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The Effects of Ethanol on Striatal Dopamine and Frontal Cortical D-[^{3}H]Aspartate Efflux Oscillate with Repeated Treatment

Relevance to Individual Differences in Drug Responsiveness

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Numerous inconsistencies in the reported effects of drugs that can be found in both the human clinical and animal experimental literatures have prompted attempts to identify the basis of this variability. Our data suggest that one source may derive from the tendency of many systems to oscillate in their response to repeated drug or stress exposure. In the first experiment a single administration of ethanol to male rats, either 2 or 30 minutes or 2 weeks before sacrifice suppressed amphetamine-induced dopamine efflux from striatal slices. However, when ethanol was given both 2 weeks and 30 minutes before sacrifice, the two treatments significantly attenuate each other's effects. In Experiment 2, the stress of a novel environment (black box) 30 minutes before sacrifice decreased fractional D-[^{3}H]aspartate efflux from the medial frontal cortex. When a single injection of ethanol 1 week earlier was added to black box exposure, it depressed efflux still further. However, adding a third treatment (ethanol at 2 weeks and 1 week + black box at 30 minutes) significantly reversed the effects of the two treatments (ethanol + black box). When a four-treatment chain was used (ethanol at 3, 2, and 1 week + black box at 30 minutes), the attenuation of efflux was reinstated. These data complement other findings from this laboratory showing that repeated stress or drug exposure can lead to an oscillatory pattern of change in the effects of future exposures and, in this way, contribute to variability in drug responsiveness. ***[Neuropsychopharmacology 15:125–132, 1996]***

KEY WORDS: *Ethanol; Dopamine release; Aspartate release; Stress; Striatum; Frontal cortex; Oscillation*

Variability in responsiveness to drugs is a major problem in the treatment of human clinical disorders as well as in the replicability of pharmacological research results involving both humans and laboratory animals. For example, improvement rates for many therapeutic drugs range from 65 to 70% (Baldessarini 1985). Thus, roughly 30% of patients obtain little or no benefit from their treatment. Most of this cannot be accounted for by traditionally recognized variables such as incorrect diagnosis or inadequate dosage and has led to the increased establishment of drug-resistance clinics. Moreover, even within individuals, considerable variability in the effect of a drug can exist from one time to another. One well-documented instance of this is the "on-off" effect seen following chronic L-dopa therapy in Parkinson's disease (Jankovic and Marsden 1993).

The problem of variability of drug responsiveness is prominent in animal experimentation as well (Kuczenski and Segal 1988; Robinson 1988). Of particular im-

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portance for the present research are the inconsistent reports that repeated exposure to the same drugs can evoke either increases (Robinson and Becker 1986; Kalivas and Stewart 1991; Zahniser and Peris 1992) or decreases (Segal and Kuczenski 1992a, 1992b; Zahniser and Peris 1992; Kalivas and Duffy 1993) in dopamine (DA) efflux. Some of these discrepancies may be the result of differences in dose or measurement intervals. For example, it has been hypothesized that decreases are a function of high dose or early withdrawal-induced tolerance, whereas late-withdrawal paradigms induce enhanced release (Kalivas and Duffy 1993). However, this formulation cannot explain all such inconsistencies, as we have reported decreases in AM-induced DA efflux with a dose of cocaine considered a "low" dose (Kalivas and Duffy 1993) while using "late-withdrawal" periods of 1 and 2 weeks (Antelman et al., 1995).

Recently, two series of studies from this laboratory suggest that these disparities in drug response may reflect, at least in part, differences in the state of the animal at the time of measurement and, most remarkably, that this state of responsiveness can be alternately increased and decreased by successive, intermittent exposures to drugs or stress. In one series of experiments (Antelman et al. 1995), cocaine was administered to rats once, either 30 minutes, 1 or 2 weeks before sacrifice. Each treatment by itself markedly decreased the ability of amphetamine (AM) to release DA from brain slices of the corpus striatum. However, the combination of 30-minute and 1-week treatments significantly reversed the effect of either one alone. In animals that received all three treatments, the suppression of AM-induced DA efflux was completely reinstated. A similar pattern was obtained for the in vivo effects of cocaine on plasma corticosterone and glucose and on in vitro K^+-stimulated norepinephrine efflux from slices of the right atrium of the heart. These findings suggest that when a drug is given intermittently, each administration changes the animal's response to the next administration of the drug—possibly by altering the baseline responsiveness on which the next treatment acts. Under some circumstances, this pattern of drug administration may lead to an oscillation of drug responsiveness.

