ELSEVIER

Pharmacology, Biochemistry and Behavior 69 (2001) 85–92

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

www.elsevier.com/locate/pharmbiochembeh

Dose-sensitive excitation and inhibition of spontaneous amygdala activity by propranolol

Peter E. Simson[a,*], Jennifer C. Naylor[a], Benjamin Gibson[a], Allen M. Schneider[b], Dimitriy Levin[b]

[a]*Department of Psychology, Miami University, Oxford, OH 45056, USA*
[b]*Department of Psychology, Swarthmore College, Swarthmore, PA 19081, USA*

Received 1 June 2000; received in revised form 16 January 2001; accepted 22 January 2001

Abstract

The effect of systemically administered propranolol was determined on spontaneous activity of neurons in the central nucleus (CeA) of the amygdala, a brain site implicated in fear-related learning and memory. Extracellular recordings of single units in the CeA were obtained in vivo from rats administered saline or the centrally and peripherally acting β-adrenergic receptor blocker propranolol (4, 7, 10 mg/kg ip). The high dose (10 mg/kg) of propranolol markedly increased spontaneous activity of CeA neurons. In contrast, the low (4 mg/kg) and intermediate (7 mg/kg) doses of propranolol significantly decreased spontaneous CeA activity, with the suppressant effect of propranolol on CeA firing rates weakening as the dosage increased from 4 to 7 mg/kg. These results suggest that (1) spontaneous activity of CeA neurons is tonically influenced by competing excitatory and inhibitory modulatory circuits, and (2) propranolol's effect on the two modulatory circuits is dose dependent, the high dose increasing spontaneous CeA activity by preferentially blocking an inhibitory circuit, the low dose decreasing spontaneous CeA activity by preferentially blocking an excitatory circuit, and the intermediate dose weakly suppressing CeA activity by blocking both the excitatory and inhibitory modulatory circuits. Disinhibition of CeA activity by the high dose of propranolol may explain the enhancement of retention observed in the passive-avoidance task when this dose of the drug is administered systemically, and may have implications for the use of propranolol clinically in treating aversive-memory-related anxiety disorders such as posttraumatic stress syndrome.

Keywords: Propranolol; β-blocker; Memory; Retention; Amygdala; Electrophysiology; Norepinephrine; Adrenergic; Noradrenergic; Adrenoceptor; Passive-avoidance; Central nucleus

1. Introduction

The amygdaloid complex has been implicated in fear conditioning and aversive–emotional learning and memory (Davis, 1992a; Gold and van Buskirk, 1975; LeDoux, 1992). In lower animals, the presentation of fear-related stimuli, conditioned or unconditioned, increases amygdala activity (Pascoe and Kapp, 1985); stimulation of the amygdala, electrical (Gold et al., 1975) or chemical (Davis et al., 1994), enhances aversive conditioning and, within the central nucleus (CeA) of the amygdala, produces fear responses (Davis, 1992a). In contrast, lesions or pharmacological blockade of the CeA prevent acquisition of both the conditioned emotional heart-rate response (LeDoux et al., 1988) and the fear-potentiated startle response (Davis, 1992b).

In humans, amygdaloid damage results in behaviors that parallel those in lower animals: it appears to impair both conditioned emotional responses (Bechara et al., 1995) and startle responses (Angrilli et al., 1996), and it impairs memory of highly emotional events (Cahill et al., 1995). Moreover, since receptors for the benzodiazepine anxiolytics (Niehoff and Kuhar, 1983) and opiate narcotics (Freedman and Aghajanian, 1985) are found in especially high density in the amygdaloid nuclei, these nuclei (in particular, both the basolateral nucleus and the CeA to which it projects) have been postulated as a major brain site through which the benzodiazepines and opiates function to suppress fear and anxiety (Davis, 1992a).

* Corresponding author. Tel.: +1-513-529-2443; fax: +1-513-529-2420.

E-mail address: simsonpe@muohio.edu (P.E. Simson).

0091-3057/01/$ – see front matter
PII: S0091-3057(01)00503-2

Learning and memory of one particular form of aversive conditioning — the passive-avoidance task — has been shown to be modulated by the amygdala through, at least in part, adrenergic action (Davis et al., 1994; Ferry et al., 1997; Liang et al., 1990; McGaugh et al., 1992). This is perhaps most clearly evidenced by the finding that intra-amygdala administration of adrenergic agonists enhances retention, following a classic inverted-U dose–response function, of passive-avoidance to footshock (Ferry et al., 1997; McGaugh, 1989; McGaugh et al., 1992); footshock, in turn, increases turnover of norepinephrine (NE) in the amygdala in a current-dependent manner (Quirarte et al., 1998). The association of the amygdala with both fear-related memory and the adrenergic system has led investigators to suggest that β-adrenergic blockers like propranolol may be efficacious clinically in treating aversive-memory-related anxiety disorders such as post-traumatic stress disorder (Cahill, 1997).

