EFFECTS OF PROPRANOLOL ON BARBITAL DEPENDENCE FORMATION AND WITHDRAWAL SIGNS

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Abstract—We studied the involvement of β-adrenoceptors in the physical dependence formation of barbital. 1. Propranolol (at a dose of 0.5 or 1.0 mg/g food) and barbital were applied simultaneously as a mixture with animal food (barbital-propranolol combination). Barbital was applied on a schedule of gradationally increasing dosages from 0.5-and-1.0 to 6-and-8 mg/g food over 36 days. Only the animals dosed with barbital exhibited severe withdrawal signs such as spontaneous withdrawal convulsions. The animals dosed with propranolol alone showed no changes even on withdrawal of the drug. The formation of physical dependence on barbital was obviously inhibited by the combination of barbital and propranolol. 2. Cross-application of propranolol (30 and 60 mg/kg, p.o., and 10 and 30 mg/kg, i.p.) following withdrawal of barbital resulted in the inhibition of the spontaneous withdrawal convulsions, muscle rigidity and hyperirritability. It also inhibited significantly tranylcypromine-induced convulsions, while it failed to inhibit similarly induced hyperthermia. These results including previous findings of effects of monoamine-related compounds on barbital withdrawal convulsions suggest that the balance of activities of noradrenergic neurons, especially that of α- and β-receptors, has great influence on both the formation of physical dependence on barbital and the manifestation of withdrawal convulsions.

In previous papers (1–4), we described that a challenge with tranylcypromine (Tcp) 48 hr after withdrawal of barbital from barbital-dependent rats precipitated clonic-tonic convulsions which were related to the severity of their dependence. We further reported that d/-propranolol, a β-adrenoceptor blocker, inhibited Tcp-induced withdrawal convulsions significantly and that the sensitivity of β-receptor is of significance in the elicitation of barbital-withdrawal convulsions.

The CNS action of β-adrenoceptor blockers, including propranolol, is a controversial clinical subject. Some investigators have shown that such drugs were effective in treating schizophrenia (5), anxiety (6–8), tardive dyskinesia (9) or alcoholism, while others have reported that the drugs were not significantly effective (10–15). In recent years, much attention has been given to the group of drugs that are β-blockers. There are also a number of studies of the CNS action of propranolol in experimental animals (16–23). Among others, there are papers on their effects on barbiturate-induced sleeping time, spontaneous motor activity and electroencephalogram (16, 19, 21). Also, there are reports on the effects of β-blockers on convulsions induced by pentetrazole and strychnine or on electroshock convulsions (16–23).

Middlemiss et al. (25) as well as Green and Grahame-Smith (24) reported the inter-
actions of β-blockers with 5-hydroxytryptamine, and the effects of β-blockers on the central monoamine have since been called to attention.

Because dl-propranolol, as described in a previous paper (2), proved to inhibit barbital withdrawal convulsions, this study was made to investigate the potential for this drug to be a possible therapeutic agent for sedative-hypnotic-dependent or alcoholism patients and its efficacy in this regard. As is well known, benzodiazepines, diazepam in particular, have the most widespread clinical use for the treatment of alcoholism. For this reason, even if β-adrenoceptors may be useful in the treatment of some of the patients with barbiturate-alcohol type drug dependence, it will most probably be used in combination with diazepam (15). This study was made to evaluate the effects not only of propranolol applied alone, but also of the drug applied in combination with diazepam on barbital dependence formation and barbital withdrawal signs.

Materials and Methods

Male Sprague-Dawley rats (weighing 100 to 120 g) were used throughout this study.

1. Effects of propranolol on acquirement of barbital tolerance and sleeping time: The rats were dosed with barbital (B) alone or in combination with propranolol (P) as described below: G-1, dosed with 2 mg of B/g of food. G-2, dosed with 2 mg of B and 0.5 mg of P/g of food. G-3, dosed with 2 mg of B and 1.0 mg of P/g of food.

With motor incoordination as the index for acquirement of tolerance to B, the rotarod performance test was made on the animals once a day (10:00 a.m.) on every day. The rats were weighed, and their food consumptions were measured every day. The intakes of the drugs (mg/kg/day) were calculated from their daily total food intakes.

