended 165 cm above the opening which connected the two areas. A domed shade was fitted over the bulb to restrict the illumination

to the testing chamber to reduce potential distractions from outside the testing chamber. A fan was kept on but pointed away from the testing chamber throughout the testing period to mask the sudden noise made by door opening/closing and people walking down the hallway.

2.3. Experimental Design

The 54 rats were randomly assigned to three groups according to the dosage of the drug: 18 receiving 5 mg/kg/day baclofen, 18 receiving 2 mg/kg/day baclofen, 18 receiving saline, all at 3–4 ml/kg. We chose to use relatively low doses because at 10 mg/kg, baclofen produced a state of complete immobility in our pilot rats.

On the testing day, an animal experienced a total of four sessions: one familiarization session (F) and three test sessions (S_1, S_2 and S_3). All three groups were further divided into two groups: nine to experience a change in spatial arrangement of the odor containers between S_2 and S_3; the other nine to experience no change in such spatial arrangement (see procedure). Dishabituation was expected from a change in spatial arrangement while further habituation was expected from a lack of such change.

The person who handled the rats between sessions was blind to the experimental conditions (both drug treatment and spatial cues); the person who placed the odorants was blind to the drug treatment and had no direct contact with the animal; the person who injected the rats daily was not aware of the conditions for the spatial cues and had no direct contact with the animals during the experiment; the person who coded the data was also blind to all experimental conditions. In addition, the experimenter was absent in the testing room during all sessions (F, S_1, S_2 and S_3). The absence of experimenter during testing, together with the blind design was to minimize any possible expectancy effect that the experimenters may have on the behavior of the animals or on the coding of the behavior.

2.4. Procedure

To study the chronic effect, as opposed to the acute effect of baclofen administration, our long term drug treatment (IP) began when the rats were between 4 and 5 weeks old. All rats were treated for a total of 3 weeks before testing. The daily injection between 15.00 h and 18.00 h was carried out for 3 weeks prior to the testing day. The dosage was gradually increased to the final target dose: each experimental animal first received 0.5 mg/kg baclofen for 2 days, 2.0 mg/kg baclofen for 4 days. Depending on which treatment group it was in, the rat continued receiving the 2 mg/kg injection or moved on to 5 mg/kg. The last injection and the testing sessions were at least 10 hours apart to avoid the time window in which the acute effect of baclofen might still remain. All animals were handled by the experimenters 3 times on 3 consecutive days before the testing to minimize the potential fear response in the rats. Baclofen injections were continued subsequent to the testing presented here for the purpose of a separate study, though this is not relevant to the current results.

We considered pre-training injection inappropriate due to the extended testing sessions where the change in CNS baclofen concentration may confound the changes due to habituation. Post-training injection was difficult to utilize, since the inter-session intervals (ISI) were short (10 min). In our preliminary study, baclofen given at 10 mg/kg, produced complete immobility for at least 20 min in rats that weighed approximately 400–500 g. In another study, motor function in rats as measured by photoreceptor recorded motor activity in a 30-min post training interval was severely impaired [35]. In fact, baclofen treated rats (10 mg/kg) showed an activity level that was less than 10% of the control rats, and even the 10% activity was very likely due to the activity prior to the onset of the drug effect. Even if a sufficiently long ISI was to be used in our study, post-training injection could induce immobility and thereby induce conditioned fear to the testing environment in the subsequent testing sessions. This potential fear response would confound any specific drug effect on recognition memory.

On the testing day, each rat underwent a 60-min experimental procedure, consisting of a familiarization trial (F, 10 min) and three 10-min sessions (S_1, S_2 and S_3) with two 10-min breaks between the three testing sessions. During the F trial, the animal was placed in the empty chamber while during the S sessions, the two scented cheese shakers were placed 25 cm apart and symmetrically with respect to the opening between the two chambers.

The animal entered either the left or the right field throughout all four sessions, facing the horizontal gratings. The choice of entry was counter balanced across conditions. The relative positions of odor containers with respect to the grating spatial cues were also counter balanced across conditions during S_1. During S_2, the odorants were replaced at the same location for all conditions to induce habituation. In S_3, depending on the conditions (C, change; NC, no change), the odor containers were either switched (C) or replaced (NC) at the same location.

