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Pharmacology, Biochemistry and Behavior 71 (2002) 401–406

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

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Amygdala priming results in conditioned place avoidance

Shelley K. Thielen[a], Anantha Shekhar[b,*]

[a]Department of Pharmacology, University of Texas Health Sciences Center at San Antonio, San Antonio, TX, USA
[b]Departments of Psychiatry, Pharmacology and Toxicology, and Program in Medical Neurobiology, Indiana University School of Medicine, Indianapolis, IN, USA

Received 19 June 2001; received in revised form 28 September 2001; accepted 1 October 2001

Abstract

Priming involves daily stimulation of the basolateral nucleus of the amygdala (BLA) for 5 days using a dose of the $GABA_A$ receptor antagonist, bicuculline methiodide (BMI), that is subthreshold to generate anxiogenic-like responses. The coordinated physiological and behavioral response of the primed rat is similar to the symptoms of human panic disorder and has been used as a model to study panic attacks. If the priming procedure is indeed similar to human panic disorder, then the context in which priming occurs should become associated with aversive conditioning and avoidance as seen in secondary agoraphobia following panic attacks in humans. Therefore, the purpose of this study was to further characterize the behavioral response of priming using the conditioned place avoidance (CPA) task that utilizes distinct tactile cues of a grid floor (Grid+) or hole floor (Grid −). Male Wistar rats (275–300 g) were implanted bilaterally with guide cannulae positioned 1 mm above the BLA. Grid+ animals were placed in the conditioning chamber containing grid floors immediately after a 6-pmol (in 250 nl) BMI injection into the BLA and on hole floors following a sham (250 nl vehicle) injection. Grid animals were placed in the chamber containing hole floors after the BMI injection and on grid floors following the sham injection. Animals were placed in the chamber for 20 min following each injection and injections were separated by 4 h. After 5 days of this treatment, the animals were primed. Two days later, during avoidance testing, each animal was placed in the chamber containing both floors for 30 min. Priming with daily 6-pmol BMI injections into the BLA results in CPA or an aversion to the floor paired with the BMI injection. These results suggest that priming may result in phobic-like responses, similar to the avoidance behavior exhibited by panic disorder patients.

Keywords: Anxiety; Panic; Agoraphobia; GABA; Conditioned fear; Learning

1. Introduction

Anxiety has been described as an expression of inappropriate fear (Rosen and Schulkin, 1998). Panic disorder, an anxiety disorder subtype, is characterized by recurrent panic attacks, characterized by a sudden surge in anxiety or distress associated with autonomic activation. Although panic attacks are initially spontaneous and unprovoked, the subject often fears that subsequent attacks may recur in a setting similar to that of a previous attack. Thus, a significant number of these patients develop avoidance behavior towards the situations where the panic attacks occurred, a comorbid condition called agoraphobia (Hirschfeld, 1996). The development of this phobia is an example of conditioned fear response to an environmental stimulus paired to an intrinsically aversive unconditioned stimulus, i.e., panic attack.

The amygdala is known to play a role in innate as well as conditioned fear responses (LeDoux, 1987; Davis, 1997) and phobias (File et al., 1998). Stimulation of the amygdala elicits feelings of fear and anxiety as well as autonomic reactions indicative of fear in human subjects (Chapman et al., 1954). In animals, electrical (Hilton and Zybrozyna, 1963) and chemical (Gelsema et al., 1987; Sanders and Shekhar, 1991) stimulation of the amygdala results in a coordinated autonomic and behavioral response that highly resembles fear. Our previous studies have demonstrated that a chronic panic-like state can be induced in rats by repeatedly injecting a subthreshold dose of the $GABA_A$ antagonist, bicuculline methiodide (BMI), into the basolateral nucleus of the amygdala (BLA) for a period of 5 days (Sanders et al., 1995; Sajdyk and Shekhar, 2000). In

* Corresponding author. Department of Psychiatry, Indiana University Medical Center, 550 North University Boulevard, Suite 3124, Indianapolis, IN 46202, USA. Tel.: +1-317-274-1246; fax: +1-317-278-4821.
E-mail address: ashekhar@iupui.edu (A. Shekhar).

0091-3057/02/$ – see front matter
PII: S0091-3057(01)00696-7

addition to increased baseline anxiety, this panic-like state is characterized by increased autonomic responsiveness, respiratory rate, and increased anxiety-like behavior following infusions of human panic-inducing agents such as sodium lactate (Shekhar et al., 1999; Sajdyk and Shekhar, 2000; Sajdyk et al., 1999). This phenomenon termed "priming" has been used to investigate the neurobiology of panic-like behavior in rats. If the priming procedure is indeed similar to human panic disorder, then the context in which priming occurs should become associated with aversive conditioning and avoidance as seen in secondary agoraphobia following panic attacks in humans. Previous studies have specifically implicated the BLA in the development of phobic avoidance (File et al., 1998).