It appears, then, that enhanced retention in aversive conditioning tasks such as passive-avoidance is associated with increased excitability of amygdala neurons (Davis et al., 1994), and increased excitability of the amygdala, in turn, is mediated at least in part by the adrenergic system. Consequently, it follows that treatments that enhance retention in the passive-avoidance task by affecting adrenergic activity might be expected to be associated with increased activity of amygdala neurons. One pharmacological treatment that has recently been shown to markedly enhance retention in the passive-avoidance task is *systemic* administration of the β-adrenergic antagonist propranolol, wherein the β-blocker, administered immediately after training, facilitates retention in a dose-dependent manner (Schneider et al., 2000). The purpose of the present experiment was to determine the effect of systemically administered propranolol on spontaneous activity of amygdala neurons recorded electrophysiologically in vivo.

2. Methods

2.1. Subjects

Animals were male Long–Evans hooded rats (obtained from Harlan Sprague Dawley, Indianapolis, IN) weighing 250–400 g, the same strain and approximate weight range as used in previous behavioral studies demonstrating enhancement of retention in the passive-avoidance task (Schneider et al., 2000). Animals were housed singly and were given food and water ad libitum.

2.2. Preparation of animals

Stereotaxic surgery was performed, and extracellular recordings from the CeA were obtained, under urethane anesthesia (1.5 g/kg ip). Once the incisor bar was adjusted so that both bregma and lambda suture landmarks lay in the same horizontal plane (skull flat), a burr hole was made 2.3 mm posterior to bregma and 4.0 mm lateral to the sagittal suture.

2.3. Single unit recordings

Extracellular single unit recordings were obtained using standard in vivo electrophysiological recording techniques, as previously described (Simson and Weiss, 1987). Briefly, a

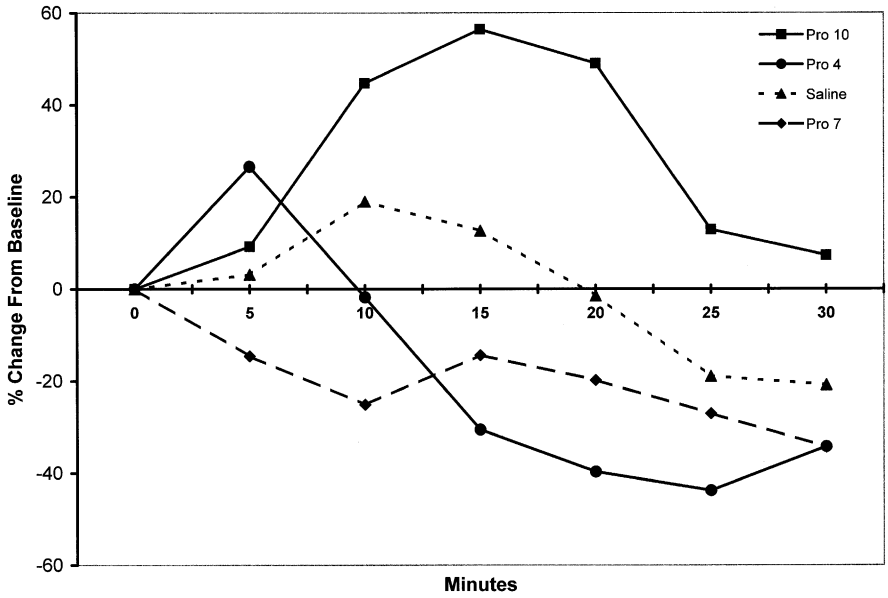

Fig. 1. Effect of propranolol (Pro) on spontaneous activity of CeA neurons. Firing rates are shown as a percent change from predrug baseline rates. Three groups of animals received a single dose of Pro intraperitoneally. The doses (mg/kg body weight) were 4 ($n=5$), 7 ($n=5$), and 10 mg/kg ($n=6$). A control group ($n=4$) received 0.9% saline intraperitoneally at a volume equivalent to that received by rats administered 10 mg/kg Pro.

single barrel glass recording electrode was produced by pulling a single-barrel micropipette (1.5 mm outside diameter, A&M Systems, Seattle, WA). The tip of the pipette was then broken back to approximately 1.0 μm to obtain a recording impedance from 5–10 MΩ. The recording electrode was filled with 0.9% NaCl saturated with Sky Blue dye, and then advanced into the central amygdala via a hydraulic microdrive (Trent Wells, MA). CeA neurons were found at a depth of 6.5–8.0 mm below the dura at the coordinates presented above. Action potentials from spontaneously firing, single units were amplified by a high impedance preamplifier and a secondary amplifier (Fintronics, Orange, CT), and then filtered and displayed on a Tektronix oscilloscope after being processed through a window discriminator (Fintronics). Signals from the amplifier also drive an audiomonitor. Individual spikes were isolated by the window discriminator, then integrated over 10-s periods by a data collection program (Brainstorm Systems, Chapel Hill, NC) and displayed in real-time on a computer monitor. Data were also stored on computer in real time.