The other series of studies demonstrating this phenomenon is reported here. Experiment 1 documents the effects of a different drug, ethanol (ETOH), on AM-induced DA efflux from striatal slices. ETOH, at the dose used here, can act as an N-methyl-D-aspartate (NMDA) antagonist (Carboni et al. 1993) and, as such, might be expected to decrease AM-induced DA efflux (Moghaddam and Bolinao 1994). In experiment 2, a nonpharmacological stressor, a novel environment, is used in sequence with ETOH administration to begin an investigation of whether drugs and nondrug stressors are interchangeable in producing the oscillatory effect, as would be predicted from our previous work (Antelman 1988; Antelman et al. 1992) as well as from the work of others (Kalivas and Stewart 1991). This second experiment also extends the generality of this effect to another transmitter system. The NMDA receptor is very sensitive to acute inhibition by ETOH, and ETOH attenuates NMDA-evoked elevations in extracellular concentrations of glutamate (Carboni et al. 1993). Similarly, restraint stress causes a regionally selective increase in the extracellular concentrations of excitatory amino acids in rat prefrontal cortex (Moghaddam 1993). Here we used the K^+-evoked release of preaccumulated D-[^{3}H]aspartate, which provided a good measure of the release of endogenous aspartate and glutamate (Palmer and Reiter 1994), to assess the effect of both ETOH and stress on excitatory amino acid release from the rat frontal cortex.

METHODS

Subjects

The subjects were adult, male Sprague-Dawley (specific pathogen free) rats obtained from a local supplier (Zivic-Miller Laboratories, that weighed 150 to 175 g upon arrival. Rats were housed in pairs in a sound, temperature-, and humidity-controlled colony room on a 12–12 hour (0600–1800) light/dark cycle and given free access to Wayne Lab Blox and water during an initial 9- to 13-day acclimation period. Animals were weighed daily during that period. All treatments and manipulations were conducted from 0800 to 1300.

Ethanol and Stress Treatments

ETOH, in a 10% w/v saline solution, was administered intraperitoneally (IP) in doses of 0.5, 1, or 2 g/kg. In Experiment 1 animals were randomly assigned to one of 15 groups (N = 8–9/group): one was untreated (home cage controls); six groups received a single ETOH injection at different times before sacrifice (1 g/kg at 2, 5, 15, or 30 minutes; 0.5 or 2 g/kg at 2 weeks); eight groups received two ETOH injections, the first (either 0.5 or 2 g/kg) at 2 weeks and the second (1 g/kg) at 2, 5, 15, or 30 minutes before sacrifice. In experiment 2, rats were randomly assigned to an untreated, home cage control group or 1 of 4 experimental groups (N = 8/group): (1) psychological stress of a novel environment (Hennessy and Levine 1978), which was induced by removing the animal from its home cage, placing it into a clean, black, opaque, plastic box (34 × 22 × 17 cm) for 10 minutes and returning it to its home cage 30 minutes before sacrifice; (2) one injection of ETOH (0.5 g/kg) 1 week before black box exposure and sacrifice 30 minutes later; (3) two ETOH injections, one at 2 weeks and the second 1 week before black box exposure; (5) three ETOH injections at 3, 2, and 1 week before black box treatment and sacrifice.

