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# Dihydropyridine-Sensitive Calcium Channels and Barbiturate Tolerance and Withdrawal

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RABBANI, M., J. BROWN, A. R. BUTTERWORTH AND H. J. LITTLE. *Dihydropyridine-sensitive calcium channels and barbiturate tolerance and withdrawal.* PHARMACOL BIOCHEM BEHAV **47**(3) 675-680, 1994. – We have shown previously that the dihydropyridine calcium channel antagonist nitrendipine, given chronically, prevents the development of ethanol tolerance and physical dependence. The present study examines the effects on barbiturate tolerance and physical dependence. Nitrendipine, given acutely during withdrawal, provided little protection against barbiturate withdrawal, as measured by convulsive behaviour on handling. When nitrendipine was given chronically concurrently with the barbiturate, a prolonged protection against the withdrawal syndrome was seen. Acute nitrendipine significantly increased the latency of seizures in response to the partial benzodiazepine inverse agonist FG7142 during barbiturate withdrawal, but there was no effect on the seizure incidence in response to bicuculline. Chronic treatment with nitrendipine did not alter the development of tolerance to the ataxic or general anaesthetic actions of barbiturates, but evidence was found of a possible interaction between nitrendipine and pentobarbitone, which may have been pharmacokinetic. The results suggest that neuronal calcium channels may be involved to some degree in the development of the changes responsible for barbiturate withdrawal, but to a less extent than found previously for ethanol dependence.

Barbiturate Dependence Dihydropyridine Calcium channels Withdrawal Tolerance

TOLERANCE to the barbiturates occurs after chronic administration, and they produce a physical dependence resembling that of ethanol, but the physiological changes that are responsible for these effects are not fully understood. Acutely, the barbiturates are well known to potentiate the effects of GABA (γ-aminobutyric acid), acting at their own receptor sites on the GABA/receptor ionophore complex (22,26). This action may be involved in the adaptations that develop on chronic treatment (11).

The high threshold, "L" subtype of voltage-sensitive calcium channels is said to be selectively blocked by dihydropyridine compounds (20). We have found that these compounds have specific actions in ethanol dependence. Chronic ethanol treatment increased the number of high affinity binding sites for dihydropyridines in the central nervous system (7). When the calcium channel antagonists were given acutely on withdrawal from chronic ethanol treatment, they protected against the ethanol withdrawal syndrome (15,16). When injected acutely with ethanol, they potentiated its pharmacological effects. However, when the dihydropyridines were given concurrently with ethanol they prevented the development of tolerance (5,29) and the ethanol withdrawal syndrome (27). These effects were suggested to be due to an adaptive response to the dihydropyridines, preventing the upregulation of dihydropyridine-sensitive binding sites, as the central concentrations during measurement of tolerance and withdrawal were too low to have acute behavioural actions (5,27). We also showed that a dihydropyridine calcium channel antagonist prevented tolerance to nitrous oxide and the withdrawal syndrome caused by this anaesthetic (6).

Barbiturates block calcium uptake into neurones (1,8). Tolerance occurred to this effect after chronic treatment (14), but little is known about the effects of long-term barbiturate administration on dihydropyridine-sensitive calcium channels. Dihydropyridine calcium channel antagonists, given acutely, potentiated the general anaesthetic actions of barbiturates (4), and the calcium channel activator Bay K 8644 had an antagonist action (2). The present work investigated whether or not a dihydropyridine calcium channel antagonist, nitrendipine, protected against the barbiturate withdrawal syndrome and whether this compound would affect the development of tolerance and physical dependence on barbiturates, when given chronically with these compounds.