The sleeping time was defined as the time from the disappearance of the righting reflex with 250 mg/kg of barbital sodium (i.p.) to arousal. The rats were dosed i.p. with 20 mg/kg of propranolol 30 min before the administration of barbital sodium. The control rats were given physiological saline. The brain and serum barbital concentrations upon arousal were measured by a modification of Broughton's method (26).

2. Physical dependence formation by barbital-propranolol combination: The dosing schedule as reported by Tagashira et al. (27) was followed for the formation of physical dependence on B. In other words, B was administered as a mixture with food (Drug-Admixed Food, DAF) on a gradationally increasing dosage schedule starting with 0.5 and 1 mg B/g food for 4 days (stage I) and increased at 1 and 2 mg B/g food for 6 days (stage II), 2 and 4 mg B/g food for 6 days (stage III), 4 and 6 mg B/g food for 10 days (stage IV), and 6 and 8 mg B/g food for 10 days (stage V) over 36 days (27). The group receiving the combination of B and P was treated with fixed doses of P as an additive to the B-admixed food during the B-dosing period. The dosed groups are shown below: G-1, dosed with 0.5-and-1 mg of P/g of food. G-2, dosed with 0.5-and-1 to 6-and-8 mg of B/g of food. G-3, dosed with B and 0.5 mg of P/g of food. G-4, dosed with B and 1.0 mg of P/g of food.

At the final day of each dose level (stage I to V) during the treatment with B on the gradedly increasing dosage schedule, the drug-admixed food was replaced with a drug-free normal food; and the rats were examined for the onset of withdrawal signs and changes in body weight during the following 48 hr.

At 48 hr of B withdrawal following the dosing with B at the final dose level (6-and-8 mg/g food), the rats were challenged with 15 mg/kg of tranylcypromine, i.p.; and the
time to the appearance of kangaroo-like posture or mild clonic convulsion was defined as the (convulsion) onset time, and the time to the appearance of C-TC designated as the C-TC time. The Tcp-induced convulsions were divided into the following 5 grades: no convulsion (0), exaggerated pinna reflex, salivation, appearance of kangaroo-like posture and transient clonic convulsion (1); 1–2 episodes of C-TC (2); 3 episodes or more of C-TC (3); and long duration of convulsive signs, some of the rats dying immediately after the convulsion (4). Other B-dependent rats were dosed with 50 mg/kg of pentetrazole and checked for the convulsion threshold during B withdrawal. The differences in severity of the convulsion between the groups were analyzed for statistical significance in the following ways: Fisher's direct probability estimation was applied to the analysis of the incidence of convulsions in the rats during the 30 min after and the mortality rate during the 24 hr after the Tcp or PTZ challenge in each group, and the Student's t-test applied to the analysis of the scores of signs.

3. Effects of propranolol or propranolol-diazepam combination on withdrawal signs of barbital: The rats were made B dependent by the gradationally increasing B dosing schedule as described in 1 above. After the rats were fed the B-admixed food at the final B dose level, the drug-containing food was replaced with a B-free normal food. At this stage, the B-dependent rats were divided into 6 groups of 6 with similar average body weights. During the period from 17 hr to 47 or 48 hr of withdrawal, moderate to severe withdrawal signs such as anorexia, hyperrespiration, muscle rigidity, aggressiveness, hypersensitivity, mild tremors and dyskinesia were manifested. At 47 or 48 hr of withdrawal when almost all withdrawal signs had already been manifested, the rats were examined for withdrawal signs, and their body temperatures and weights were measured. The following dosages were given: Diazepam (DZP), 10 mg/kg, p.o. DZP, 30 mg/kg, p.o. P, 30 mg/kg, p.o. P, 60 mg/kg, p.o. DZP, 10 mg/kg, p.o. +P, 15 mg/kg, p.o. DZP, 10 mg/kg, p.o. +P, 30 mg/kg, p.o.

Drug solutions were adjusted to the volume of 0.5 ml per 100 g of body weight.

4. Tranylcypromine-induced convulsions following cross-dosing with propranolol: Other B-dependent rats were cross-dosed with the following drugs at 6-hr intervals 5 times in total during 24 to 48 hr of B withdrawal: P-admixed food. 1 mg/g food. P, 10 mg/kg, i.p. P, 30 mg/kg, i.p. P, 30 mg/kg, p.o. Nitraze, 20 mg/kg, p.o. Vehicle control (saline), i.p. Drug solutions were adjusted to the volume of 0.2 ml per 100 g of body weight.