Amphetamine-Evoked Dopamine Efflux

AM-evoked DA efflux from rat striatal slices was determined using the method of Snyder et al. (1990). After the animals were sacrificed by decapitation, their brains were rapidly removed, and freshly dissected striata were cut with a McIlwain tissue chopper to obtain 350-μm-thick coronal slices. For superfusion, four slices were placed in each chamber of a six-chamber superfusion system (Superfusion 6, Brandel, Gaithersberg, MD). They were then perfused with Krebs buffer, bubbled with 95% O_2-5% CO_2 and containing 113 mM NaCl, 4.7 mM KCl, 2.5 mM $CaCl_2$, 1.2 mM $MgSO_4$, 25 mM $NaHCO_3$, 1.2 mM KH_2PO_4, 11.5 mM glucose, and 0.3 mM ascorbic acid at a rate of 0.24 ml/minute at 37°C. After a 60-minute equilibration period, fractions were collected at 5-minute intervals into disposable plastic tubes containing 50 μl of 0.1 N perchloric acid and 1 ng of the internal standard, 3,4-dihydroxybenzylamine. After the first two baseline fractions were collected, DA efflux was evoked by adding 10 μM AM to the perfusion buffer for 5 minutes, and seven additional fractions were collected. The superfusate fractions were then stored at −20°C until DA concentrations were determined by HPLC with electrochemical detection. The DA was extracted from each superfusate by adding 50 mg of alumina and 200 μl 1 M Tris buffer-EDTA-sodium metabisulfite (pH 8.6). The alumina was washed twice in 0.1 M Tris buffer (pH 8.6), and the catechols were eluted by adding 0.1 N perchloric acid. The samples were injected by a Waters WISP autoinjector onto a 5-μm Biophase ODS column (mobile phase 0.1 M chloroacetic acid, 2 mM EDTA, 1.5 mM octanesulfate, and 13% methanol, pH 3.2). The amperometric detector was set at an oxidizing potential of +0.7 V (vs. Ag/AgCl). Mean baseline values were calculated in each superfusion experiment as the average of the two pre-AM fractions and the last (9th) fraction. Total AM-evoked efflux for each rat was determined by adding the six post-AM fractions and subtracting six times the mean baseline value.

Superfused Efflux of D-[^{3}H]aspartate

The neocortex was sliced at 300-μm intervals in two directions separated by an angle of 45°C using a McIlwain tissue chopper (Mickle Laboratories, Gomshall, Surrey, UK). The resultant minislices were then placed in ice-cold, oxygenated (95%O_2–5%CO_2), CA^{2+}-free Krebs-ringer medium (Ca^{2+}-free KRM, composition in mM: NaCl, 128; KCl, 5; $MgSO_4$, 1.2; Na_2PO_4 1; $MgCl_2$; 2.7; glucose 10; HEPES, 20, pH 7.4). After being washed with Ca^{2+}-free KRM, the minislices were oxygenated (1 minute) and equilibrated at 37°C in a water bath with shaking for 5 minutes. D-[^{3}H]aspartate (200 nM, 4.1 μCi/ml) was then added and the preincubation continued for an additional 25 minutes. The minislices were washed three times with ice-cold Ca^{2+}-free KRM, decanted into a beaker, and then transferred to a chamber (300 μl void volume) of the superfusion apparatus. After a 15-minute period of superfusion (1.6 ml/minute) with KRM (composition the same as Ca^{2+}-free KRM except $MgCl_2$ was replaced by $CaCl_2$), the chambers were exposed to CA^{2+}-free KRM or KRM. Collection of 15 successive 0.5-minute fractions was begun at t = 30 minutes, and the minislices exposed to a depolarizing stimulus (KRM with 50 mM KCl replacing an equimolar portion of NaCl) at t = 32 to 33 minutes. Superfusate fractions were collected into 7-ml vials and radioactivity determined by liquid scintillation spectrometry, following the addition of biodegradable scintillation fluid (Ecolite, ICN, Costa Mesa, CA). D-[^{3}H]aspartate efflux was calculated as the fraction of the radioactivity in the minislices at the onset of the respective collection period (fractional efflux). Mean baseline values were calculated in each superfusion experiment from predepolarization fractions and the total K^+-evoked efflux determined by estimating the area under the curve. The area under the curve was calculated as the sum of the amount of D-[^{3}H]aspartate efflux in seven samples after depolarization minus the mean baseline value.