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## METHODS

### *Chronic Drug Treatment*

Barbital was used for all the chronic barbiturate treatment. This compound does not induce microsomal enzymes (17), so its use avoided the complications of metabolic tolerance. Male TO strain mice were used, weighing between 20–35 g with not more than a 5-g range in any one experiment. They were given barbital in powdered food for seven days (unless otherwise stated): 3 mg/g food for two days, 4 mg/g food for two days, and 5 mg/g food for three days. The mean intakes of barbital were 400 mg/kg/day at the beginning of the treatment, rising to 700 mg/kg/day at the end. Controls received a matched amount of powdered food only. All mice were weighed regularly during the treatments and no significant differences in weights were found. In all studies the amount of food, and hence barbital, taken in by the mice was measured daily. The concurrent administration of nitrendipine did not alter the amount of barbital received by the animals in any of the experiments.

Nitrendipine was suspended in Tween 80, 0.5%, and injected by the IP route. All solutions were prepared under red safe-light. For the chronic nitrendipine treatment, the compound was injected at 50 mg/kg twice daily for the period of barbital administration, at 1000 and 2200. Separate groups of mice, not treated with barbital, were also given the nitrendipine injections. The last injections were given 12 h or 24 h before the barbital withdrawal so that the effects of the chronic treatment, rather than any acute actions, would be studied.

For the withdrawal measurements, the mice were placed in clean cages at the end of the seven-day treatment and given powdered food without barbital for at least 19 h before testing with the exception of the second chronic nitrendipine study, where testing began 13 h from barbital withdrawal. Our previous studies showed that the withdrawal syndrome was seen clearly between 12 and 24 h from withdrawal.

### *Measurement of the Barbiturate Withdrawal Syndrome*

The barbiturate withdrawal syndrome was measured by ratings of convulsive behaviour on handling. This method was first established by Goldstein and Pal (10) for ethanol withdrawal. Our method was similar to this, with slight modifications (12). Mice were gently picked up by the tail and turned, first in one direction and then the other. Rating numbers were allocated as follows: 0, no signs of tremor or hyperexcitability; 1, occasional signs of tremor; 2, continuous tremor; 3, intermittent clonic convulsions, consisting of repeated contractions of the limbs, particularly the hind legs; and 4, continuous clonic convulsions.

The ratings of convulsant behaviour on handling were carried out once an hour over periods of time after the removal of the barbital. All the mice were coded so that the observer was unaware of the prior drug treatment. A minimum of 10 animals was used in each treatment group.

### *Responses to Convulsive Drugs*

The effects of nitrendipine during barbiturate withdrawal were also tested by its effects on seizures produced by the GABA antagonist bicuculline and by FG7142, a partial inverse agonist at benzodiazepine receptors. Both convulsants were given by the IP route: bicuculline at 3.5 mg/kg and FG7142 at 40 mg/kg. We have shown previously that barbital withdrawal increases the effects of both of these compounds (unpublished results), and these doses were chosen to produce seizures in about 95% of mice during barbital withdrawal. Injections of nitrendipine, 50 mg/kg IP, were given 30 min before the convulsants. The effects of this dose of nitrendipine were also tested when it was given 5 h before the FG7142. In each case the convulsant was given 24 h after cessation of chronic barbital treatment. The seizure incidence was noted for 40 min following the convulsant injections. A full seizure was recorded when clonic movements of the limbs were observed, accompanied by loss of posture. In all cases the observer was blind to the prior drug treatment.

### *Tolerance to the Ataxic Actions of Barbiturates*

Tolerance to the barbiturate was assessed at 24 or 48 h after the cessation of chronic barbital treatment. Nitrendipine, 50 mg/kg, or vehicle injections were given as described above during the barbital treatment, the last injections being given 24 h before barbital withdrawal (unless otherwise stated). Separate groups of mice received nitrendipine or vehicle injections, but no barbital, although powdered food was given, as above.

