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Behavioral Withdrawal Following Several Psychoactive Drugs[1]

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SIMPSON, D. M. AND Z. ANNAU. *Behavioral withdrawal following several psychoactive drugs.* PHARMAC. BIOCHEM. BEHAV. 7(1) 59-64, 1977. – The chronic administration of several psychoactive drugs has been suggested to produce behavioral withdrawal syndromes in the absence of physical withdrawal. The present study employed four representative psychoactive drugs, amphetamine, chlorpromazine, iproniazid, and desipramine, in a common behavioral paradigm using electrical stimulation of the brain to test for behavioral withdrawal. Behavior differing from both predrug and drug produced behavior occurred following the termination of amphetamine, iproniazid and chlorpromazine administration. The first two drugs produced an increase in self stimulation during administration, followed by a very significant decrease after the drugs were discontinued. Chlorpromazine administration on the other hand, produced a decrease in self stimulation rates, followed by a rebound increase after termination of treatment. No systematic effects were observed with desipramine. The relationship between the behavioral effects of these drugs during and following treatment and possible homeostatic mechanism influencing response tendencies is discussed.

Physical withdrawal Behavioral withdrawal Psychoactive drugs Self-stimulation rates

EXPERIMENTAL studies of withdrawal syndromes associated with chronically administered drugs have dealt primarily with drugs that produce physical dependence. Weight loss, alterations in seizure threshold, hyperthermia, and a variety of other physiological variables have been used to study the physical withdrawal syndromes that appear following the chronic administration of these drugs [7,13]. The study of behavioral changes that occur concomitantly with physical symptoms is difficult in light of the severity of the symptoms. There is evidence to suggest, however, that several behaviorally active drugs which produce no marked physical withdrawal symptoms have an associated withdrawal syndrome best characterized as behavioral in nature. Amphetamine is one such drug.

Human studies of chronic amphetamine intake have linked withdrawal with the symptoms of fatigue, decreased activity, and depression of several days duration, following the elevation of mood and activity during drug ingestion [16, 30, 38]. Several different measures of locomotor activity in animals similarly indicate a decrease in activity below predrug levels upon withdrawal from chronic amphetamine [6, 9, 12, 36, 38]. Changes in rate of more complex behaviors such as decreases in avoidance responding and increases in hoarding, have also been described following discontinuation of amphetamine treatment [11,17]. While amphetamine, within limits, tends to increase the rate of various behaviors acutely, chlorpromazine, another drug characterized by lack of physical withdrawal, produces opposite acute effects. Additionally, the behavioral withdrawal syndrome associated with chlorpromazine appears opposite to that associated with amphetamine. Studies in animals have shown an increase in avoidance responding and locomotor activity following termination of drug administration [2,18].

Despite these suggestions of a behavioral withdrawal syndrome for psychoactive drugs, there has been no systematic attempt to study the behavioral effects of withdrawal from several different types of psychoactive drugs using a common behavioral variable. The purpose of the present set of experiments was to provide such a study using four drugs, each representing a class of agents that have been used to alter CNS function. None of the drugs produces classical physical dependence [13]. Amphetamine was chosen as a psychomotor stimulant, chlorpromazine (CPZ) as a neuroleptic, desipramine (DMI) as a

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tricyclic antidepressant, and iproniazid as a monoamine oxidase inhibitor. The behavior variable chosen for this study was electrical self-stimulation of the brain (ESB). Each of the four drugs has been previously shown to produce changes in rates of ESB when administered acutely [9, 21, 22, 24, 31, 32, 33, 34]. In order to study chronic effects of these drugs, rats were given unlimited 24 hr access to ESB. It has been previously shown that under these conditions, rats develop stable daily rates of responding that are sensitive indicators of environmental manipulation [1,15].

METHOD

All experiments used male, hooded rats weighing 350–500 g. Under pentobarbital anesthesia, bipolar stainless steel electrodes (Plastic Products 303) were placed at coordinates relative to bregma, posterior 4.5 mm, lateral right 1.5 mm, 8.5 mm below the level of the skull. After recovery from surgery, animals were placed in individual chambers, acoustically isolated on a 12 hr light/dark cycle with light from 8 a.m. to 8 p.m. These chambers were 24 × 24 × 24 cm clear plastic with a stainless steel grid floor. A metal lever attached to a microswitch, when depressed with a 5 g force, activated the brain stimulation circuit, on a continuous reinforcement schedule. The animal was connected to the stimulator by way of a flexible cord (Plastic Products MS304) connected to a commutating device, which allowed the animal unrestricted movement in the chamber. Food and water were available ad lib. Each lever press delivered a 0.25 sec 60 Hz pulse train from a constant current source. Stimulating current for each rat was adjusted to give 2000–5000 lever presses per day (83–208 lever presses/hr). A stable baseline was considered to be at least three days of unchanged current setting, during which the rates of ESB remained within these limits.