Because the oral administration of P proved to cause no intense inhibition of B withdrawal signs in 3 above, P was administered i.p. in this experiment.

Results

1. Effects of propranolol on acquisition of barbital tolerance and sleeping time: Although there was practically no difference in daily B intake between the 3 groups, P inhibited the development of tolerance to B (Fig. 1). There was no difference in the weight gain curve during the dosing period between the groups. In other words, P at the tested dose levels proved to be non-toxic.

P failed to prolong the barbital-induced sleeping time (Table 1).

2. Physical dependence formation by the combination of barbital and propranolol: Withdrawal of B after the dosing at 1-and-2 mg/g food (stage II) was in 24 hr followed by obvious weight losses (1 to 4%) in all G-2 to G-4 groups. P alone failed to either retard weight gain or cause weight loss upon its withdrawal (Fig. 2). The combination of P and B tended to be followed by less severe
B withdrawal signs of shorter duration. In other words, P already inhibited the formation of B dependence at an early period of B administration (at low B dose levels). The withdrawal of B after the dosing at 2-and-4 mg/g food (stage III) or 4-and-6 mg/g food (stage IV) inhibited the body weight loss dose-relatedly. Furthermore, P inhibited the formation of B dependence even at the B dose level of 6-and-8 mg/g food (stage V) at which spontaneous convulsions appear. The dosing with P inhibited not only clonic-tonic convulsions but also such withdrawal signs as weight loss (Fig. 2), hyperkinesia, tremors, systemic muscle rigidity, etc.

Challenge with Tcp at 48 hr of B withdrawal was followed by an obviously low incidence of clonic-tonic convulsions in the groups dosed by the combination of B and P. In these groups, pentetrazole-induced convulsions during B withdrawal were also inhibited (Table 2).

3. Effects of propranolol or propranolol-diazepam combination on withdrawal signs of barbital: Cross-dosing with P alone inhibited the hyperirritability and muscle rigidity in the rats, with the animals remaining sedated. The drug, however, did not serve to recover the anorexia at all nor did it inhibit the weight losses. Neither did the low dose

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**Table 1.** The sleep time and the barbital concentration upon awaking in propranolol treated rats

| Treatment with drug | Sleep time (min) | Brain (μg/g) | Plasma (μg/g) |
|---------------------|-----------------|--------------|--------------|
| Naive control       | 255.1±35.9      | 28.9±2.1     | 342.5±17.8  |
| Propranolol         | 241.4±42.7      | 30.1±1.5     | 327.4±30.5  |

The rats were dosed i.p. with 20 mg/kg of propranolol 30 min before the administration of barbital sodium.
of diazepam inhibit the weight losses intensely. The combination of the low dose of diazepam with P failed to inhibit the weight losses as much as the high dose of diazepam (Fig. 3). However, the 2 drugs either singly or in combination obviously inhibited the frequency of clonic-tonic convulsions. P failed to inhibit the hyperthermia during B withdrawal.

4. Tranylcypromine-induced convulsions after cross-dosing with propranolol: P was administered i.p. However, as observed in 3 above, not any of the 3 doses of this agent inhibited the weight losses as intensely as nitrazepam. From the observations after the cross-dosing, however, P obviously inhibited the frequency of spontaneous withdrawal convulsions. P partially inhibited the B withdrawal signs such as muscle rigidity and hyperirritability as compared with the findings in the vehicle-given control group. P, when administered as a mixture with food, scarcely inhibited the B withdrawal signs, while nitrazepam inhibited completely almost all B withdrawal signs. Challenge with Tcp after the final cross-dosing resulted in the prolonged onset time and C-TC time in the P-dosed groups. In these groups, the incidence of convulsions and the severity of the convulsions (frequency+duration of convulsions) were both reduced (Table 3). Especially in the group treated i.p. with the high dose of P, the convulsion were strikingly inhibited. No convulsions appeared in the nitrazepam-dosed group.