The rotorod method was used to measure ataxia. The ataxic effects were measured using a rotating rod with a rotation speed of 4.5 rpm. Injections of either pentobarbital, 30 mg/kg, or sodium barbital, 150 mg/kg, were given, and then the mice were placed on the rotating rod at intervals and the time spent on the rod measured. The doses of barbiturates used in the rotorod test were chosen on the basis of prior experiments to almost, but not completely, prevent the ability of the naive mice to stay on the rotating rod. Tolerance to this action would therefore be seen easily. A maximum time of 180 s was allowed. There were eight mice in each treatment group in the first tolerance studies, in which pentobarbital was used as the "challenge" drug. When sodium barbital was used in the rotorod test, between 10 and 17 mice were used in each treatment group.

### *Tolerance to the General Anaesthetic Effect of Pentobarbital*

The test used in the assessment of anaesthesia was the loss of righting reflex in response to pentobarbital. This was tested after withdrawal from the 7-day barbital diet used in the other studies and after 12 days of such barbital treatment. In both cases, the tests were made 24 h after the removal of the barbital diet. Nitrendipine 50 mg/kg IP was given twice daily, as above, with the last injection given 24 h before the withdrawal of barbital.

Loss of righting reflex was said to have occurred if a mouse failed to regain the upright posture (i.e., all four legs on the benchtop) within 60 s of being placed on its back. Following administration of pentobarbital 40 mg/kg, each animal was rolled onto its back at intervals until the righting reflex was regained. A minimum of 10 animals was used in each treatment group.

### *Statistical Analysis*

The ratings of convulsive behaviour during withdrawal were compared by two-way nonparametric analysis of variance (18). Seizure incidences were compared using Fisher's exact probability test. The rotorod times were compared by the Mann–Whitney $U$ test. Comparisons of the seizure incidence were made using Fisher's exact probability test, and the latencies to convulsions were compared by Student's unpaired $t$ test.

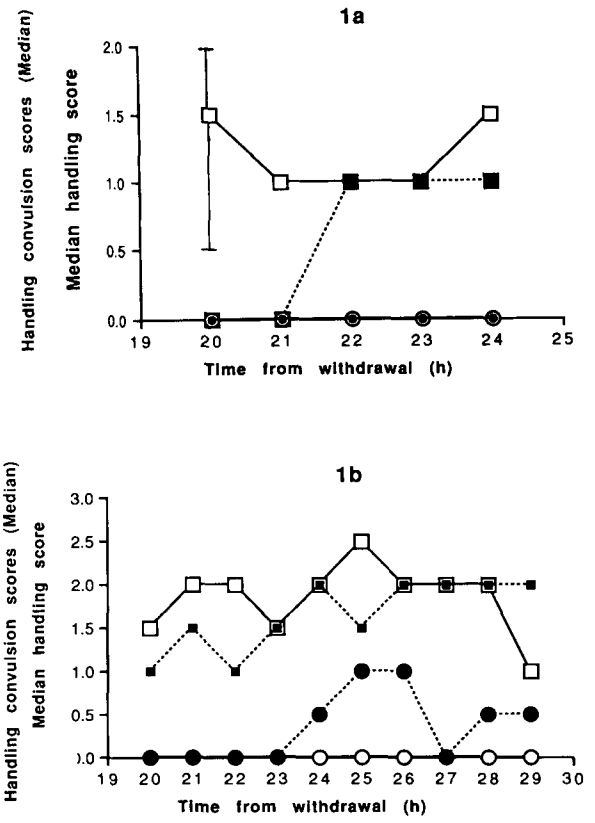


FIG. 1. The effects of acute administration of nitrendipine, 50 mg/kg IP, on the barbiturate withdrawal syndrome. The nitrendipine was given 19 h after cessation of chronic barbital treatment in both studies. Values are medians, with an example of the interquartile range. ○, control diet + acute vehicle; ●, control diet + acute nitrendipine; □, barbital diet + acute vehicle; ■, barbital diet + acute nitrendipine.