Following the establishment of a baseline rate for each animal, drug injections were begun. All drugs were injected intraperitoneally in a 0.5 cc saline vehicle, and the doses were given as salts. Four groups of animals were used, one for each drug. These groups were further subdivided to provide a separate subgroup for each dose schedule. d-Amphetamine sulphate was tested at three doses, 2.5 mg/kg (6 rats), 5 mg/kg (7 rats) and 10 mg/kg (5 rats). Each amphetamine dose was administered three times a day at 9 a.m., 5 p.m. and 1 a.m. for five days. Due to the short half-life of amphetamine in the rat brain of about 90 min [19], this multiple injection schedule was selected to prevent complete drug withdrawal from occurring within each 24 hr period. Chlorpromazine hydrochloride was administered once a day at 1 p.m. for three days at three different doses, 3 mg/kg (7 rats), 10 mg/kg (7 rats) and 30 mg/kg (7 rats). Desipramine hydrochloride was administered daily at 1 p.m. according to three dose schedules, 10 mg/kg was given for either three days (6 rats) or five days (8 rats), and 30 mg/kg was given for only three days (6 rats). Iproniazid was given daily at 1 p.m. for three days at two doses, 25 mg/kg (7 rats) and 100 mg/kg (4 rats).

Rates of ESB were monitored during drug injection and for a minimum of five days following the last injection. A day was defined as noon to noon. For statistical analyses, all data were expressed as percent control rate for each animal. Control rate was taken by averaging the number of responses over the three predrug baseline days, and ranged from 122 to 147 bar presses per hour for the various groups. Day one postdrug was not included in the analyses to prevent the carryover of acute drug effects into the withdrawal period. Split-plot analysis of variance was run for each drug comparing Days 2–4 postdrug against the different dose schedules [5]. The mean response rate during drug administration, the grand mean response rate for Days 2–4 postdrug and Days 2–4 postdrug analyzed separately, were compared to control levels using a two-tailed *t*-test for matched pairs. In the presence of a significant between-dose effect in the analysis of variance, or in the presence of large heterogeneity of variance between doses, a *t*-test for nonhomogeneous variance was used for between-dose comparisons.

RESULTS

Histology on a random selection of brains showed consistent placement of electrode tip in the posterior hypothalamus around coordinates 1.5 mm lateral, 2.5 mm inferior, 2.95 mm anterior [14] (Fig. 1).

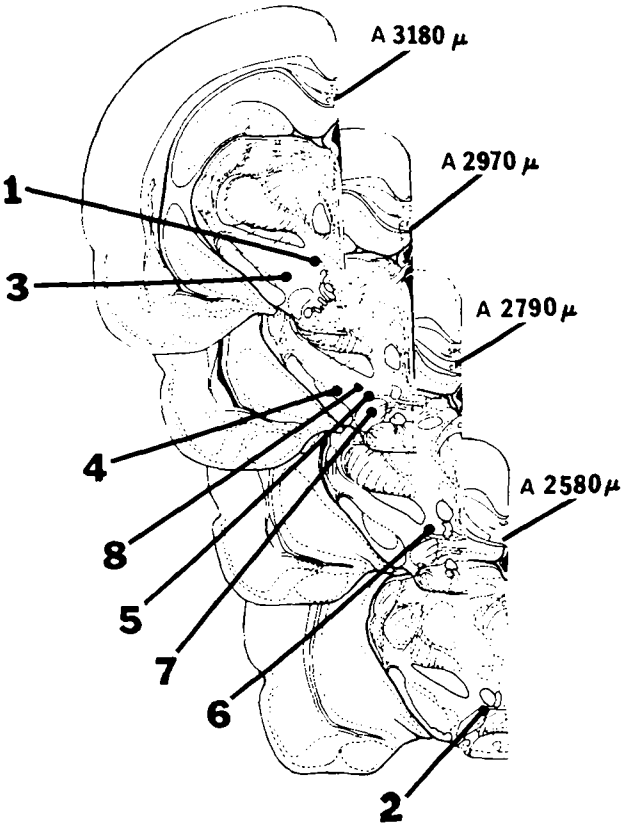

FIG. 1. Representative histological sections taken from animals used in the experiments with the electrode placements drawn on the appropriate coronal sections taken from the Konig and Klippel Stereotaxic Atlas [14]. Animals 6 and 8 received amphetamine, 1 and 4 desipramine, 2 and 5 chlorpromazine and 3 and 7 iproniazid.