Discussion

There are a few papers on the CNS action of P (16-23), while there is no report on the interaction of P with barbiturates. In this study, the combination of P and B proved to obviously reduce the formation of physical
dependence on B. The dose level, the frequency of drug administration and the period of drug administration are factors influential to the intensity of drug dependence. Especially in sedative-hypnotic dependence, it is essential that the CNS remains in a depressive state for more than a given period of time (28). In a previous paper (29), we described that when phenobarbital was used in combination with diphenhydramine or chlorpromazine which is free of dependence liability but has a CNS depressive action, phenobarbital withdrawal signs, and especially, convulsions were obviously enhanced. Since the 2 drugs are known to prolong the barbiturate sleeping time and enhance the phenobarbital-induced motor incoordination (29), they can be readily presumed to enhance barbiturate dependence. It has been reported that P also causes CNS depression (16, 19, 21). In this study, however, P failed to additively enhance the B sleeping time or B-induced motor incoordination. For this reason, its interaction with B, which is different from the aforementioned interaction with chlorpromazine, may be considered.

In our previous experiment (unpublished data), we observed that the combination of α-methyl-p-tyrosine (α-MT) with B enhanced B dependence formation, and the combination of methamphetamine with B attenuated the formation. α-MT further proved to enhance the lethal effect of B. Therefore, it may be thought that the interaction of B with the noradrenergic (NA) neurons plays an important role in B dependence formation. Thomas and Handly (30) reported that the chronic administration of methamphetamine rendered α-adrenoceptors hypersensitive. It

Fig. 3. Comparison between suppression of barbital-withdrawal signs (loss in body weight and hyperthermia) and maintenance of dependence on barbital by diazepam (DZP) alone and those by DZP combinations.
Table 2. The time to onset of prodromal signs of convulsion (onset time), time to onset of clonic-tonic convulsion (CTC time), grades of CTC (see text) and 24-hr mortality following challenge with pentetrazol (PTZ) or tranylcypromine (Tcp) on withdrawn rats. Parentheses indicate the number of convulsed rats/animals used.

| Physical states of animals | Drugs (mg/kg) | N | Onset time (min) | CTC time (min) | Mortality (24 hr) | Score of signs |
|---------------------------|--------------|---|------------------|----------------|------------------|---------------|
| Withdrawn rats, 48 hr     |              |   |                  |                |                  |               |
| Propranolol (0.5 and 1 mg/g food) | Tcp 15 | 5 | – (0/5) | – (0/5) | 0/5 | 0** |
| Barbital (6 and 8 mg/g food) | Tcp 15 | 5 | 11.1±1.6 (3/5) | 12.3±1.4 (3/5) | 0/5 | 2.6±0.4 |
| Barbital+Propranolol (0.5 mg/g food) | Tcp 15 | 5 | 18.3±3.5 (4/5) | 18.4±3.5 (4/5) | 0/5 | 2.8±0.2 |
| Barbital+Propranolol (1 mg/g food) | Tcp 15 | 5 | 7.7 (1/5)* | 7.7 (1/5)* | 0/5 | 0.4±0.4** |
| Propranolol (0.5 and 1 mg/g food) | PTZ 50 | 5 | 20.9±3.6 (2/5) | 17.3 (1/5)* | 0/5 | 0.6±0.4** |
| Barbital (6 and 8 mg/g food) | PTZ 50 | 5 | 10.0±3.0 (4/5) | 10.0±3.0 (4/5) | 0/5 | 2.8±0.2 |
| Barbital+Propranolol (0.5 mg/g food) | PTZ 50 | 5 | 9.3±3.0 (3/5) | 10.3±4.0 (2/5)* | 0/5 | 1.6±0.2** |
| Barbital+Propranolol (1 mg/g food) | PTZ 50 | 5 | 9.8±4.2 (2/5)* | 9.9±4.1 (2/5)* | 0/5 | 1.4±0.2** |