## RESULTS

### *The Barbiturate Withdrawal Syndrome*

Figure 1 shows the effects of acute nitrendipine on the barbiturate withdrawal syndrome when the drug was given at 50 mg/kg IP 19 h from withdrawal. In the first experiment nitrendipine slightly lowered the median ratings in barbital-treated mice for the first 3 h of the study (Fig. 1a) but did not appear to affect the withdrawal after this time. The difference during the first 2 h between the ratings after barbital withdrawal with nitrendipine or with vehicle injections was significant ($p < 0.05$). The study was repeated (Fig. 1b) with measurements made over a longer time period, again starting at 20 h withdrawal. Although nitrendipine 50 mg/kg given at 19 h withdrawal decreased the median ratings in the first two hours of measurement, the difference was not significant ($p > 0.05$).

When given chronically with the barbital, nitrendipine decreased the behavioural ratings during withdrawal (Fig. 2). Figure 2a shows that this effect lasted longer than that after the acute administration. When the values in this study were compared over the whole of the 8-h measuring period, the difference between nitrendipine and vehicle injections was significant ($p < 0.001$). Figure 2b illustrates the results of a separate study using chronic nitrendipine treatment when measurements were made between 13 h and 24 h from barbital withdrawal. Again, the ratings after treatment with barbital plus nitrendipine were significantly lower than those after barbital alone, compared over the whole of the testing period ($p < 0.001$). In neither study did administration of nitrendipine alone for seven days alter the behavioural rating scores.

### *Bicuculline Convulsions*

Administration of nitrendipine did not alter the incidence of seizures after bicuculline during barbital withdrawal, illustrated in Table 1 ($p > 0.05$, compared with vehicle injection during barbital withdrawal). However, the occurrence of seizures during barbital withdrawal in response to FG7142 was reduced and the latencies significantly prolonged ($p < 0.01$) by nitrendipine given 30 min prior to the convulsant (Table 1). When a 5-h pretreatment time was used for nitrendipine, the effects on the actions of FG7142 were not significant ($p > 0.05$).

### *Tolerance to the Ataxic Actions of Barbiturates*

In the first study on barbiturate tolerance, we tested the ataxic actions of pentobarbital after chronic barbital treatment rather than those of barbital because the onset and offset of the effects of pentobarbital were more rapid and could be measured more clearly. No difference was seen in the degree of tolerance to the ataxic actions of pentobarbital 24 h after

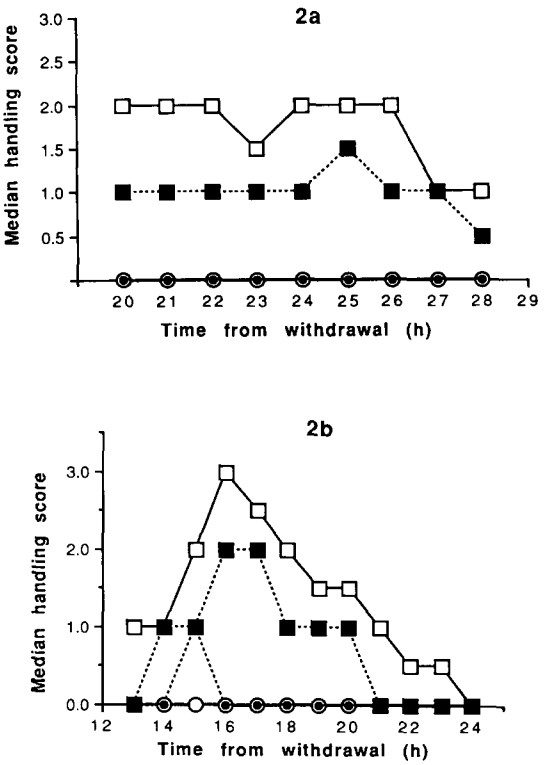


FIG. 2. The effect of concurrent chronic nitrendipine treatment on the barbiturate withdrawal syndrome. The last nitrendipine injections were given 12 h before barbital withdrawal. Values are medians. ○, control diet + vehicle injections; ●, control diet + nitrendipine injections; □, barbital diet + vehicle injections; ■, barbital diet + nitrendipine injections.