Neurons were isolated at random, with no preselection based on firing rate. However, a small percentage (fewer

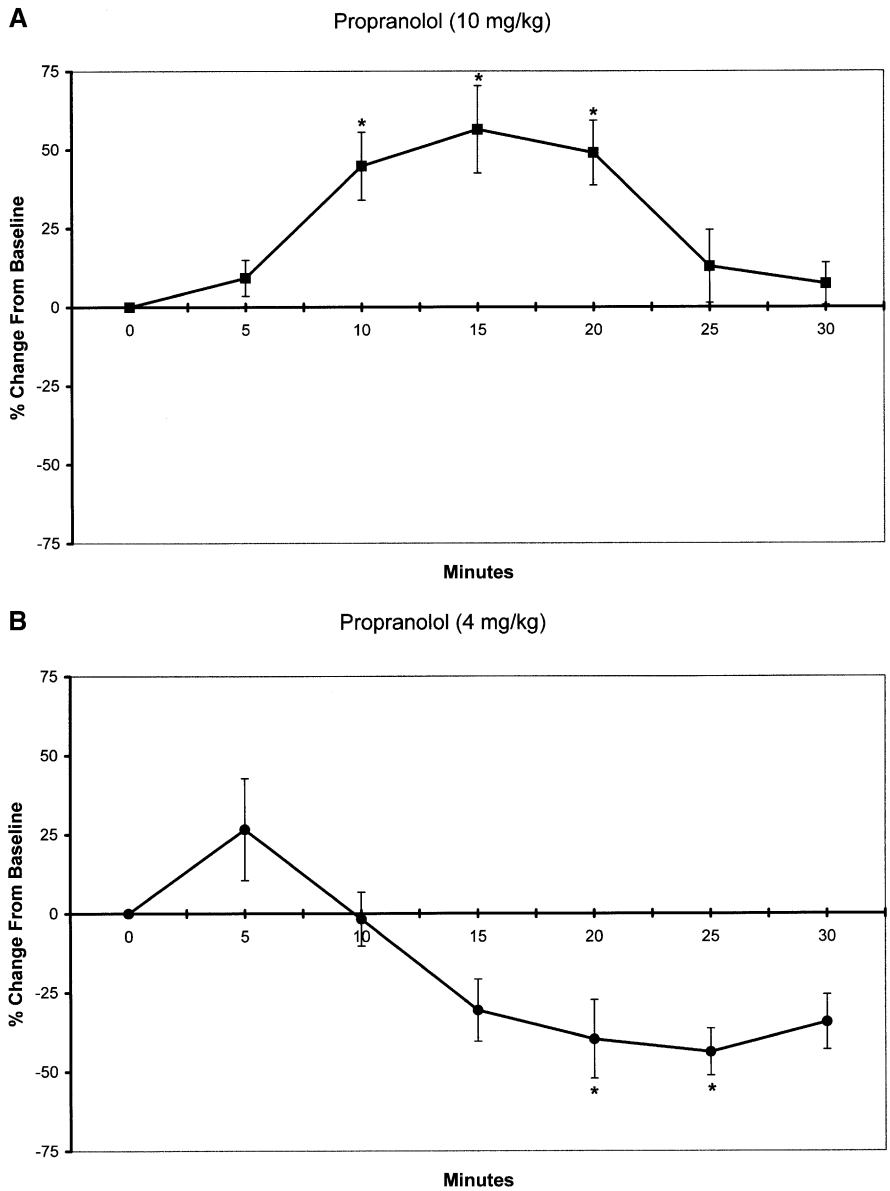

Fig. 2. Effect of propranolol (Pro) on spontaneous activity (mean ± S.E.M.) of CeA neurons. Firing rates are shown as a percent change from predrug baseline rates. (Panel A) Pro (10 mg/kg ip, $n=6$) significantly increased spontaneous amygdala activity. (Panel B) Pro (4 mg/kg ip, $n=5$) significantly decreased spontaneous amygdala activity. (Panel C) Pro (7 g/kg ip, $n=5$) moderately, but nonetheless significantly, decreased spontaneous amygdala activity. (Panel D) Saline ($n=4$) had no effect on spontaneous amygdala activity. Mean baseline (predrug) rates of firing for the various groups were as follows: Pro (4) = 10.3 ± 5.5 Hz; Pro (7) = 13.6 ± 1.2 Hz; Pro (10) = 7.6 ± 2.5 Hz; saline = 14.0 ± 5.5 Hz. Baseline (predrug) rates of firing of CeA neurons did not differ significantly between any of the groups [$F(3,16)=1.45$, $P>.05$]. * $P<.05$ compared to baseline (predrug) rates of firing.