*Fisher's direct probability estimation was applied to analysis for a statistically significant difference from barbital, P<0.05. **Student's t-test was applied to analysis for a statistically significant difference from barbital, P<0.05.
| Physical states of animals | Drugs (mg/kg) | N | Onset time (min) | CTC time (min) | Mortality (24 hr) | Score of signs |
|---------------------------|--------------|---|-----------------|----------------|------------------|---------------|
| Propranolol (1.0 mg/g food, DAF) | Tcp 15 | 6 | 10.5±1.8 (3/6) | 10.6±1.7 (3/6) | 0/6* | 1.0±0.4** |
| Propranolol (10 mg/kg, i.p.) | Tcp 15 | 6 | 11.5±3.7 (3/6) | 12.9±0.4 (2/6)* | 0/6* | 0.8±0.4** |
| Propranolol (30 mg/kg, i.p.) | Tcp 15 | 6 | 14.8 (1/6)* | 14.8 (1/6)* | 0/6* | 0.3±0.3** |
| Propranolol (30 mg/kg, p.o.) | Tcp 15 | 6 | 9.6±0.9 (3/6) | 10.6 (1/6)* | 0/6* | 0.7±0.3** |
| Nitrazepam (20 mg/kg, p.o.) | Tcp 15 | 6 | — (0/6)* | — (0/6)* | 0/6* | 0** |
| Control (vehicle, i.p.) | Tcp 15 | 6 | 8.2±2.4 (6/6) | 9.2±2.4 (6/6) | 5/6 | 4 |

*Fisher's direct probability estimation was applied to analysis for a statistically significant difference from the control (vehicle), P<0.05. **Student's t-test was applied to analysis for a statistically significant difference from the control (vehicle), P<0.05.
was not clear only from the results of our present study whether the blocking of $\beta$-receptors by the continuous administration of P would enhance the sensitivity of $\alpha$-receptors relatively. However, the data available at the present moment suggest that the formation of physical dependence on B may depend on the activity of NA neurons. In other words, the depression of NA neuron activity results in the enhancement of dependence on B, while the elevation of NA neuron activity, especially the hypersensitive state of the $\alpha$-adrenoceptors, reduces B dependence formation. It is of interest that this phenomenon is inversely correlated with our previous finding (3, 4) that under B withdrawal, the depression of NA neuron activity by $\alpha$-MT or disulfiram was accompanied by a striking reduction in withdrawal convulsions.

The continuous cross-dosing with P during B withdrawal inhibited not only spontaneous withdrawal convulsions but also muscle rigidity and hyperirritability. Tcp- and PTZ-induced convulsions also tended to be inhibited. These findings were well consistent with the results of the administration of P only once as described in our previous papers (1-4). Furthermore, from the results of this study, P, free of cross-physical dependence on B, proved to inhibit B withdrawal signs only partially. It further failed to maintain B dependence. On the other hand, the finding that the cross-dosing with P by P-admixed food failed to inhibit B withdrawal signs may be thought to indicate that P always occurred in the blood, but not at a sufficient level to inhibit the withdrawal signs.

Goldstein (31) reported that P aggravated alcohol withdrawal signs. From their study using phenobarbital-dependent mice, Waddingham and Belknap (32) thought that because the d- and the l-isomer of P inhibited the withdrawal convulsions at similar levels, this suggested its cell membrane stabilizing action rather than its $\beta$-blocking action. On the other hand, in our previous studies (2, 3), we observed that B withdrawal convulsions were inhibited with the l-˃d-˃d-isomer of P in decreasing of intensity, the last having practically no such inhibitory action. For this reason, we drew the conclusion that this phenomenon was derived chiefly from its $\beta$-blocking action. However, these authors still have various opinions about the behavior of $\beta$-blockers to barbiturate-alcohol type dependence. Although these reports describe the use of P at similar dose levels (10 to 40 mg/kg, i.p.), there have been various results. The reason for such discrepancies may be that not only the difference in animal species and strains, but also the difference in the method of evaluation of convulsions (Goldstein (31) and Waddingham and Belknap (32) using convulsions on handling in mice, and the present authors using spontaneous convulsions or Tcp-induced convulsions in rats) is responsible.

On the other hand, French et al. (33), Kuriyama et al. (34) and Aiso (35) using the means of biochemical pharmacology, reported that supersensitivity of cerebral $\beta$-receptors occurred during alcohol withdrawal. Since their data indicate no changes in the binding number of $\beta$-adrenoceptors in an alcohol dependent state, the sensitivity of $\beta$-receptors is related with the elicitation of withdrawal signs rather than with alcohol dependence formation. Considering the findings in this study and the results of studies of alcohol dependence by French et al. (33), Kuriyama et al. (34) and Aiso (35), we may speculate that P has the possibility of partial effectiveness in treating alcoholism.

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