TABLE 1

SEIZURE INCIDENCE IN RESPONSE TO BICUCULLINE OR FG7142 DURING BARBITAL WITHDRAWAL

| | Convulsion Incidence | Latency to First Seizure |
|---|---|---|
| 1) Bicuculline, 3.5 mg/kg | | |
| Pretreatment 30 min before bicuculline | | |
| Tween vehicle | 8/10 | 122 ± 15 |
| Nitrendipine, 50 mg/kg | 9/10 | 139 ± 27 |
| 2) FG7142, 40 mg/kg | | |
| Pretreatment 30 min before FG7142 | | |
| Tween vehicle | 9/10 | 155 ± 16 |
| Nitrendipine, 50 mg/kg | 5/10 | 310 ± 57* |
| Pretreatment 5 h before FG7142 | | |
| Tween vehicle | 10/10 | 163 ± 26 |
| Nitrendipine, 50 mg/kg | 8/9 | 234 ± 55 |

The convulsants were given 24 h after cessation of chronic barbital treatment. Latencies are given as mean ± SE. *$p < 0.01$ compared with vehicle treatment.

barbital withdrawal when either nitrendipine or its vehicle was given chronically with the barbital treatment (Fig. 3a). However, as illustrated in this figure the effects of pentobarbital appeared to be increased by chronic treatment with nitrendipine in the absence of barbital. The experiment was therefore repeated using a longer time interval, 48 h, between tolerance testing and the end of the barbital administration. A similar pattern of results was obtained (Fig. 3b). The concurrent nitrendipine treatment did not appear to alter the development of tolerance to pentobarbitone, but six days of treatment with nitrendipine alone appeared to increase the effects of the challenge dose of pentobarbital, although the difference was not quite significant ($p = 0.08$, comparison between mice given nitrendipine and those given vehicle, at the 40-min test interval).

In view of the latter result, it was thought that a similar effect in the barbital-treated mice might be masking changes in barbiturate tolerance. The study was therefore repeated using the nonmetabolised compound, barbital, as the challenge drug, since it was thought possible that the above effect of nitrendipine could have been due to interference with the metabolism of pentobarbital. The results, obtained 24 h after withdrawal from barbital, are illustrated in Fig. 3c. There was no significant effect of the concurrent nitrendipine treatment on the tolerance developed to the barbital, although it was slightly less. In contrast to the results obtained when pentobarbital was used, no effect was seen of chronic nitrendipine treatment on the ataxic effects of barbital when nitrendipine was given alone.

### *Tolerance to the General Anaesthetic Actions of Pentobarbital*

The results of the anaesthesia studies are illustrated in Fig. 4. Clear tolerance was produced to the general anaesthetic effects of pentobarbital when measured 24 h after withdrawal from the 7-day chronic barbital treatment. This appeared to be unaltered by the concurrent administration of nitrendipine (Fig. 4a). This was in contrast to our previous results on ethanol tolerance (5), but as the duration of the nitrendipine treat-