The results of amphetamine treatment are presented in Fig. 2. The mean rate for the five days of drug administration is compared with the mean rate for Days 2–4 postdrug for each of the three amphetamine doses. Data are shown as percent change from control rate ± standard error of the mean. During amphetamine administration, the mean percent increases in ESB were 407% for the 2.5 mg/kg group,

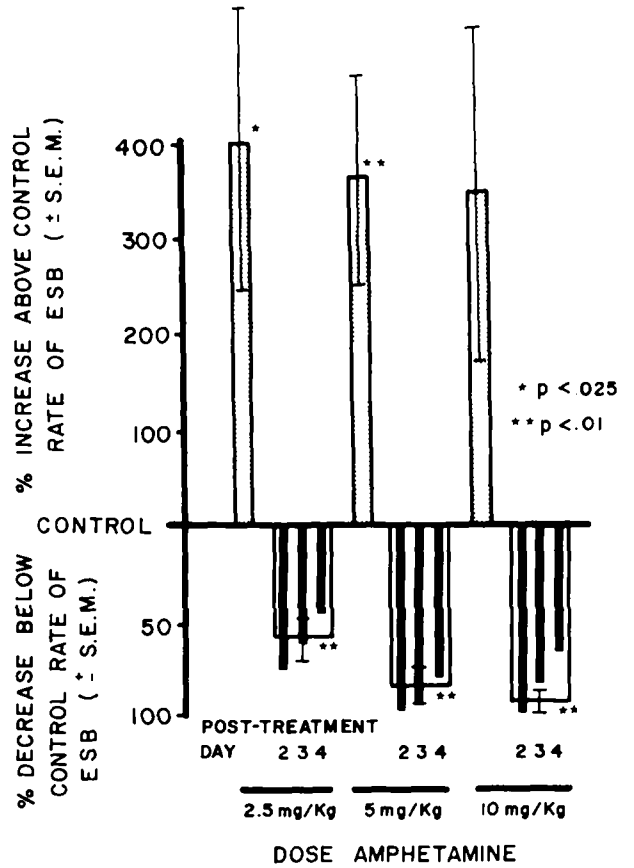

FIG. 2. Rates of ESB during (stippled bars) and following (clear bars) d-amphetamine treatment. Mean rates for days 2–4 of withdrawal are shown by solid lined bars. Note expanded scale below 100% control rate. Statistical significance is based on comparison to control rate with *t*-test for matched pairs.