At the end of each testing session, (S_1, S_2, and S_3), the animal was removed to its home cage. The fan was set to rotate during these breaks to remove excessive odor accumulation in the chamber. Upon completion of the testing of each rat, the odor containers and their caps were thoroughly cleaned with detergent followed by baking soda after the testing of each animal. The cap was covered during the break to preserve the odor. The

odorants were reapplied for each individual animal. The testing chamber was cleaned similarly.

2.5. Data Recording and Analysis

The F trial and all testing sessions (S_1 through S_3) were recorded with a video camera (Sony, Video 8 Handycam) on Sony 8 mm video tapes and analyzed later by coders after the completion of the experiment. During the F trial, the animal's activity level was most efficiently described by the number of times the rat crossed the opening between the two chambers. The number of times that an animal entered the center circles (Fig. 1) was measured as an index of fear (emotional state). The number of contacts made during each session was counted. Contrast analyses were performed to test hypotheses that address specific research questions [31,32]. Analysis of variance was also performed to facilitate between-study comparisons although one should be aware that a significant F-value does not necessarily guarantee answers to meaningful research questions and ANOVA often has less statistical power than a contrast analysis [31].

3. Results

Baclofen decreased the amount of habituation between the first two sessions (S_1 and S_2) in a dose dependent manner (Fig. 2). The habituation score for each individual animal was calculated as the change in the number of contacts ($N_1 - N_2$) made between S_1 and S_2. The planned contrast predicted a decrease in the amount of habituation in the 5 mg/kg group and little, if any, changes in the 2 mg/kg and saline groups. The between group contrast analysis on the habituation scores yielded a significant drug effect ($t = 1.938$, $P = 0.0291$, contrast coefficients are -2, 1,1 for group means of the 5 mg/kg, 2 mg/kg, 0 mg/kg animals) [31,32]. Cohen's d-value is 0.192, indicating a small effect [32]. We noticed the slight increase in group mean of the 2 mg/kg group compared with 0 mg/kg group and we feel that the difference is most likely due to variance and not indicative of a different direction of effect for the 2 mg/kg and 5 mg/kg treatment groups. One-way ANOVA did not yield a significant result. Note, our hypothesis concerns a particular trend in the mean habituation scores, not just any differences between the treatment groups. In most rat studies, acute post-training IP injection of 3 mg/kg or even 5 mg/kg produced no significant difference between the treatment and saline groups [24,35]. The lowest dose level (IP) reported in the literature that produced a significant effect for post-training injection in memory tasks was around 10 mg/kg. Thus, considering the low dosage used in our experiment, the small effect observed was not unexpected.

Due to the well known effect of baclofen on the motor system, it can not be assumed, even with long term treatment (non acute), that the above drug effect on habituation was not confounded by a similar dose dependent effect on motor function. Therefore, we examined the frequencies of crossing the opening between the two chambers during the familiarization trial. An active rat tended to run frequently between the two chambers during the initial exploration of the testing chambers. Fig. 3 shows the level of motor activity as measured by the crossing frequency as a function of drug treatment.

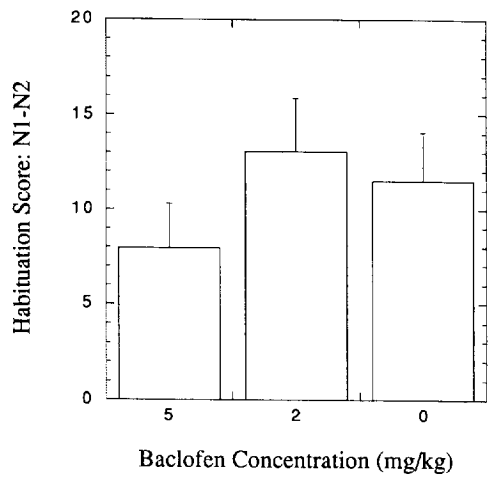

Fig. 2. Habituation as a function of baclofen dosage. For each rat, habituation score was computed as the difference between the number of contacts made during session one (S_1) and session two (S_2). The bar height indicates the mean habituation score for each treatment group and the error bar indicates the standard error of mean. For each group, $N = 18$. A contrast analysis was performed for a nonlinear decreasing trend (–2 1 1) in the amount of habituation as the baclofen dose increases.