One approach to demonstrate the development of conditioned fear to the conditioning environmental cues is by utilizing a place-conditioning test. In the place-conditioning paradigm, the response-producing properties of a drug or nondrug treatment serve as unconditioned stimuli and a neutral set of environmental stimuli becomes the conditioned stimulus. During the course of conditioning training, the constant pairing of these two stimuli results in the development of a conditioned place preference (CPP) for, or conditioned place avoidance (CPA) of, the neutral environment depending on the nature of the unconditioned stimulus. Previous studies have implicated a role for the amygdala in place-conditioning paradigms, primarily in lesioning studies (Everitt et al., 1991; White and McDonald, 1993; Brown and Fibiger, 1993). Therefore, the purpose of this study was to test if there developed an avoidance behavioral response following priming using the place-conditioning task that utilizes distinct tactile cues.

2. Methods

2.1. Animals and surgical techniques

Experiments were conducted in male Wistar rats (Harlan Laboratories, Indianapolis, IN; 300–350 g). Animals were individually housed in plastic cages and maintained on a 12-h light/dark cycle. Animals were given free access to food and water. Room temperature was maintained at 72 °F.

The Indiana University Animal Care and Use Committee approved all surgical procedures. Chronic microinjection cannulae (26 gauge; Plastics One, Roanoke, VA) were implanted bilaterally into the BLA using a stereotaxic apparatus (David Kopf, TuJunga, CA). The incisor bar was set at −3.3 mm and the coordinates with respect to bregma were: AP −2.3 mm, ML +5.0 mm, and DV −7.5 mm (Paxinos and Watson, 1986). All surgeries were carried out under isoflurane anesthesia. Animals were returned to their home cage for recovery. Recovery was monitored until the animal was fully awake and behaving. Animals were allowed to recover for 5 days before the experiment.

2.2. Acute microinjections

Acute microinjections of BMI or saline were administered in behaving animals. Microinjectors (33 gauge; Plastics One) connected to 10-μl syringes via Teflon tubing were used for delivery using a microinfusion pump (Harvard Apparatus, Holliston, MA). Injection volumes of 250 nl were delivered at a rate of 0.5 μl/min.

2.3. CPA

The $47.6 \times 16.5 \times 17.5$ cm apparatus was constructed from acrylic and aluminum (Cunningham et al., 1993). The apparatus was mounted on two removable floors — each floor representing one-half of the floor surface. The floors were constructed from either stainless steel rods mounted 13 mm apart or perforated stainless steel (16 GA) with 6.4-mm round holes on 19-mm staggered centers. This experimental protocol consisted of one habituation day, five conditioning trials — two sessions per day, and a single test day, respectively. During habituation, each rat was given a sham injection and then placed in the apparatus for 30 min. Neither floor was used during habituation in order to avoid the development of latent inhibition (Lubow, 1973). Instead, the apparatus was mounted on a smooth wooden surface. The sham injection procedure involved inserting injectors, which did not extend beyond the tip of the guides. Also, no volume was delivered during the sham injection. These two precautions were taken in order to minimize tissue damage at the injection site.

The first conditioning day occurred 24 h after habituation. Rats were assigned to either the grid floor (G+) or the hole floor (G− group) as their conditioning floor. Animals in the G+ group were placed in the apparatus mounted on two hole floors immediately following the sham injection and on grid floors immediately following the BMI or saline (vehicle) injection. Animals in the G− group were placed in the apparatus mounted on two grid floors following the sham injection and on hole floors following the BMI or saline injection. Sham injections were always given first and the BMI or saline injection 4 h later in order to prevent drug carryover effects. Conditioning sessions were 20 min in duration. The test day was 48 h after the last conditioning day. On the test day, the floor surface of the apparatus contained one-half hole floor and one-half grid floor. Floor positions were counterbalanced within each group. The test session was 30 min in duration and was videotaped.

2.4. Histological verification of injection sites

At the completion of the experiment, euthanasia was performed by lethal inhalation of isoflurane. The injection site was marked with a 50% solution of India ink. Animals were decapitated and the brains removed. Brains were sectioned using a cryostat. Sections (40 μm) were mounted on slides and stained using neutral red.