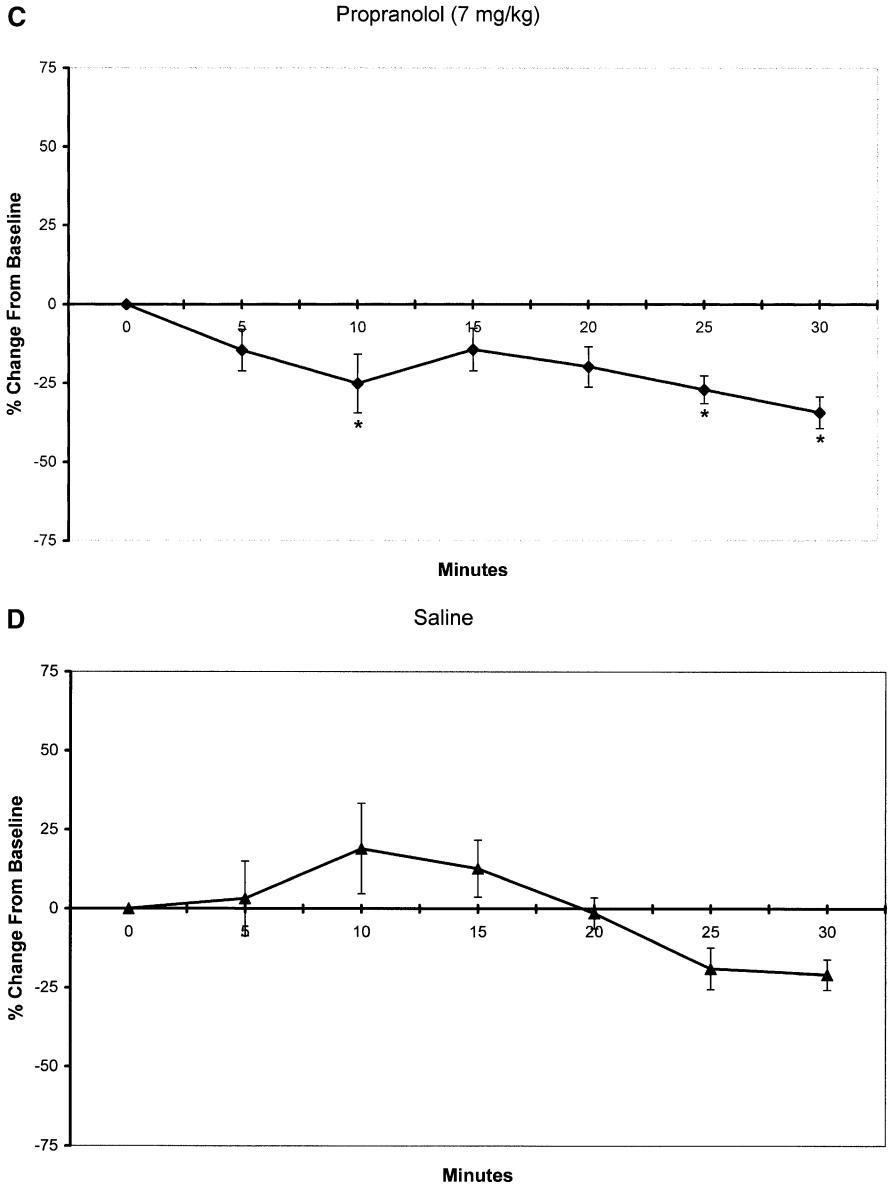

Fig. 2 (*continued*).

than 10%) of neurons in the CeA displayed a strongly rhythmic, bimodal firing pattern. Neurons displaying this rhythmic firing pattern were not recorded from in the present study. The majority of neurons in the CeA fired at a steady rate of 1.5–15 spikes/s, with most cells firing around 10 spikes/s. Waveforms were homogenous and mostly positive-going, and of only moderate amplitude. Only neurons meeting a criterion of at least a 3:1 signal/noise (i.e., signal to background activity) ratio during the baseline recording period were used. Only one neuron was recorded from each rat to avoid residual drug effects. Neurons showing signs of injury or marked irritability during the recording procedure, as evidenced by dramatic changes (typically increases) in firing rate accompanied by marked alterations in waveform and/or amplitude, were not included in the study. If a neuron showed signs of injury after drug administration, the experiment was terminated, the rat was sacrificed, and the data were discarded.