Statistical Analyses

Preliminary analyses indicated that no baseline differences existed between groups. To determine group differences in efflux, total evoked efflux (see before) was first subjected to one-way analyses of variance (ANOVAs) followed by comparisons between individual groups. For Experiment 2, this took the form of preplanned linear contrasts within the general linear model. They were limited to four comparisons of successive experimental treatments (i.e., no treatment group vs. black box group; black box group vs. group receiving 1 ETOH treatment before black box; etc.). However, since Experiment 1 included many more groups and potential comparisons, post hoc analyses were conducted using the Tukey HSD test, with p values set below .05. In order to approximate the homogeneity assumptions of these parametric analyses, all data from Experiment 1 were first normalized by using $\log_{10}$ transformations. Such assumptions were not violated in Experiment 2.

RESULTS

AM-Induced DA Efflux

Overall, one injection of ETOH reduced AM-induced DA efflux, and two injections substantially reversed each other's effect [$F(14,114) = 30.10$, $p < .001$]. A single IP injection of ETOH (1 g/kg) significantly reduced AM-induced DA efflux to 53 to 35% of control, when

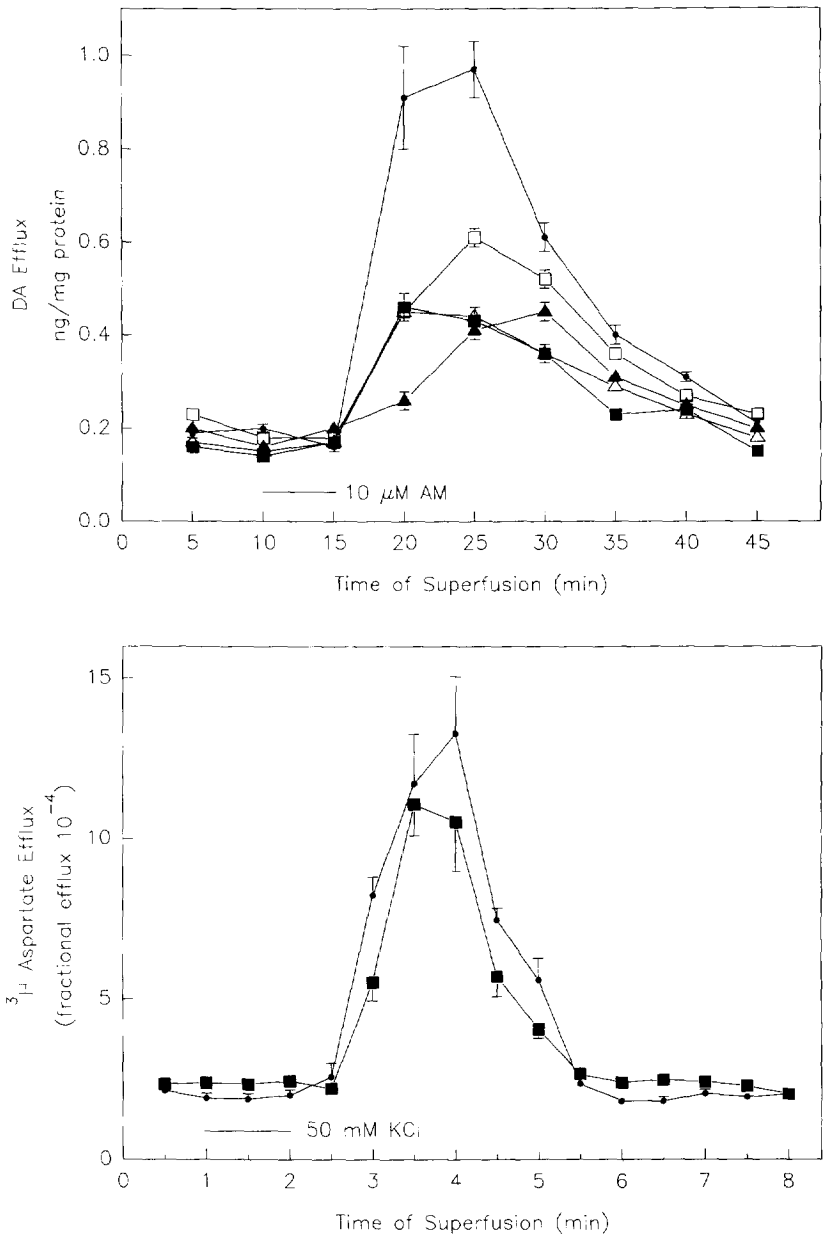

Figure 1. *Top*: Amphetamine (AM)-evoked DA efflux from striatal slices taken from untreated, control rats or rats given one injection of ETOH (1 g/kg) 2 (*solid triangles*), 5, (*empty squares*) 15 (*solid squares*) or 30 minutes (*empty triangles*) before sacrifice ($p < .05$ or greater for each group vs. control). *Bottom*: KCl-evoked D-[^{3}H]aspartate efflux from slices of medial frontal cortex taken from control rats or rats placed into a black box (*solid squares*) for 10 minutes, 30 minutes before sacrifice ($p < .01$ vs. control). Statistics were done on the total efflux values for each group, as described in Experimental Procedures. *Black dots* for both panels, no treatment.