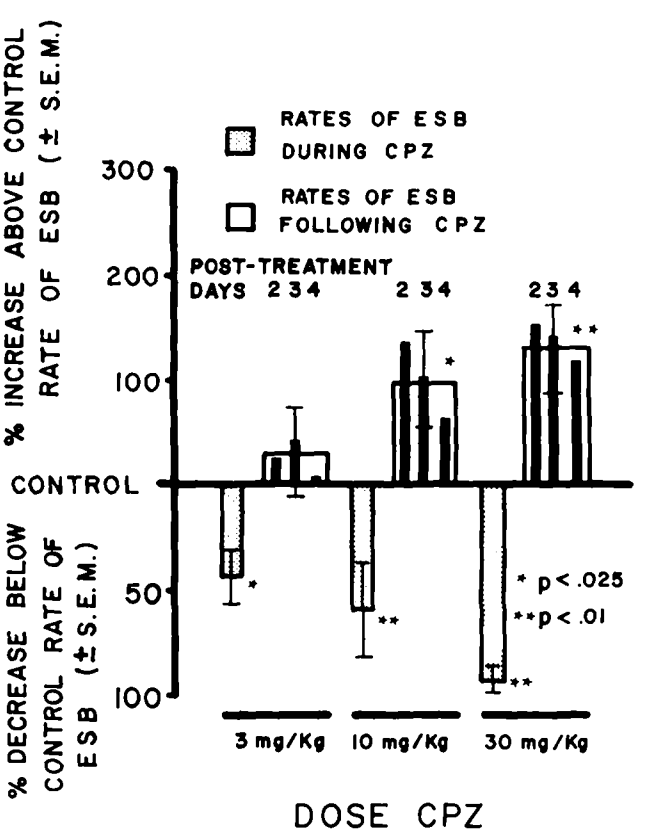

FIG. 3. Rates of ESB during and following CPZ treatment. Mean rates across days are shown by solid-lined bars. Significance based on comparison to control rate with *t*-test for matched pairs.

376% for the 5 mg/kg group, and 351% for the 10 mg/kg group. This 5 mg/kg dose produced a significant elevation of ESB rates ($p < 0.01$). The 2.5 mg/kg treatment also produced a significant elevation in rates ($p < 0.05$), but the 10 mg/kg treatment showed a nonsignificant elevation of rates during drug, due in part to the increased variance in this group. As can be seen in Fig. 2, all doses of amphetamine were followed by a significant decrease in the mean rate for Days 2–4 postamphetamine when compared to control levels ($p < 0.01$). The mean rates during withdrawal were 57% below control for the 2.5 mg/kg group, 78% below control for the 5 mg/kg group, and 91% below control for the 10 mg/kg group. The lowest rates of ESB were seen on the second day of withdrawal for all groups. There was a gradual return toward control rates across Days 2–4. Analysis of variance performed on the daily postdrug rates yielded a significant difference between doses $F(2,15) = 4.20$, $p < 0.05$, and a significant difference across days $F(2,30) = 4.88$, $p < 0.05$. The higher doses of amphetamine produced a greater decrease in rate of ESB during withdrawal, and for all doses, there was a significant recovery toward baseline during the three days postdrug.

The effects of CPZ administration are shown in Fig. 3. The mean rate of ESB during and postdrug is shown for the three CPZ doses. All doses significantly decreased rates of ESB during administration. The decreased rates were 38% below control for the 3 mg/kg group ($p < 0.025$), 79% below control for the 10 mg/kg group ($p < 0.01$), and 93% below control for the 30 mg/kg group ($p < 0.01$). Following the termination of chlorpromazine injections, the two higher dose groups showed a significant increase in rates above control levels. The 10 mg/kg group increased 98% above control ($p < 0.025$) and the 30 mg/kg group increased to 129% above control ($p < 0.01$). The increase in rates of ESB during withdrawal from chlorpromazine was greatest on Day 2 postdrug and decreased toward baseline across the three days. Analysis of variance on the post-CPZ daily rates demonstrated a significant difference between doses $F(2,18) = 3.92$, $p < 0.05$, and a significant effect across Days 2–4, $F(2,36) = 5.00$, $p < 0.025$.

The results of iproniazid administration are shown in Fig. 4. The lower dose of ipronizid, 25 mg/kg, did not produce a reliable elevation of rates during or following administration. The higher dose, 100 mg/kg, produced a significant elevation of ESB rates to 260% above control ($p < 0.025$) which was followed by a significant decrease in rates to 58% below control during withdrawal ($p < 0.05$). These effects are similar to those seen for amphetamine.

The 100 mg/kg group which showed a significant decrease in rates postdrug, also showed a recovery toward control levels during the three postdrug days. Analysis of variance for these data yielded a significant difference

