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β-Adrenergic Receptor Blockade by Propranolol Enhances Retention in a Multitrial Passive-Avoidance Procedure

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The effect of β-adrenergic receptor blockade on retention in a mildly aversive passive-avoidance procedure was investigated. Rats were given passive-avoidance training—1 trial per day for 4 days—and were administered saline, the centrally and peripherally acting β-adrenergic blocker propranolol (4 or 10 mg/kg ip), or the peripherally acting β-adrenergic blocker sotalol (4 or 10 mg/kg ip) immediately or 2 hr after the 1st trial. Enhanced retention occurred only with the higher dose (10 mg/kg) of propranolol and only when it was administered immediately after training. The enhanced retention produced by propranolol is discussed in terms of opposing, regionally specific actions of β-adrenergic receptor-mediated neural circuits on modulation of memory.

It is well established that adrenergic systems in both the central nervous system (CNS) and the peripheral nervous system (PNS) modulate the strength of retention (Introini-Collison, Saghafi, Novak, & McGaugh, 1992; McGaugh, Liang, Bennett, & Sternberg, 1984). One site in the brain in which norepinephrine clearly plays an important role in the modulation of retention is the amygdala (Liang, McGaugh, & Yao, 1990; McGaugh, Introini-Collison, Cahill, Kim, & Liang, 1992), where blockade of β-adrenergic receptors through local application of propranolol, with some exception (Izquierdo et al., 1992), impairs retention (Gallagher, Kapp, Musty, & Driscoll, 1977; Lennartz, Hellems, Mook, & Gold, 1996). Less clear, however, is the effect on modulation of antagonizing β-adrenergic activity in the brain as a whole, the PNS, or both. Indeed, although evidence from the literature on humans is mixed regarding the ability of systemically administered β-adrenergic blockers to impair retention (Cahill, Prins, Weber, & McGaugh, 1994; Dimsdale, Newton, & Joist, 1989; McAinsh & Cruikshank, 1990; van Stegeren, Everaerd, Cahill, McGaugh, & Gooren, 1998), in rats or mice systemic administration of the centrally and peripherally acting β-adrenergic blocker propranolol, with some exception (Przybyslawski, Roullet, & Sara, 1999), appears unable to impair retention in the passive-avoidance procedure (Decker, Gill, & McGaugh, 1990; McGaugh, 1989; Saha, Datta, & Sharma, 1991).

One explanation for the inability of systemically, as opposed to locally, administered propranolol to impair retention in the passive-avoidance procedure is that blockade of β-adrenergic receptors at sites outside the sphere of influence of the locally applied drug either directly (through receptor activity per se) or indirectly (e.g., via β-adrenergic receptor-mediated neural circuits) opposes the impairment of retention produced by local application of the β-adrenergic blocker. That is, these findings raise the intriguing possibility that, depending on the site of action of β-adrenergic blockade, impairment or enhancement of retention may occur.

That blockade of β-adrenergic receptors at different sites in the brain may have opposing effects on modulation of retention is suggested by in vitro electrophysiological studies showing that stimulation of β-adrenergic receptors in different parts of the amygdala has opposing effects on short-term potentiation (STP). Specifically, stimulation of β-adrenergic receptors in the medial amygdala enhances STP, whereas stimulation of β-adrenergic receptors in the lateral amygdala suppresses STP (Watanabe, Ikegaya, Saito, & Abe, 1996).

If the opposing action of β-adrenergic receptors on STP in different regions of the amygdala also occurs with the action of β-adrenergic receptors on modulation of retention, and if the mode of drug administration affects β-adrenergic receptors in different regions of the amygdala to different degrees, one might expect local and systemic administration of β-adrenergic blockers to affect retention differentially. Indeed, one might predict that blockade of β-adrenergic receptors through systemic drug administration would enhance retention. The purpose of the present study was to test the hypothesis that blockade of β-adrenergic receptors through systemic administration of propranolol enhances retention.