given 2, 5, 15, or 30 minutes before sacrifice [$p < .05$ or greater, each group vs. untreated control; $p > .05$ from each other, except for the 5-minute group (higher than the 2-minute group); $p < .05$; Figure 1]. A similar degree of attenuation (35 to 31% of control) was achieved when 0.5 or 2 g/kg of ETOH was injected 2 weeks before sacrifice (Figure 2; $p < .05$). However, when additional animals received two ETOH injections, one at 2 weeks and the second at 2 to 30 minutes before sacrifice, the two treatments substantially reduced each other's effects (Figure 2). That is, for eight groups that received two injections, the degree of attenuation was significantly less than the corresponding single-injection groups in 22 of 24 comparisons ($p < .05$ or greater).

Finally, there was some evidence for time-dependent sensitization (Antelman 1988), because single treatments at the 2-week interval produced significantly greater attenuation of AM-induced DA efflux than single treatments at the shorter interval for the 5-, 15-, and 30-minute, but not the 2-minute conditions (Figure 2).

KCl-Evoked D-[^{3}H]asparate Efflux

In Experiment 2, the novel environment (black box) produced a 19% decrease in fractional D-[^{3}H]aspartate efflux [to 81% of untreated control; $p < .01$ vs. control; Figure 1; Overall ANOVA, $F(4,35) = 16.70$ $p < .001$]. When a single injection of ETOH 1 week earlier was added to black box exposure, it depressed efflux (significantly) further (to 68% of control; $p < .01$ vs. black box alone; Figure 3). However, adding a third treatment (ETOH at 2 weeks and 1 week + black box at 30 min-