2.4. Drug administration and drug doses

Animals ($n=20$) were injected intraperitoneally (ip) with DL-propranolol hydrochloride (Sigma, St. Louis, MO) at a dose of 4 mg/kg ($n=5$), 7 mg/kg ($n=5$), or 10 mg/kg ($n=6$). Propranolol was dissolved in 0.9% saline to a concentration of 10 mg/ml. Control animals received 0.9% saline ($n=4$). Propranolol was administered systemically since (1) that is the route utilized in previous behavioral studies demonstrating facilitation of retention by the β-adrenergic antagonist (Schneider et al., 2000), and (2) that is the normal route of admin-

istration (i.e., as opposed to central administration) of the drug in humans, in which it has been suggested that propranolol may be useful in treating disorders such as posttraumatic stress related to aversive memories (Cahill, 1997).

After a stable baseline (predrug) recording period of at least 5 min, wherein spontaneous firing rates did not vary by more than 10% over the 5-min period, drug was administered via a 1-cc tuberculin syringe attached to a 27-gauge (1/2 in.) needle placed intraperitoneally before electrophysiological recording commenced.

2.5. Histology

Histological verification of electrode placement was obtained by passing 5 μA of negative-going current through the recording electrode for 5 min, thereby depositing a spot of Sky Blue at the electrode tip. The brains were removed, frozen, and cut in 20-μm sections, and then analyzed for placement of the dye deposit.

2.6. Statistics

Data were analyzed by *protected-t* multiple comparison tests following repeated measures analyses of variance. P values (2-tailed) of less than .05 were taken as statistically significant.

3. Results

3.1. Systematically administered propranolol, at a dose of 10 mg/kg, markedly increased spontaneous single unit activity of neurons in the CeA

The β-adrenergic antagonist propranolol, when administered systemically at a dose of 10 mg/kg, markedly increased spontaneous neuronal activity in the CeA within 10–15 min of administration. As revealed in Figs. 1 and 2(panel A), spontaneous firing rates of CeA neurons ($n=6$) began increasing within 10 min of propranolol (10 mg/kg ip) administration, and showed a marked and significant ($t=2.34$; 30 df, $P<.05$) increase of 45.1 ± 13.9% within 15 min of administration. Spontaneous neuronal activity remained maximally elevated over baseline (predrug) firing rates until approximately 20–25 min postdrug administration, at which time spontaneous neural activity gradually returned to predrug baseline activity rates for the remainder of the recording period. A rate histogram of the effect of propranolol (10