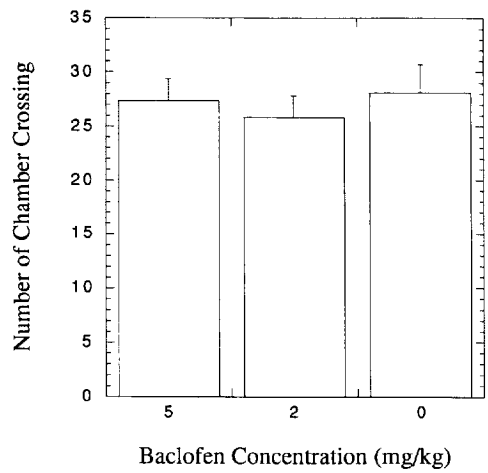

Fig. 3. Level of motor activity as a function of dosage. Motor activity was measured as the number of times a rat crossed the opening connecting the two circular fields during the familiarization trial (F trial). Mean number of crossings did not show the same dose dependent pattern as the amount of habituation.

The dose level that created the greatest effect on the motor activity (2 mg/kg) did not coincide with the dose level that created the greatest effect on habituation (5 mg/kg).

It is also conceivable that the baclofen treatment may affect the function of the olfactory system and, in turn, account for the trend in the amount of habituation across treatment groups. If baclofen does impair odor perception, we would expect that the number of contacts made during their first exposure to the odor stimuli (S_1) should reflect such a difference in perceptual capacity. Again, the mean contact numbers across the treatment groups (Fig. 4) do not predict the trend of habituation across the three dose levels. In addition, sensory adaption as a confounding factor for habituation could be ruled out by two earlier pilot studies. In the first, habituation occured in rats of comparable age, even after a 6-day delay between the two testing sessions. In the other, even in the state of severe immobility, a rat at 4 weeks of age could habituate to a repeatedly presented odor and dishabituate to the introduction of a new odor (habituation and dishabituation measured as a change in sniffing responses). The 10-min intersession breaks used in this experiment also made sensory adaption a less likely confounding factor.

Another well known phenomenon in rats is their fear of open field. Rats tend to spend less time in the center area of an open field. Due to the proximity of the odor stimuli to the center of the circular fields in our experiment, it is reasonable to ask whether the observed drug effect on habituation can be explained by a drug effect on the emotional state of the animal. To examine such a possibility, we marked the centers of the two circular fields (the diameter of the center circle equals 32 cm) and measured the number of times that a rat entered the circle during the familiarization trial. Again, the

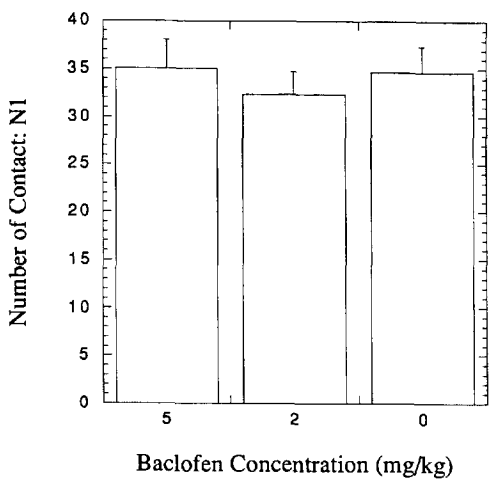

Fig. 4. The number of contacts made during session one (S_1) as a function of dosage. Mean number of contacts did not show the same dose dependent pattern as the amount of habituation.

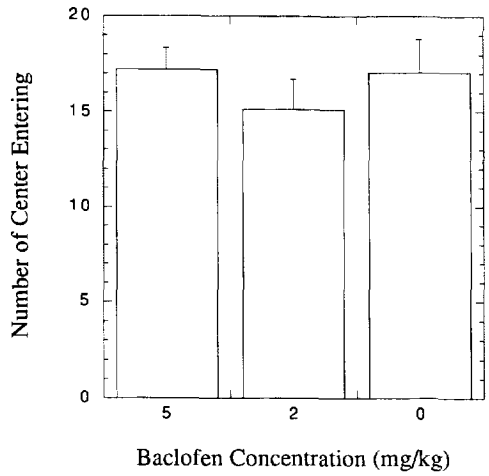

Fig. 5. Fear of open field as a function of baclofen dosage. The fear of open field was measured as the number of times a rat entered the two inner circles. The mean number of center enterings did not show the same dose dependent patterns as the amount of habituation.

trend in the number of center-entering (Fig. 5) does not agree with the trend in habituation.