We tested this hypothesis by administering, immediately after training of a mildly aversive passive-avoidance task, the peripherally and centrally acting β-adrenergic antagonist propranolol (4 or 10 mg/kg ip) or the peripherally acting β-adrenergic antagonist

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sotalol (4 or 10 mg/kg ip). The passive-avoidance task was otherwise identical to the commonly used one-trial passive-avoidance procedure (i.e., rats were given a mildly aversive footshock for stepping from a lighted to a dark compartment), with one exception: Instead of a single training trial, a multitrial procedure consisting of one trial per day for 4 days was used. Saline or drugs were administered only after the first training trial, and the enhancing or impairing effect of the drugs on retention, relative to saline controls, was measured in terms of their effect on step-through latencies (STLs) during subsequent training trials.

Method

Experimental Design

Before training on Day 1, the rats were randomly assigned to one of five groups—saline, propranolol 4 mg/kg, propranolol 10 mg/kg, sotalol 4 mg/kg, or sotalol 10 mg/kg—then were trained, and then immediately after training were given their designated treatment. Because the higher dose (10 mg/kg) but not the lower dose (4 mg/kg) of propranolol was found to increase STLs, two control experiments were conducted. In one experiment, for the assessment of the time-dependent effects of the higher dosage of propranolol, subjects received saline or propranolol (10 mg/kg) 2 hr after the first training trial. In a second experiment, for the assessment of the potentially aversive effect of the higher dosage of propranolol in and of itself, subjects received saline or propranolol (10 mg/kg ip) immediately after the first training trial in the absence of shock (no-shock control groups).

Subjects

The subjects (n = 86) were male Long-Evans hooded rats (obtained from Harlan Sprague Dawley, Indianapolis, IN) weighing 250–325 g at the start of the experiment. The rats were housed 2 to a cage with access to food and water ad libitum. The colony room was maintained at 70 °F and was illuminated on a 12-hr light–dark cycle (lights on at 9:00 a.m.). Each rat was handled daily for 15 s and was in the laboratory for at least 9 days, but not more than 18 days, before the start of the experiment. All experiments were conducted between 10:00 a.m. and 3:00 p.m.

Apparatus

The rats were trained in a standard trough-shaped passive-avoidance apparatus that consisted of a small lighted compartment (20 × 28 × 18 cm), illuminated by a 95-W bulb, connected to a larger dark compartment (20 × 28 × 42 cm). A manually operated sliding door separated the two compartments. The top of each compartment was hinged, and the floor of each compartment was made of stainless steel plates. A constant-current Lafayette Master Shocker (Model 2400SS; Lafayette, IN), set to deliver 0.35 mA of 1-s duration, was connected to the floor of the large compartment. The apparatus was located in a quiet, dimly illuminated room.

Training and Testing Procedure

The rats received four training trials, one trial per day. On each trial, with the exception of the last, all rats (except those in the no-shock control groups, which did not receive shock on the first or last trial) received shock for stepping from the lighted to the dark compartment. STLs on the first trial provided a measure of the subject's inherent (i.e., baseline) aversion of the dark compartment. STLs on each of the next three trials provided a measure of the subject's learned aversion of the dark compartment (i.e., a measure of retention). Saline or drugs were administered immediately or 2 hr after the first—and only the first—trial.

A trial consisted of the following: Each rat was placed in the lighted compartment facing away from the sliding door. After 15 s the door was raised, the rat was allowed to step into the dark compartment, the door was lowered, and shock (if this was one of the first three trials and if the rat was not in the no-shock control groups) was delivered to the floor of the compartment. The rat remained in the dark compartment for 15 s and was then removed and administered drug or saline (if this was the first trial) either immediately or 2 hr later. After each rat completed a trial, the apparatus was cleaned.

STLs on Trials 2–4 served as the measure of retention. If STLs exceeded 180 s, the trial was terminated and the rat was retired from the experiment.