2.5. Data analysis

All conditioning trials as well as the test trial were scored for locomotor activity. Locomotor activity was scored from videotaped sessions and was determined as the number of times the rat crossed the center of the apparatus with all four paws. The time spent on the conditioning floor (floor paired with BMI or saline) was scored from the videotaped session of the test trial.

Comparisons of the amount of time spent on the grid floor were made within groups and between groups and were analyzed using repeated measures ANOVA. Posthoc comparisons were made using Fisher's t test. Significance was at a level of $P<.05$. All statistical analyses were performed using SPSS version 10.0. Results are presented as mean ± S.E.M.

3. Results

All of the data included in the analysis were from animals that had bilateral cannulae placements confirmed to be in region of the BLA. Data from cannulae placements outside the anterior regions of the BLA were not included.

3.1. Effect of BMI injections into the BLA on exploratory activity during priming

Exploratory activity, as measured by the number of center crossings, decreased across conditioning days in both treatment groups (Fig. 1). A repeated measures ANOVA showed a significant effect of Time [$F(3,33)=59.461$, $P<.05$] as well as Day [$F(4,44)=13.678$, $P<.05$]; however, there was no significant effect of Treatment [$F(1,11)=1.048$, $P>.05$].

3.2. Effect of BLA priming on place conditioning

Overall, there was a clear reduction in the time that the animals spent on the floor associated with priming versus the floor associated with sham priming. Within the BMI treatment group, there was a significant main effect of Floor ($F=11.366$, $P<.05$) and Time ($F=3.676$, $P<.05$) with a significant Time × Floor interaction ($F=7.256$, $P<.05$). When the time course of the two floor explorations was examined during the 30-min sessions, the G+ animals spent significantly less time on the grid floor than the G− animals during time 15 through 30 min (Fig. 2a). Within the saline

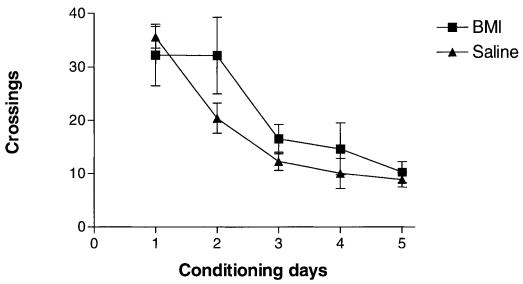

Fig. 1. The effect of BMI and saline on exploratory activity during BMI and saline conditioning sessions. Data represented as total activity across conditioning days (mean crossing ± S.E.M.). Both the BMI- and saline-injected groups showed the same level and pattern of locomotor/exploratory activity.

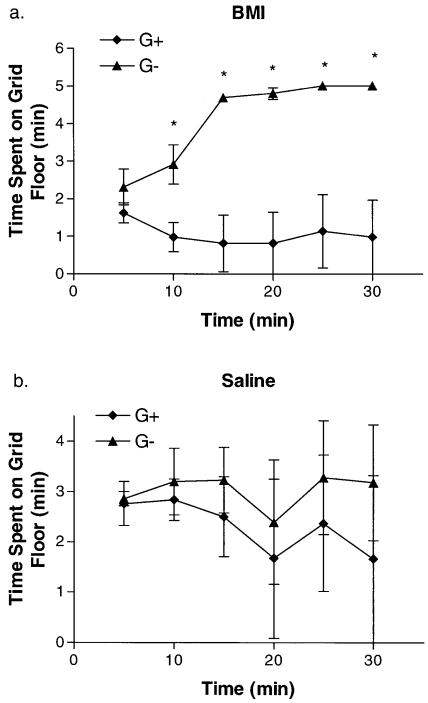

Fig. 2. (a) BMI-treated animals conditioned on the grid floor (G+; $n=5$) spent less time on the grid floor than BMI-treated animals conditioned on the hole floor (G−; $n=3$). Data are presented as time spent on grid floor out of a 5-min bin ± S.E.M. An overall repeated measure ANOVA shows a significant effect of Floor ($P<.05$). *$P<.05$ by independent t test. (b) Saline-treated animals conditioned on the grid floor (G+; $n=3$) and saline-treated animals conditioned on the hole floor (G−; $n=4$) did not differ in the amount of time spent on the grid floor. Data are presented as time spent on grid floor out of a 5-min bin ± S.E.M.