There appeared to be a correlation between the measures used for evaluating the functions of the motor, sensory and emotional systems. Baclofen at 2 mg/kg produced a decrease in all three measures compared with the saline group. Such a decrease was absent for the group with the highest dose (5 mg/kg). This correlation between measures may reflect the fact that all three measurements were based on motor activity (contact and locomotion), since all underlying processes eventually have to be manifested in the form of motor output. It is interesting to note that the greatest drug effect on all three measures were not produced by the highest dosage.

Between S_2 and S_3, half of each drug treatment group experienced a change in the spatial arrangement of the odor stimuli (C) and the other half experienced no change in the spatial arrangement (NC). It was expected a lack of change should induce further habituation and a change should either reduce the amount of habituation or induce dishabituation (negative habituation scores). The habituation scores between the last two sessions (S_2 and S_3) measured as $(N_2 - N_3)$ were broken down according to the baclofen treatment and spatial arrangement groups (treatment by spatial arrangement) (Fig. 6). First, unlike the hamsters who showed dishabituation (negative habituation scores) to a change in spatial arrangement, our rats did not show significant amount of dishabituation. A similar observation in rats was reported by another laboratory (W.T. Tomlinson, personal communication). The change in spatial arrangement only reduced the amount of habituation in the 5 mg/kg group (mean habituation score for Change and No Change groups were -1 ± 2.70 and 5.5 ± 4.07). In other words, the changes in spatial arrangement pro-

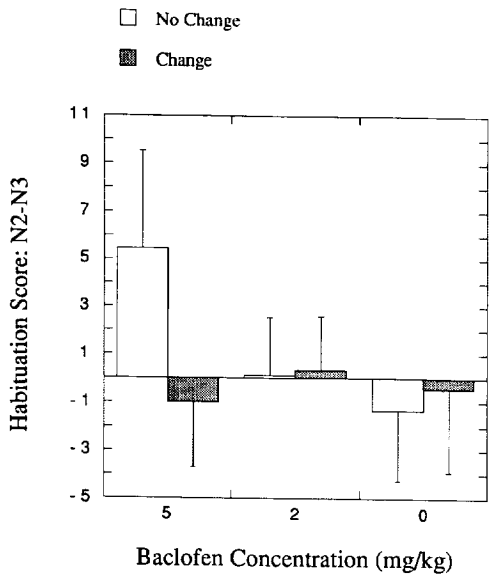

Fig. 6. Habituation as a function of baclofen dosage and spatial arrangement (change vs. no change). The habituation score for each rat was computed as a difference between the number of contacts ($N_2 - N_3$) during session two (S_2) and three (S_3). Spatial arrangement manipulation had the greatest effect in the treatment group with the highest baclofen dosage (5 mg/kg) and made little difference in the saline and 2 mg/kg groups.

duced the greatest difference in habituation scores in the treatment group with the highest dose of baclofen (compare the open bar with the shaded bar for each dose level). A post hoc between group contrast analysis indicates that this effect was significant at $P=0.0411$ ($t=1.775$, contrast coefficient for the group mean of NC-5 mg/kg group is 5, the rest are all -1's) [31,32]. Two-way ANOVA did not yield a significant interaction effect between baclofen treatment and spatial arrangement. Again, the post hoc contrast analysis focuses on one particular pattern of the mean habituation scores, not just any difference at all between the drug by spatial arrangement groups.

4. Discussion

Our results suggest that long term baclofen treatment, even at relatively low dosage (5 mg/kg), impairs recognition memory as reflected in the amount of habituation to familiar odor stimuli. This effect of baclofen on recognition memory appeared to be resistant to the development of tolerance, at least within a 3-week time window. These results are consistent with the general notion that $GABA_B$ agonists produce memory impairment as suggested by laboratory animal studies and clinical case reports (although two studies reported a lack of effect of baclofen on the eight-arm radial maze learning [34] and the Morris water maze learning [40]). In a few clinical cases, baclofen overdose resulted in an inability in the patients to recognize familiar names [33]. Considering the size of the patient population (patients suffering from spinal cord injury, multiple sclerosis and cerebral palsy), systematic clinical studies based on more sophisticated memory tests may shed new light on our understanding of the role of $GABA_B$ receptors in human learning and memory.