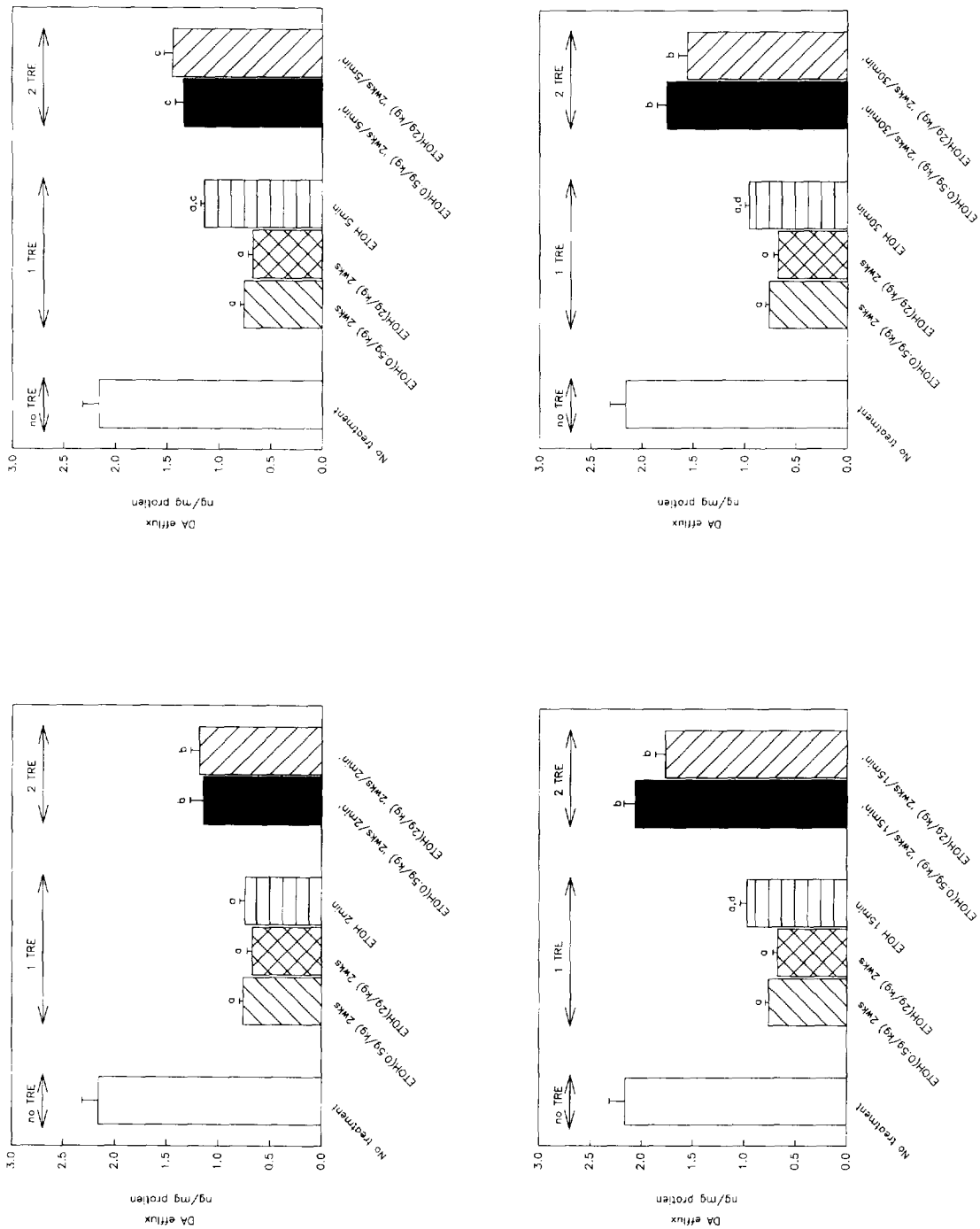

Figure 2. Amphetamine-evoked (10 μM) total DA efflux from striatal slices taken from untreated, control rats (no TRE) or rats given one (1-TRE) or two (2-TRE) injections of ETOH at various times before sacrifice (see Experimental Procedures for calculation of total efflux). All ETOH injections given either 2, 5, 15, or 30 minutes before sacrifice were at a dose of 1 g/kg. The first three groups are repeated in each panel for clarity of illustration. The following comparisons were significant at $p < .05$ or greater: a, *vs.* no TRE; b, *vs.* all 1-TRE groups; c, *vs.* only 1-TRE groups at 2 weeks; d, *vs.* ETOH (2g/kg) at 2 weeks.