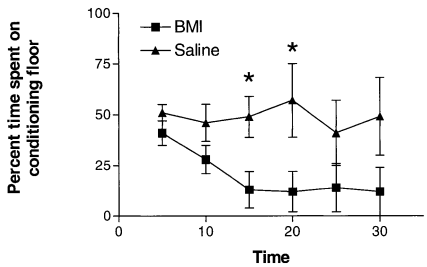

Fig. 3. The effect of priming the BLA of rats with repeated BMI injections on place conditioning test. Data are presented as percent of time spent on the conditioning floor during each 5-min interval of the avoidance test session. Rats that were primed (i.e., repeatedly injected in the BLA with BMI, $n=8$, for five consecutive days) spent less time on their respective conditioning floor ($P<.05$) in comparison to sham-primed (i.e., animals repeatedly injected with saline, $n=7$, for 5 days) rats over the 30-min avoidance test session. *$P<.05$ by ANOVA coupled with Fisher's t tests.

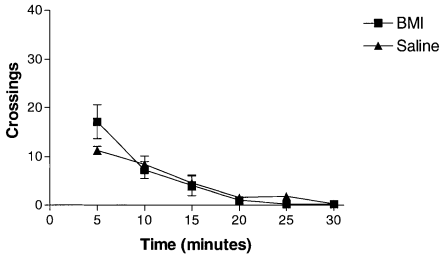

Fig. 4. The effects of either priming (i.e., repeated BMI injections) or sham priming (repeated saline injections) in the BLA of rats, on exploratory activity of the animals during avoidance testing. No significant differences in activity were noted between BMI ($n=8$)- and saline ($n=7$)-treated animals.

treatment group, there were no significant main effects or interactions detected (Fig. 2b). The comparison between groups (Fig. 3) showed a significant main effect of Treatment ($F=29.514$, $P<.05$) on the amount of time spent on the conditioning floor. The BMI treatment group spent less time on their respective conditioning floor than saline-treated animals with significant differences at time bins of 15, 20, and 30 min. The overall locomotor activity in the test chamber was similar in the saline- and BMI-treated groups. Activity during avoidance testing (Fig. 4) showed a significant effect of Time [$F(5,55)=28.158$, $P<.05$]; however, there was no effect of Treatment [$F(1,11)=0.251$, $P>.05$].

4. Discussion

The present study indicates that repeated injection of a subthreshold dose of BMI into the BLA, when paired with a distinct environment, results in avoidance of the treatment-paired environment. Activation of structures in the defense pathway, such as the amygdala, hypothalamus, and periaqueductal gray, using the $GABA_A$ antagonist BMI results in arousal states that resemble panic-like behavior or fear. Some studies have also shown that activation of these structures results in an aversive motivational state. For example, microinjection of BMI into the dorsomedial hypothalamus elicits increased locomotor activity and cardiorespiratory stimulation (Shekhar and DiMicco, 1987) and significantly increased shock avoidance in rats trained on a Sidman shock avoidance schedule (Shekhar et al., 1987). $GABA_A$ receptor blockade in the periaquaductal gray increased heart rate, blood pressure, and respiratory rate. Intracranial injection of the glutamate decarboxylase inhibitor, semicarbazide, into the periaquaductal gray (Aguiar and Brandao, 1996; Di Scala and Sandner, 1989) results in conditioned place aversion. Specifically, the BLA is implicated as a neural substrate that is involved in the development of phobic avoidance of innately feared situations such as heights (File et al., 1998). This is in agreement with the present report on BMI priming in the BLA and development of conditioned avoidance. Acute injection of BMI into the BLA increases heart rate and blood pressure, and induces anxiety-like behavior (Sanders and Shekhar, 1991). Therefore, it appears that GABAergic tone is important in the modulation of physiological and motivational aspects of behavior in structures that comprise this site in the defense system pathway.

The amygdala and its efferent connections form a critical neurocircuit that coordinates the behavioral and neuroendocrine responses to threatening stimuli. Activation of this system in the presence of a perceived threat is a normal survival reflex. However, hypersensitivity and inappropriate activation of the pathway are thought to be key abnormalities in pathological states such as the anxiety disorders, specifically panic disorder (Gorman et al., 2000). Panic disorder patients appear to perceive bodily sensations, especially those experienced during panic attacks, as dangerous and life-threatening. Phobic avoidance often becomes a pathological coping mechanism in a significant number of these patients. The development and the expression of avoidance behavior in response to panic attacks are critical elements of any animal behavior paradigm attempting to model this pathological state.