Repeated $GABA_B$ receptor activation in long term treatment may result in down regulation of receptor binding sites. Down regulation of $GABA_B$ receptors in the frontal cortex has been demonstrated in a postmortem study of Alzheimer's patients [11], although there has been no evidence in the animal literature what effect the down regulation of receptor binding will have on learning and memory. A receptor autoradiography study following long term baclofen treatment would be necessary for understanding the cellular changes underlying the resulting memory impairment. The effect of baclofen on recognition memory may be mediated via its direct modulatory effect on synaptic transmission [1,12,23,36] in a number of brain regions or via an indirect effect on the output of cholinergic neurons [2,16–18] in the basal forebrain [15].

The lack of further habituation between S_2 and S_3 in the saline and 2 mg/kg groups may indicate that the contact frequency for the NC group had reached the minimum level (floor). Nevertheless, the lack of differences between the change and no change groups (C, NC) within the two lowest dose groups does suggest a lack of difference in habituation scores attributable to the spatial arrangement manipulation. It is only in the group with the highest baclofen dose that spatial arrangment change made the greatest difference in habituation scores. Thus, long term baclofen treatment seemed to facilitate spatial novelty detection. The lack of spatial arrangement induced difference in the saline and 2 mg/kg rats may suggest that the spatial change used in our experiment was perhaps not salient enough for the saline and 2 mg/kg groups, but sufficient to induce a difference in the highest baclofen treatment group.

If detection of novelty in spatial arrangement depends on memory of previous spatial arrangement and baclofen impairs memory for spatial locations as it does for stimulus identity, then spatial novelty detection should have been impaired in the highest baclofen group as was recognition memory. The opposite effects of baclofen on habituation and novelty detection may reflect the working of two separate neural substrates–one responsible for odor recognition and the other responsible for the spatial location of the odor stimuli. The dissociation between object memory and spatial memory has been demonstrated in monkeys [25] and in rats [21] (using an eight-arm radial maze for spatial memory and an object recognition taks). However, it is not clear whether the observed opposite drug effects on odor recognition memory and spatial novelty detection can be attributed

to the separate neural substrates responsible for processing identity and spatial location of an odor stimulus. Electrophysiological studies have shown that baclofen has similar effects on neurons in the hippocampus and piriform cortex, which are known for spatial and olfactory information processing respectively. Furthermore, hippocampus and piriform cortex share a similar laminar organization [18] and baclofen has a similar modulatory effect on synaptic transmission within the two regions [36].

On the other hand, the dissociation may indicate two different operations–one for recognition and the other for novelty detection–performed by the same anatomical structures. There is no reason for us to believe that we need to remember everything we experienced in order to judge whether a given stimulus is novel. Dissociation between recognition and novelty detection was demonstrated in a neural network study [29], in which a network of neuron-like units can detect novel inputs without being able to recognize the familiar inputs. In addition, studies of infants' ERPs revealed a waveform morphology difference between the familiar and novel stimulus conditions, suggesting different neural and cognitive processes/representations were being engaged by the same underlying structures [27].

Mathematical modeling of the modulatory effect of $GABA_B$ agonist baclofen provides a possible explanation for our observation. It has been shown that, in olfactory cortex and CA1 of the hippocampus, baclofen selectively suppresses synaptic inputs of intrinsic origin while leaving afferent inputs little affected [1,12,23,36]. Implementing this physiological feature in a mathematical model [37], it has been demonstrated that activation of $GABA_B$ receptors by endogenous GABA can serve to modulate (reduce) the influence of the intrinsic synaptic inputs. Perhaps, under global exogenous $GABA_B$ agonist application, it is this $GABA_B$ receptor mediated bias against the intrinsic inputs that increased the probability of the neural network seeing the stimuli as new (novelty detection) and at the same time, decreased the probability of the same network settling into an activity pattern that represents familiar stimuli (recognition of familiarity). Although a simultaneous impairment of recognition memory and enhancement of novelty detection represents a theoretically interesting interpretation of the data, further experiments are needed to confirm this effect.

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