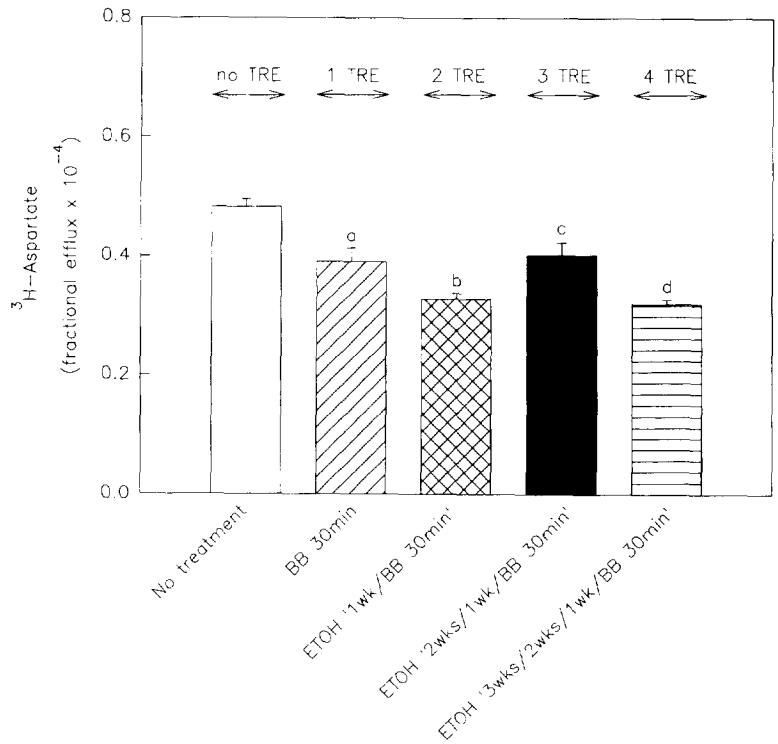

Figure 3. Total D-[^{3}H]aspartate efflux from medial frontal cortex, evoked by 50 mM KCl, following administration of 0.5 g/kg ETOH 1–3 weeks and/or a 10-minute period in a black box (BB) 30 minutes, before sacrifice. a, BB 30 minutes, $p < .001$ versus no TRE; b, ETOH 1 week, $p < .01$ versus BB 30 minutes; c, ETOH 2 weeks, $p < .004$ versus ETOH 1 week/BB 30 minutes; d, ETOH 3 weeks, $p < .002$ vs. ETOH 2 weeks/1 week/BB 30 minutes. See Experimental Prodecures for calculation of total efflux.

utes) significantly reversed the effects of the two exposures (back to 83%; $p < .004$ vs 1 ETOH pretreatment before the black box). When a four-treatment sequence was used (ETOH at 3, 2, and 1 week + black box at 30 minutes), the attenuation of efflux was reinstated to 66% of control ($p < .002$ vs. the three-exposure group).

DISCUSSION

The results of the present study show that successive drug administration, even at intervals up to 2 weeks, can alternately increase and decrease the response to subsequent drug treatment. This pattern was seen for the effects of ETOH on AM-induced DA efflux from the striatum in Experiment 1 and on KCl-evoked D-[^{3}H]aspartate efflux from the medial frontal cortex in Experiment 2. The present results are virtually identical to those we have obtained for the effects of cocaine on striatal DA efflux, plasma corticosterone, and glucose levels and norepinephrine efflux from the heart (Antelman et al. 1995). Our findings suggest that over a wide array of physiological systems, variability in the effects of drugs may reflect, in part, oscillations in the animal's state of responsiveness that are induced by successive, intermittent drug exposure.

In the first experiment, a single administration of ETOH, either 2 to 30 minutes or 2 weeks before sacrifice suppressed AM-induced DA efflux from striatal slices, and in Experiment 2, a similar decrease in KCl-evoked D-[^{3}H]aspartate efflux was produced by the stress of a novel environment. The observation that suppression of DA efflux can also be obtained with cocaine or with physical stressors such as immobilization (Antelman et al. 1995) or an IP injection of isotonic saline (unpublished observations) indicates that this effect is not peculiar to the specific pharmacological characteristics of ethanol. The proposal that the long-term effects of drugs on future responsiveness are more a function of their common, stressful properties than of their unique pharmacological characteristics is consistent with a wealth of data (Antelman 1988; Antelman et al. 1992; Jankovic and Marsden 1993). It also suggests that this oscillatory effect can be induced by nonpharmacological stressors. The fact that nonpharmacological stressors, including vehicle injections (see before), can mimic the types of effects produced by ETOH in Experiments 1 and 2, makes the use of vehicle "controls" inappropriate, as discussed elsewhere (Antelman et al. 1995). Moreover, it is not likely that the reversal of ETOH's effects with two injections, seen in Experiment 1, was simply the result of desensitization to the stress of injection. First, one injection of ETOH at 2 weeks reduced efflux at least as much as a single injection at 2 to 30 minutes. Thus, even if the stress of the first (2-week) injection desensitized the animal to the stress of the second (2- to 30-minute) injection, the efflux-reducing effects of the 2-week injection should still have been in evidence. The other reason for rejecting a simple desensitization explanation is that we have observed alternating reversals through two to six