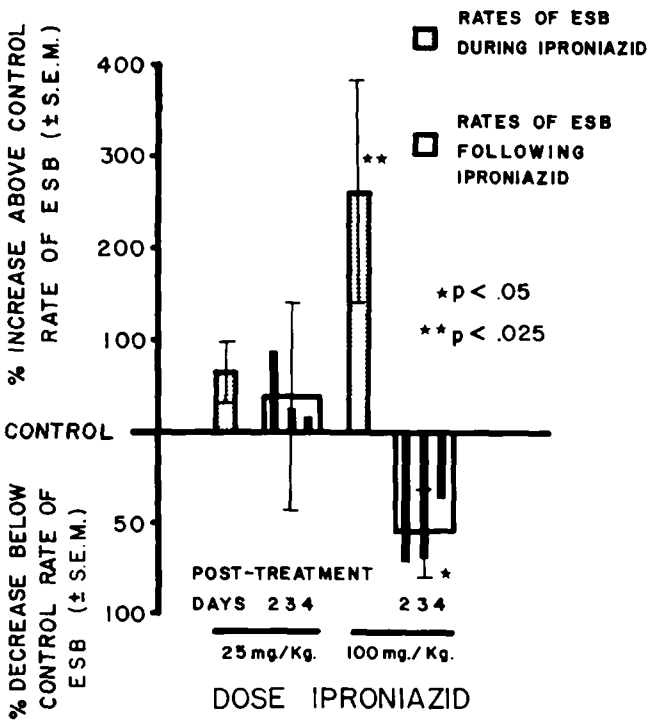

FIG. 4. Rates of ESB during and following iproniazid treatment. Means across days are shown by solid-lined bars. Significance is based on comparison to control rates using *t*-test for matched pairs.

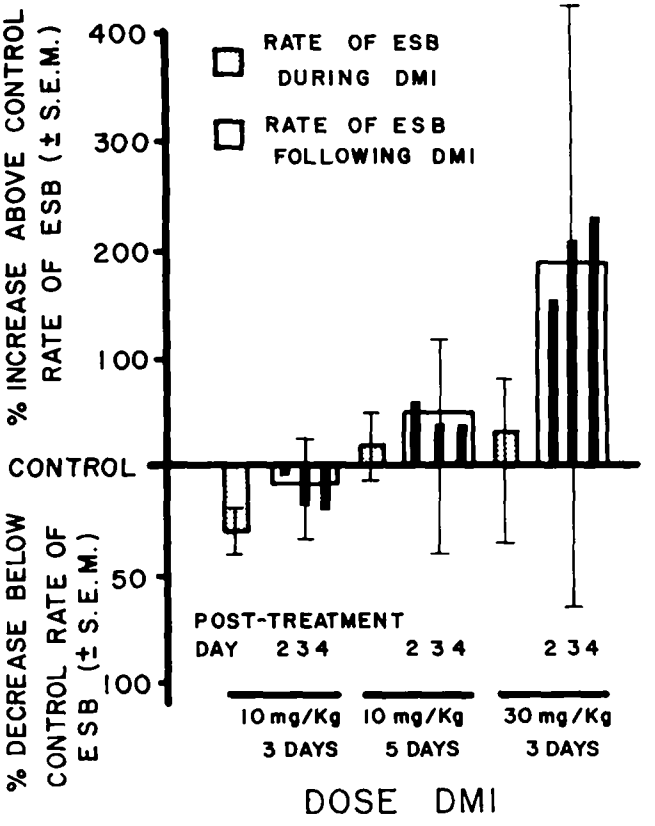

FIG. 5. Rates of ESB during and following DMI treatment. Means across days shown by solid-lined bars.

between the two doses of iproniazid, $F(1,9) = 5.78$, $p < 0.05$.

Of the four drugs tested in this experiment, DMI was the only one which did not produce statistically significant changes from baseline levels. Figure 5 presents the data for DMI treatment. As can be seen, the most striking effect was the large increase in rate following the 30 mg/kg treatment together with the associated increase in variance. The mean postdrug rate in the 30 mg/kg group was 183% above control with a standard error of 280% of control rate. The observed heterogeneity of variance was a product of between animal differences. Thus of the six animals in the 30 mg/kg group, four showed increases of more than 100% above control for all three postdrug days, while two animals showed little or no change.

In addition to increasing rates of ESB, the four animals mentioned lost up to 25% of body weight over a two-week period. All died within four weeks. The elevated rates of ESB are thus difficult to interpret since the nutritional state of the animals was markedly altered. The two animals which showed no postdrug elevation of rates at this dose of DMI also showed no weight loss. In light of the heterogeneity of variance between DMI groups, a *t*-test for nonhomogeneous variance was employed to compare the postdrug data for the three doses. The 30 mg/kg group was significantly different from either of the other two groups ($p < 0.05$, *t*-test for nonhomogeneous variance).

DISCUSSION

While the CRF schedule is not customarily used in investigating the behavioral effects of pharmacologic agents, the behavioral pattern produced by animals having continuous access to ESB is very different from the typical continuous responding seen with such a schedule. The pattern observed in the present experiments under predrug conditions has been described previously in detail [1], and it consists of periodic bursts of rapid lever pressing, followed by periods of inactivity. This type of response patterning allows both for great increases and decreases in daily response totals, so that depressants as well as stimulants can be tested effectively [15].