Drug Administration and Drug Doses

The rats were injected intraperitoneally with saline, the peripherally and centrally acting β-adrenergic antagonist dl-propranolol hydrochloride (4 or 10 mg/kg; Sigma Chemical, St. Louis, MO), or the peripherally acting β-adrenergic antagonist sotalol hydrochloride (4 or 10 mg/kg; Berlex Laboratories, Wayne, NJ). Drugs were dissolved in saline to a concentration of 4 or 10 mg/ml.

Statistics

Data were analyzed with one-way analyses of variance (ANOVAs) and protected-t tests. Any p values (two-tailed) of less than .05 were taken as statistically significant.

Results

The results indicate, first and foremost, that blockade of β-adrenergic receptors through systemic administration of propranolol (10 mg/kg) markedly enhanced retention in the passive-avoidance procedure, an effect that was both dose and time dependent.

That the enhanced retention produced by propranolol could not be attributed to aversive effects of the β-adrenergic blocker is evidenced by results from the no-shock control rats: In the absence of shock, the STLs (mean ± *SEM*) on Day 2 (the first retention day) for no-shock control rats receiving 10 mg/kg propranolol (0.64 ± 0.40 min; n = 6) did not differ significantly, $t(10) = 0.97$, $p = .35$, from STLs for no-shock control rats receiving saline (0.24 ± 0.11 min; n = 6). The results of rats receiving shock (i.e., trained rats), however, revealed a much different picture.

Figure 1 shows the effect of β-adrenergic receptor blockade on retention over Days 2–4 in trained rats. The figure shows that propranolol significantly affected retention on Day 2: Trained subjects receiving the higher dose but not the lower dose of propranolol immediately after the first trial (Day 1) exhibited significantly greater retention on Day 2 than saline control subjects. This description of the data is confirmed by an ANOVA that revealed a significant drug effect on Day 2, $F(4, 53) = 2.88$, $p < .05$, and by multiple comparison tests that indicated that the higher but not the lower dose of propranolol enhanced retention: Rats that received the higher dose of propranolol (10 mg/kg) had significantly longer STLs than saline controls on Day 2, protected $t(53) = 3.33$, $p < .01$; rats that received the lower dose of propranolol (4 mg/kg), although they showed a tendency toward longer STLs than saline controls on Day 2, did not, protected $t(53) = 1.62$, $p > .05$. The lack of difference in STLs between saline controls and the lower dose of propranolol continued on Day 3, $F(4, 53) = 1.19$, $p > .05$, and Day 4, $F(4, 53) = 2.34$, $p >$