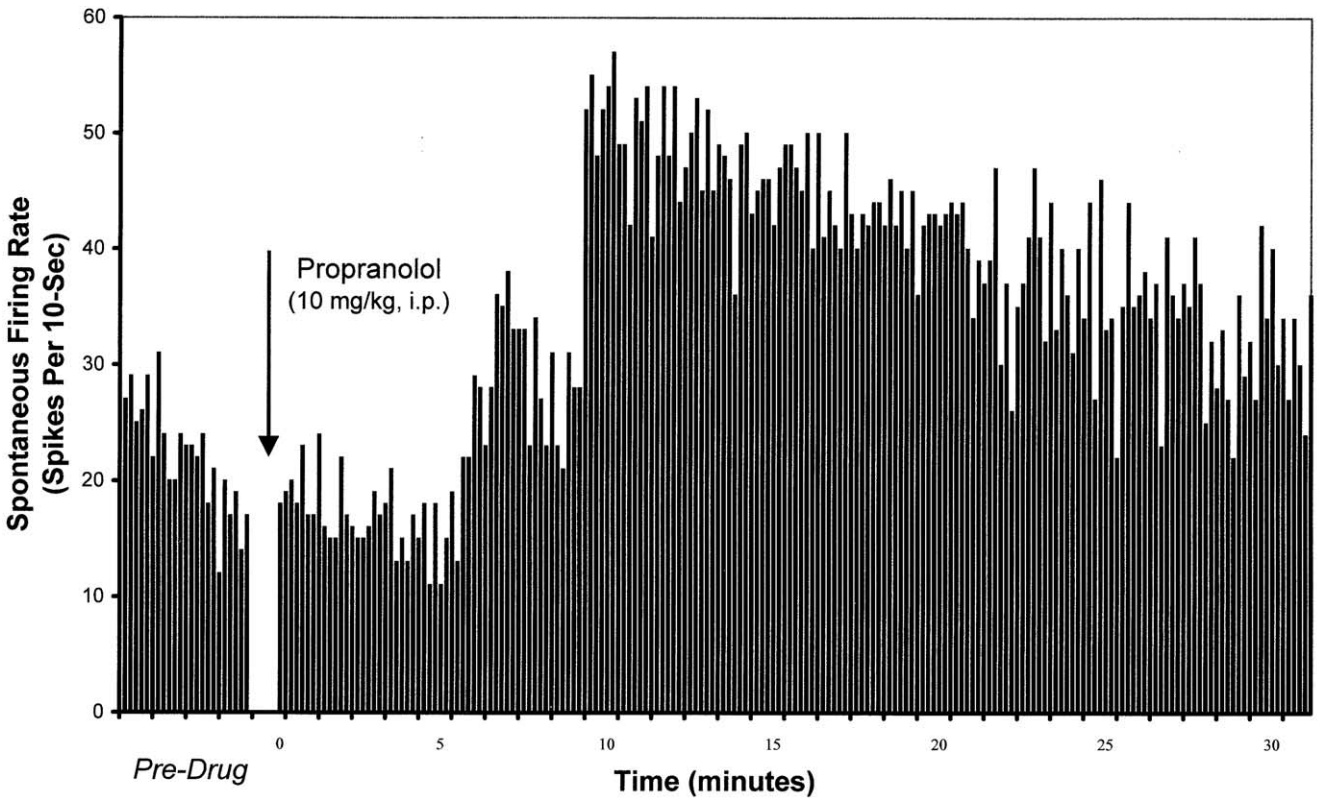

Fig. 3. Rate histogram of the effect of propranolol (10 mg/kg ip) on spontaneous activity of a single neuron in the CeA over a 35-min recording period. After a baseline recording period (predrug), propranolol was administered (0 min). The ordinate represents the number of action potentials per 10-s bin.

mg/kg ip) on an individual neuron in the CeA over the 35-min recording period is shown in Fig. 3.

3.2. Systemically administered propranolol, at a dose of 4 mg/kg and 7 mg/kg, decreased spontaneous single unit activity of neurons in the CeA

In contrast to the 10 mg/kg dose, the low (4 mg/kg) and intermediate (7 mg/kg) doses of propranolol not only failed to increase spontaneous activity of CeA neurons, but *decreased* firing rates (Fig. 2, panels B and C). The greatest inhibition of spontaneous CeA activity occurred with the lower dose (4 mg/kg; $n=5$) of propranolol (Fig. 1), with inhibition reaching statistical significance within 20 min of propranolol administration ($t=2.29$; 24 *df*, $P<.05$) and achieving maximal suppression of CeA firing rates by up to $43.7\pm7.4\%$ within 25 min of administration ($t=2.54$; 24 *df*, $P<.02$). Spontaneous activity began returning to predrug baseline rates by the end of the recording period.

As revealed in Fig. 1, at the intermediate dose of 7 mg/kg, propranolol had far less of an inhibitory effect on CeA firing rates compared to the 4 mg/kg dose. Nevertheless, significant inhibition of CeA activity occurred at the 7 mg/kg dose (Fig. 2, panel C) within 10 min of drug administration ($t=2.57$; 24 *df*, $P<.02$) and continued throughout most of the recording period.

As expected, in control animals saline failed to significantly affect CeA firing rates (Figs. 1 and 2, panel D; $P>.05$).

4. Discussion

The present results indicate that propranolol, when administered systemically, can have opposite effects on spontaneous activity of neurons in the CeA depending on the dose employed. Specifically, at a relatively high dose (10 mg/kg), propranolol increased spontaneous CeA activity; at a relatively low dose (4 mg/kg), propranolol strongly suppressed spontaneous CeA activity; at an intermediate dose (7 mg/kg), propranolol weakly suppressed spontaneous CeA activity.

These results suggest that spontaneous activity of CeA neurons is tonically influenced by competing excitatory and inhibitory modulatory circuits that are differentially blocked by varying doses of propranolol. It follows, then, that (1) the high dose of propranolol preferentially blocked a modulatory circuit that normally functions to tonically inhibit CeA activity, (2) the low dose of propranolol preferentially blocked a modulatory circuit that normally functions to tonically excite the CeA, and (3) the intermediate dose of propranolol blocked, at least partially, both the inhibitory and excitatory modulatory circuits. Accordingly, the result of preferential blockade of a tonically active inhibitory modulatory circuit by the high dose of propranolol would be an increase (via disinhibition) of CeA activity; the result of preferential blockade of a tonically active excitatory modulation circuit by the low dose of propranolol would be a decrease in CeA activity; the result of simultaneous blockade of competing inhibitory and excitatory modulation circuits by an intermediate dose of propranolol would be an effect on CeA activity reflecting the relative extent to which the drug blocked the inhibitory versus excitatory modulatory influences.

Given the evidence that increased activity of nuclei within the amygdala is associated with enhanced fear-related learning and memory, the present finding that the high dose of propranolol (10 mg/kg) significantly elevated spontaneous single unit activity of the CeA may provide a neurophysiological basis for the enhanced retention observed following systemic administration of this dose of propranolol in the passive-avoidance procedure (Schneider et al., 2000). Indeed, these electrophysiological results parallel, to a remarkable degree, the results from our behavioral study (Schneider et al., 2000) investigating the effect of systemically administered propranolol on retention in the passive-avoidance task. Specifically, systemically administered propranolol at a dose of 10 mg/kg both enhances retention (Schneider et al., 2000) and increases spontaneous amygdala activity; systemically administered propranolol at a dose of 4 mg/kg both fails to enhance retention (Schneider et al., 2000) and fails to increase spontaneous amygdala activity.