cycles of injections (Experiment 2; Caggiula et al. 1994; Antelman et al. 1995).

As discussed, we have found that prior exposure to cocaine can, like ETOH, reduce AM-induced DA efflux from striatal slices. In contrast, others have reported both increases and decreases of in vitro DA efflux using basically the same paradigm (Zahniser and Peris 1992). A similar disparity is seen with in vivo measurements of DA release. Thus some have reported increased release of DA after repeated AM or cocaine administration, using microdialysis (Akimoto et al. 1989; Robinson and Camp 1991), whereas others have reported decreases employing the same measure (Segal and Kuczenski 1992a, 1992b). It has been suggested that differences in dose and drug-measurement interval may account for these disparities (Kalivas and Duffy 1993). Our findings that the effects of stress, ETOH, or cocaine on DA efflux can be substantially altered by the existence and number of previous treatments suggest that disparities such as those found in the literature may also reflect differences in the state of the animal at the time of measurement and may have resulted from previous drug or stress exposures. A somewhat similar pattern of reversals may have occurred in Experiment 2. Stress has been reported to increase the extracellular level of excitatory amino acids in the rat prefrontal cortex (Moghaddam 1993). ETOH can act as an NMDA receptor antagonist and should decrease the release of excitatory amino acids (Carboni et al. 1993). However, in this study, stress partially reversed the increase in D-[^{3}H]aspartate release evoked by K^+, and the influence of repeated ETOH treatments was successively to enhance or attenuate this stress effect. This perspective has been greatly strengthened by a recent finding in our laboratory. The effects of cocaine pretreatment on AM-induced DA efflux oscillated over six cycles; animals given cocaine 30 minutes before sacrifice exhibited an increase in stimulated efflux above controls, if there had been no earlier exposure, but a decrease below controls if previously given five cocaine injections at 4-day intervals (Caggiula et al. 1994).

Finally, earlier research, as well as some of the present results, suggest that these oscillatory effects of repeated drug exposure may be related to sensitization. Both are induced by drugs and nonpharmacological stressors, affect an array of physiological systems, and are extremely long-lasting (Antelman 1988; Antelman et al. 1992). In the present study the suppression of KCl-evoked D-[^{3}H]aspartate efflux produced by the novel stressor (black box) was even greater in animals that received an ETOH injection 1 week earlier (i.e., ETOH may have sensitized the effect of exposure to the black box). Only after the second and subsequent ETOH injections did the effects on efflux exhibit the oscillation. This pattern leads us to suggest that sensitization to stressors would be expected when a system is well within its physiological boundaries or limits, whereas oscillations or resetting of systems would occur when those boundaries are approached. The apparent relationship between sensitization and oscillation may also suggest where to look in seeking the underlying mechanism(s) of the latter. There is considerably more support for presynaptic than for postsynaptic changes that may form the basis of stimulant-induced sensitization, and some of the presynaptic changes that have been proposed include an increase in the pools of releasable DA, diminished DA uptake and/or decreased DA metabolism, DA autoreceptor subsensitivity, and increased DA synthesis (Robinson and Becker 1986; Zahniser and Peris 1992). Similarly, in our initial efforts along these lines, we are looking at the effects of a repeated cocaine treatment paradigm that produces oscillation of AM-induced striatal and n. accumbens DA efflux on tyrosine hydroxylase activity from the same tissue.

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