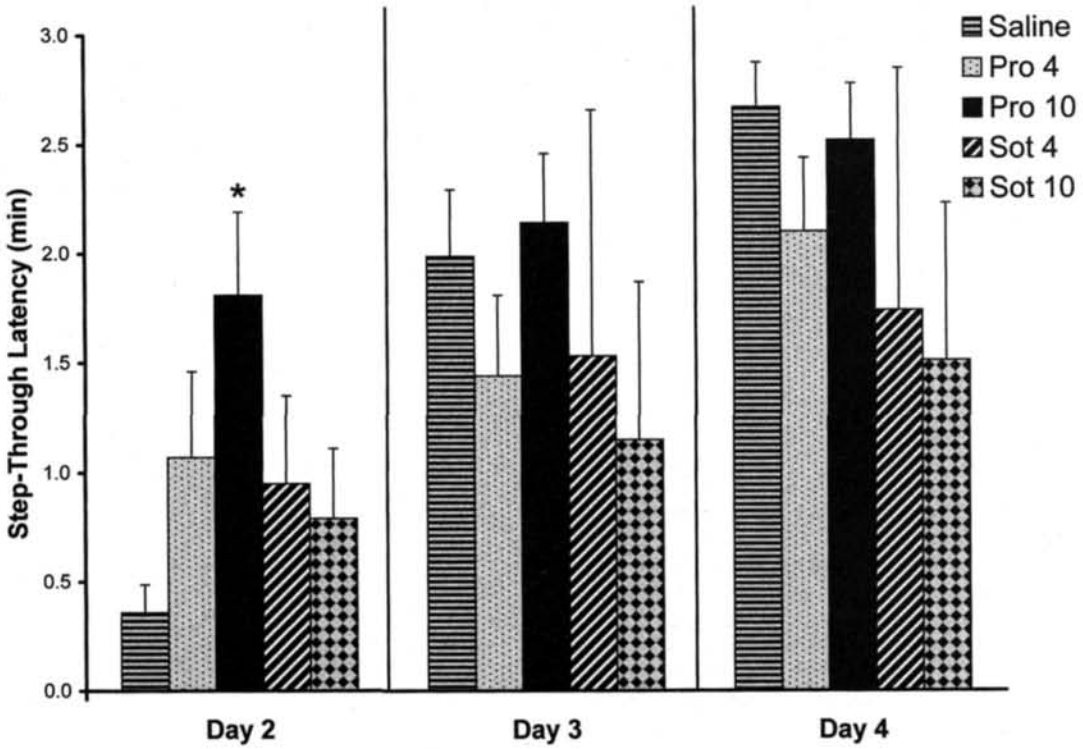

Figure 1. Mean (+*SEM*) step-through latency on Days 2, 3, and 4 for rats that received the β-adrenergic antagonists propranolol or sotalol, or saline, immediately after the first trial (Day 1). Rats receiving propranolol at a dose of 10 mg/kg (Pro 10; $n = 13$) had significantly longer STLs on Day 2 than saline controls (Saline; $n = 14$). Rats receiving propranolol at a dose of 4 mg/kg (Pro 4; $n = 13$) or sotalol at a dose of 4 mg/kg (Sot 4; $n = 9$) or 10 mg/kg (Sot 10; $n = 9$) did not differ in STLs on Day 2 compared with saline controls. The attrition rate that occurred when rats met the 180-s cutoff on a given trial is reflected in the day-by-day sample size for each group as follows: Saline, Day 2 = 14, Day 3 = 14, Day 4 = 7; Pro 10, Day 2 = 13, Day 3 = 7, Day 4 = 5; Pro 4, Day 2 = 13, Day 3 = 10, Day 4 = 8; Sot 10, Day 2 = 9, Day 3 = 8, Day 4 = 7; Sot 4, Day 2 = 9, Day 3 = 8, Day 4 = 5 . *$p < .01$, compared with saline controls.

.05. That the higher but not the lower dose of propranolol enhanced retention indicates that the β-adrenergic antagonist facilitates retention in a dose-dependent manner.

Figure 1 also shows the effects of the selective peripheral β-adrenergic antagonist sotalol on retention. Unlike propranolol, sotalol administered immediately after passive-avoidance training did not enhance retention regardless of whether subjects received the higher dose or the lower dose. This description of the data is confirmed by multiple comparison tests that indicated that rats that received the higher dose, protected $t(53) = 0.90$, $p > .05$, or the lower dose, protected $t(53) = 1.22$, $p > .05$, of sotalol did not show significantly longer STLs than saline controls on Day 2. The lack of difference in STLs between saline controls and both doses of sotalol continued on Day 3, $F(4, 53) = 1.19$, $p > .05$, and Day 4, $F(4, 53) = 2.34$, $p > .05$. That the selective peripheral β-adrenergic antagonist sotalol failed to enhance retention indicates that blockade of peripheral β-adrenergic receptors, by itself, is not sufficient to enhance retention.

In contrast to the enhancement of retention observed when propranolol (10 mg/kg) was administered immediately after the first trial, when it was administered 2 hr after the first trial, STLs (mean ± *SEM*) on Day 2 for rats receiving 10 mg/kg propranolol (1.29 ± 0.51 min; $n = 8$) did not differ significantly, $t(14) = 0.26$, $p = .40$, from STLs for rats receiving saline (1.11 ± 0.47 min; $n = 8$). This finding indicates that enhancement of retention produced by propranolol is indeed time dependent and, therefore, most likely the result of blockade of β-adrenergic receptors occurring during a critical period shortly after training when the strength of retention is regulated by adrenergic activity.