The finding that propranolol can increase spontaneous activity of CeA neurons is also supportive of, and extends, an earlier electrophysiological study showing that at least some β-adrenergic receptor subtypes in the amygdala are inhibitory (Freedman and Aghajanian, 1985). This prior study found not only that NE inhibits spontaneous firing rates throughout the central and medial portions of the amygdala, but also that this inhibition was mediated by both α_2-NE and non-α_2-NE (presumably β-NE) receptors. Thus, one explanation for the present result of markedly increased CeA activity produced by systemically administered propranolol (10 mg/kg) is disinhibition of an inhibitory modulatory influence mediated by β-adrenergic receptors.

On the other hand, that propranolol's action at the receptor level is not exclusively adrenergic — that is, that propranolol blocks subtypes of the 5-HT receptor (Middlemiss et al., 1977) in addition to β-adrenergic receptors, raises the possibility that propranolol activates the amygdala by blocking modulatory influences mediated by 5-HT receptors. Indeed, given (1) the tendency for drugs to become less selective as dosage is increased, and (2) that propranolol decreased CeA activity at relatively low doses but had the opposite effect on CeA firing rates at a relatively high dose, raises the possibility that propranolol activates the CeA by a mechanism other than blockade of β-adrenergic receptors.

That propranolol can have opposite effects on spontaneous CeA activity has implications for the existing literature, both electrophysiological and behavioral. First,

with regard to electrophysiology, the opposing effects of propranolol on CeA activity extend and support earlier studies in which stimulation, rather than blockade, of β-adrenergic receptors both increases and decreases amygdala activity: (a) in the basolateral amygdala stimulation of β-adrenergic receptors increases fast and slow excitatory postsynaptic potentials (Ferry et al., 1997); (b) in the medial amygdala stimulation of β-adrenergic receptors enhances short-term potentiation while in the lateral amygdala it suppresses short-term potentiation (Watanabe et al., 1996).

Second, with regard to behavior, the opposing effects of different doses of propranolol on CeA activity may explain how different *modes* of administration of propranolol produce opposing effects on retention in the passive-avoidance task; that is, the finding that propranolol, when administered directly into the amygdala, impairs retention (Gallagher et al., 1977), while propranolol, when administered systemically (10 mg/kg ip), enhances retention (Schneider et al., 2000). The explanation may be that, in contrast to systemic administration, locally applied propranolol suppresses rather than increases spontaneous amygdala activity, if in fact excitatory β-adrenergic receptors in the amygdala are more susceptible to blockade by locally applied propranolol than inhibitory β-adrenergic receptors in the amygdala

Alternatively, if the inhibitory control of the amygdala is indirect and originates in circuits outside the amygdala, local administration — as opposed to systemic administration — of propranolol would not be expected to block this tonic inhibition, and thus only systemically administered drug would increase amygdala activity. Indeed, it is conceivable that local application of propranolol blocks β-adrenergic receptors within the amygdala, while systemic administration additionally blocks 5-HT receptors outside the amygdala that differentially affect CeA activity.

Regardless of the mechanism, if spontaneous CeA activity and strength of retention are indeed positively correlated, one would expect that, in contrast to systemic administration, local administration of propranolol suppresses CeA activity to such an extent that retention in the passive-avoidance task is impaired.

In summary, the present results show that systemically administered propranolol can either increase or decrease spontaneous CeA activity, depending on dose. At a dose of 10 mg/kg, propranolol activates the CeA, presumably through preferential blockade of a tonic inhibitory influence. At a dose of 4 mg/kg, propranolol suppresses spontaneous CeA activity, presumably through preferential blockade of a tonic excitatory influence. At intermediate doses, propranolol has effects on CeA activity intermediate between those of the high and low doses, presumably through concurrent blockade of both excitatory and inhibitory modulatory influences.

Whether it is through its effects on the CeA alone or through its effects on the CeA and/or other nuclei in the amygdala (e.g., the basolateral nucleus) connected to the CeA, the increased CeA activity may at least partially explain why propranolol, when systemically administered at a dose of 10 mg/kg, enhances retention in the passive-avoidance procedure (Schneider et al., 2000). Finally, from a clinical standpoint, these results suggest that systemic administration (the normal route of administration in humans) of propranolol may, depending on dosage employed, have effects on aversive memories opposite to those expected and desired, and thus the efficacy of utilizing β-blockers clinically to treat aversive-memory-related disorders may require further study.