The results of the present experiment demonstrate that repeated administration of behaviorally active drugs can produce behavior, following discontinuation of treatment, that differs both from control ESB behavior and from drug induced ESB behavior. Of the four drugs tested, three changed rates of ESB during drug administration. All of the drugs produced changes in ESB rates upon termination of treatment. Amphetamine and iproniazid, at appropriate doses, elevated rates of ESB during treatment, and upon discontinuation produced a decrease in rates to below baseline levels. Rates following drug termination gradually returned toward predrug levels. Decreases in ESB were produced by CPZ administration while discontinuation of CPZ was associated with increases in ESB. DMI, the fourth drug tested, produced no statistically significant effects

either during administration, or following termination of treatment, largely because of the large variance observed. The former effect confirms previous observations [32].

The behavioral effects of withdrawal seen in the present study are in agreement with many previous studies [2, 6, 9, 11, 12, 16, 17, 18, 36, 37, 38], and additionally, with studies of the effect of phenothiazine treatment upon drug induced stereotyped behavior. Acutely phenothiazine blocks the stereotyped behavior produced by psychomotor stimulants and apomorphine. Following termination of repeated phenothiazine treatment, however, both apomorphine and methylphenidate are reported to produce an increased amount of stereotyped behavior [26, 27, 35].

In order to determine whether tolerance developed during drug treatment, daily rates were compared with control rates. The only drug that produced reliable changes was CPZ, in that at both 3 and 10 mg/kg, there was a recovery of responding toward control rates with repeated administration. At both of these doses significantly fewer ($p < 0.05$) responses were made on Day 1 of drug administration than on the last control day when compared with t-tests for paired means. On the third day of drug administration response rates were no longer singificantly different from control. Despite this evident recovery, the increase in responding on the first day following termination of drug administration was highly significant ($p < 0.01$). These results not only show tolerance developing to the effects of CPZ, but also indicate that the rebound effect was not due to a recovery from general ataxia during drug administration. No such tolerance effects were seen with any of the other drugs.

The rate of FSB increased markedly during amphetamine administration. This increase in lever pressing was not due to the generally activating effects of the drug since it has been shown that animals receiving the drug and having access to two levers, one for FSB another for food will only show increased response rates on the FSB associated lever [25]. Thus while at high doses of amphetamine (above 5 mg/kg) stereotyped behavior will appear, this will be noted as a decrease in response rate, as it is an incompatible behavior with lever pressing.

The depression of self stimulation following drug termination could be interpreted as being related to the punishing effects of the induced self stimulation during the peak drug effect. If this were a likely explanation, one would expect rapid extinction of this effect once the drug was withdrawn. Recent observations (in our laboratory) indicate that this depression may persist for at least 10 days, and reflects a change in the reinforcing effects of the stimulation, since a small increase in current (5 μA) will restore rapid self stimulation behavior.

A general pattern exists between the acute effects of these behaviorally active drugs, and the effects of withdrawal from these drugs. In both the present results and previous studies, the acute behavioral effect of the drug is associated with an opposite effect during withdrawal. The changes in behavior upon withdrawal are not merely a return to predrug levels, but a change in a direction opposite to that of the acute drug effects. Since the active drug is effectively absent during withdrawal, the existence of a behavioral withdrawal syndrome suggests a change, produced by drug administration, in the factors which determine the drug-free levels of behavior. The influence of these factors appears to counter the effects of the drug on behavior. At a broad theoretical level the withdrawal syndrome can be seen as a manifestation of adaptive changes in the organism. Such changes occur in response to the presence of the drug, and counteract the effects of the drug. Upon drug withdrawal these changes continue to influence behavior for a period of time. A theory of this sort is appealing, since it also explains drug tolerance. Indeed, such homeostatic mechanisms are common to most current theories of tolerance and dependence on opiates, barbiturate, and ethanol [3, 4, 8, 13, 20, 23, 28, 29]. These theories differ primarily with regard to the hypothesized biological basis of these adaptive changes. The concept of homeostatic mechanisms implies no particular biological mechanism.

The present study supports the value of this concept of adaptive change in the study of the effects of repeated drug treatment. This concept can serve as a guide to further exploration of the biological mechanisms of tolerance and dependence to psychoactive drugs.

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