Place conditioning has been widely used to study the rewarding effects of drugs of abuse in rodents. This paradigm is also useful in assessing aversive motivational states. An environment or context repeatedly paired with an aversive stimulus, such as shock, can result in the avoidance of the environment or freezing in instances where escape is not possible. Therefore, the environment becomes paired with the effects of a drug or nondrug treatment. Substances of abuse generally cause a CPP, as do natural reinforcers such as sex and novelty (Tzschentke, 1998), while conditioned place aversion is a consequence of, for instance, opiate antagonist-induced withdrawal in morphine-dependent rats. Panic disorder patients will often avoid situations or places associated with a previous panic attack. In the present study, the effects of priming are a sufficient stimulus for the acquisition of a conditioned place aversion in BMI-treated rats.

One possible neurochemical mechanism by which BMI is inducing conditioned avoidance is enhanced excitatory amino acid neurotransmission resulting in increased excitatory output to efferent structures in the defense pathway. We have previously demonstrated that BMI priming is also modulated by EAA neurotransmission (Sajdyk and Shekhar, 1997a,b). Acute concurrent injections of either *N*-methyl-D-aspartate or non-*N*-methyl-D-aspartate antagonists and BMI into the BLA resulted in a dose-dependent attenuation in the acute effect of BMI injection alone, suggesting that activation of EAA receptors may be necessary for the responses elicited by $GABA_A$ receptor blockade in the basolateral amygdala. The amygdala is known to play a role in the formation and storage of memories (McGaugh et al., 1996). Long-term potentiation (LTP) is the predominant model used to study learning and memory and has been shown to be modulated by EAA neurotransmission. LTP has been demonstrated in the amygdala as well as the hippocampus. Our present finding suggests that this LTP-like phenomenon may

facilitate the association of an aversive motivational state with a distinct environment. It would further be of interest to determine whether EAA receptor blockade in the BLA attenuates the acquisition and expression of avoidance behavior in the place-conditioning paradigm.

Another possible mechanism of inducing an aversive motivational state following activation of the BLA is activation of the stress axis. The neuroendocrine response elicited by the defense pathway is mediated by activation of the hypothalamic–pituitary–adrenal (HPA) axis. Corticotropin-releasing factor (CRF) is also implicated in pathological states such as anxiety disorders and depression (Arborelius et al., 1999). CRF receptors in the amygdala mediate both anxiety-like and avoidance behavior (for review, see Gray and Bingaman, 1996). Centrally administered CRF results in anxiety-like behavior in rodents and treatments that activates the HPA axis, thereby increasing plasma corticosterone and anxiety-like behavior in rodents. CRF administered intracerebroventricularly also produces a dose-dependent conditioned place aversion (Cador et al., 1992). The role of CRF and HPA axis activation in anxiety-like behavior induced by BMI priming has not been directly assessed; however, we have reported that repeated injections of the endogenous CRF receptor ligand, urocortin, results in an increase in anxiety-like behavior — an effect that is blocked using the nonselective CRF antagonist, astressin (Sajdyk et al., 1999). It would be of interest to determine the effect of astressin on BMI-induced CPA.

In previous studies, the behavior of the BLA-primed rat has been assessed in tests of anxiety, such as the conflict paradigm and the social interaction test (Sanders et al., 1995), as well as the elevated plus maze (Sajdyk and Shekhar, 1999). In all of these tests, the primed rats show an increase in anxiety-like behavior in comparison to saline-treated controls. It is has also been shown that primed rats exhibit an increase in anxiety-like behavior following infusion with the panic-provoking agent, sodium lactate (Sajdyk and Shekhar, 2000). Our results indicate the formation of an association between the physiological and behavioral responses to BMI and the environment the animal was placed in immediately following the BMI injection, since the BLA-primed rat will exhibit conditioned place aversion in the place-conditioning paradigm. These effects were not influenced by locomotor behavior of the animals since BMI-treated animals did not differ from saline animals with respect to activity during conditioning or during avoidance testing. Based on previous reports, we can postulate that the acquisition and expression of this aversive motivational state may be mediated by EAA neurotransmission as a result of $GABA_A$ receptor blockade in the BLA- and CRF-mediated behavioral and neuroendocrine responses. The effect of antagonizing both of these neurotransmitter systems in the primed rat would be of interest in further characterizing the avoidance behavior exhibited by this putative animal model for studying the neurobiology of panic-like behavior.

5. Conclusion

The present study has shown that the BLA-primed rat exhibits conditioned place aversion to the environment associated with priming in the place-conditioning paradigm. These effects were not secondary to locomotor activity during conditioning or during avoidance testing. These findings further strengthen the heuristic value of the BLA-primed rat in the study of the neurobiology of panic-like behavior and the consequent development of phobic avoidance.

Acknowledgments

This study was supported by PHS grants MH 63591 and MH 52619.

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