Acknowledgments

This research was partially supported by grants from the Alcoholic Beverage Medical Research Foundation (PES) and the Howard Hughes Medical Institute (AMS), and by the Eugene M. Lang Research Professorship in Psychology (AMS).

References

Angrilli A, Mauri A, Palomba D, Flor H, Birbaumer N, Sartori G, Dipaola F. Startle reflex and emotional modulation impairment after a right amygdala lesion. Brain 1996;119:1991–2000.

Bechara A, Tranel D, Damasio H, Adolphs R, Rockland C, Damasio AR. Double dissociation of conditioning and declarative knowledge relative to the amygdala and hippocampus in humans. Science 1995;269:1115–8.

Cahill L. The neurobiology of emotionally influenced memory: implications for understanding traumatic memory. Ann NY Acad Sci 1997;821:238–46.

Cahill L, Babinsky R, Markowitsch H, McGaugh JL. The amygdala and emotional memory. Nature 1995;377:295–6.

Davis M. The role of the amygdala in fear and anxiety. Annu Rev Neurosci 1992a;15:353–75.

Davis M. The role of the amygdala in fear-potentiated startle: implications for animal models of anxiety. Trends Pharmacol Sci 1992b;13:35–41.

Davis M, Rainnie D, Cassell M. Neurotransmission in the rat amygdala related to fear and anxiety. Trends Neurosci 1994;17:208–14.

Ferry B, Magistretti P, Pralong E. Noradrenaline modulates glutamate-mediated neurotransmission in the rat basolateral amygdala in vitro. Eur J Neurosci 1997;9:1356–64.

Freedman J, Aghajanian G. Opiate and alpha-2 adrenoceptor responses of rat amygdaloid neurons: co-localizations and interactions during withdrawal. J Neurosci 1985;5:3016–24.

Gallagher M, Kapp BS, Musty RE, Driscoll PA. Memory formation: evidence for a specific neurochemical system in the amygdala. Science 1977;198:423–5.

Gold PE, vanBuskirk RB. Facilitation of time-dependent memory processes with posttrial epinephrine injections. Behav Biol 1975;13:145–53.

Gold PE, Hankins L, Edwards RM, Chester J, McGaugh JL. Memory interference and facilitation with posttrial amygdala stimulation: effect on memory varies with foot shock level. Brain Res 1975;86:509–13.

LeDoux JE. Brain mechanisms of emotion and emotional learning. Curr Opin Neurobiol 1992;2:191–7.

LeDoux JE, Iwata J, Cicchetti P, Reis DJ. Different projections of the central amygdala nucleus mediate autonomic and behavioral correlates of conditioned fear. J Neurosci 1988;9:2517–29.

Liang KC, McGaugh JL, Yao HY. Involvement of amygdala pathways in

the influence of posttraining amygdala norepinephrine and peripheral epinephrine on memory storage. Brain Res 1990;508:225–33.

McGaugh JL. Involvement of hormonal and neuromodulatory systems in the regulation of memory storage. Annu Rev Neurosci 1989;12:255–87.

McGaugh JL, Introini-Collison IB, Cahill L, Kim M, Liang KC. Involvement of the amygdala in neuromodulatory influence on memory storage. In: Aggleton JP, editor. The amygdala: neurobiological aspects of emotion, memory, and mental dysfunction. New York: Wiley-Liss, 1992. pp. 431–51.

Middlemiss D, Blakeborough L, Leather SR. Direct evidence for an interaction of beta-adrenergic blockers with the 5-HT receptor. Nature 1977;267:289–90.

Niehoff DL, Kuhar MJ. Benzodiazepine receptors: localization in rat amygdala. J Neurosci 1983;3:2091–7.

Pascoe JP, Kapp BS. Electrophysiological characteristics of amygdaloid central nucleus neurons during Pavlovian fear conditioning in the rabbit. Behav Neurosci Res 1985;16:117–33.

Quirarte GL, Galvez R, Roozendaal B, McGaugh JL. Norepinephrine release in the amygdala in response to footshock and opioid peptidergic drugs. Brain Res 1998;808:134–40.

Schneider AM, Koven N, Lombardo K, Levin D, Simson PE. β-adrenergic receptor blockade by propranolol enhances retention in a multi-trial passive-avoidance procedure. Behav Neurosci 2000;114:1256–60.

Simson PE, Weiss JM. Alpha-2 receptor blockade increases responsiveness of locus coeruleus neurons to excitatory stimulation. J Neurosci 1987;7:1732–40.

Watanabe Y, Ikegaya Y, Saito H, Abe K. Opposite regulation by the beta-adrenoceptor-cyclic AMP system of synaptic plasticity in the medial and lateral amygdala in vitro. Neuroscience 1996;71:1031–5.