Discussion

The present results indicate that propranolol (10 mg/kg), administered systemically immediately after training, markedly enhances retention in a mildly aversive passive-avoidance task. The enhancement produced by propranolol depends on dose (occurring at a dose of 10 mg/kg but not 4 mg/kg), time of administration (occurring with immediate, but not delayed, administration), and action in the CNS (occurring with propranolol but not sotalol).

That these results stand in marked contrast to the impairment of retention found in the passive-avoidance procedure when propranolol is administered directly into the amygdala immediately after training (Gallagher et al., 1977) indicates that the mode of propranolol administration is a critical factor in determining whether

the β-adrenergic blocker enhances or impairs retention. One explanation for these results is that when propranolol is administered systemically, its sphere of influence—and thus its effect on β-adrenergic receptors—is different than when it is administered directly into the amygdala. Thus, unlike locally administered adrenergic drugs that may have effects limited to particular regions (e.g., the basolateral nucleus) within the amygdala (Ferry & McGaugh, 1999; Ferry, Roozendaal, & McGaugh, 1999), systemically administered drugs can enhance retention through adrenergic blockade of different regions to different degrees inside or outside the amygdala, or both.

It is our contention that propranolol's effect on retention, regardless of the mode of administration, is the result of blockade of excitatory and inhibitory β-adrenergic receptors, receptor-mediated neural circuits, or both. By virtue of their differential regional distribution in the brain, however, we contend that these opposing excitatory and inhibitory β-adrenergic receptors or circuits are differentially blocked by propranolol depending on the mode of administration; the blockade that dominates in turn determines the strength of retention despite the counter-influence of the other. It follows, then, that when systemic administration of propranolol facilitates retention, it does so because the facilitating effect of blockade of one type of β-adrenergic receptor or circuit (a receptor or circuit that in the absence of propranolol inhibits retention) outweighs the impairing effect of blockade of the opposing type of β-adrenergic receptor or circuit (a receptor or circuit that in the absence of propranolol facilitates retention). By the same reasoning, local administration of propranolol impairs retention (Gallagher et al., 1977) because the impairing effect of blockade of one type of β-adrenergic receptor or circuit (a receptor or circuit that in the absence of propranolol facilitates retention) outweighs the facilitating effect of blockade of the opposing type of β-adrenergic receptor or circuit (a receptor or circuit that in the absence of propranolol inhibits retention).

In view of the relative importance given to the role of the adrenergic system in memory modulation, it is perhaps surprising that a β-adrenergic receptor or circuit inhibiting retention was not uncovered earlier. One reason—the one that distinguishes the present study— may be methodology: the unique combination of a training procedure that produces weak retention with a drug procedure using systemic administration of a relatively high dose of β-adrenergic blocker. On the other hand, although the notion of an adrenergic memory-modulation circuit whose function is to inhibit retention is new, the notion of inhibitory memory-modulation circuits, in general, is not. Like the β-blocker propranolol, the opiate and gamma-aminobutyric acid (GABA) antagonists naloxone and bicuculline, respectively, have been shown to enhance retention; thus, like the proposed β-adrenergic receptor or circuit in the present study, endorphin-mediated and GABAergic receptors or circuits have been postulated to inhibit retention (Brioni & McGaugh, 1988; Castellano, Brioni, & McGaugh, 1991; Gallagher, 1982; Izquierdo, 1979; Messing et al., 1979). Moreover, the fact that propranolol has at least some antiserotonergic activity (Middlemiss, Blakeborough, & Leather, 1977) leaves open the possibility that propranolol may enhance retention, at least in part, through a serotonergic receptor or circuit.

In conclusion, the enhancement of retention found in the present study with systemic administration of the β-adrenergic antagonist propranolol indicates that the role of the β-adrenergic system in modulation of retention is complex and multifaceted. The present results suggest the existence of a modulatory circuit that is suppressed by a relatively high dose of propranolol and that is inhibitory in nature. Precisely how this circuit is related to the known inhibitory memory modulation system remains to be determined.

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