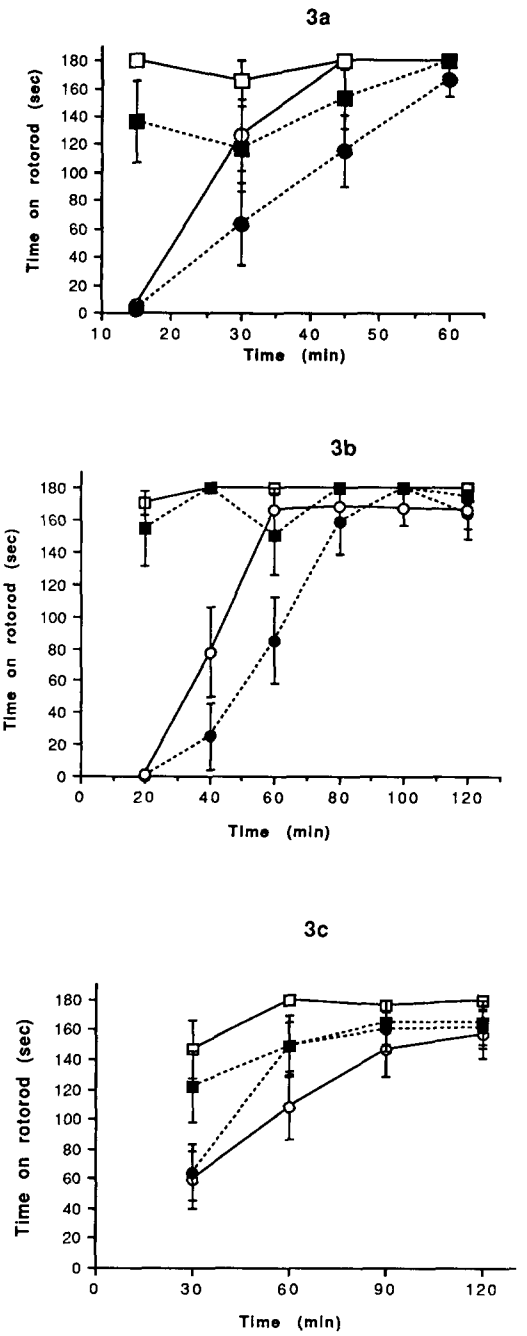


FIG. 3. The effects of concurrent chronic nitrendipine treatment on tolerance to the ataxic actions of barbiturates produced by seven days of barbital treatment. Figure 3a illustrates the effects of pentobarbital, 30 mg/kg, 24 h after cessation of the chronic treatments. The results in Fig. 3b show the rotorod times when 30 mg/kg pentobarbital was given 48 h after the cessation of chronic barbital treatment (72 h after the last nitrendipine injection). For the results in Fig. 3c, sodium barbital, 150 mg/kg, was injected 24 h after cessation of chronic barbital treatment (48 h after the last nitrendipine injection). In all the results, significant tolerance was seen after the barbital treatment, but this was unaffected by the concurrent administration of nitrendipine. Values are means ± SE. ○, control diet + vehicle injections; ●, control diet + nitrendipine injections; □, barbital diet + vehicle injections; ■, barbital diet + nitrendipine injections.

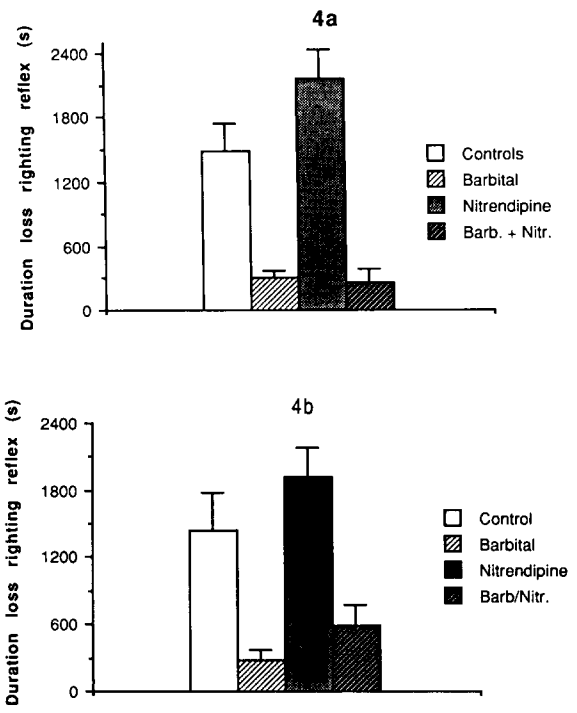


FIG. 4. Measurements of the duration of the general anaesthetic action of pentobarbitone after 7 days (Fig. 4a) or 12 days (Fig. 4b) barbital treatment, with or without concurrent administration of nitrendipine. Pentobarbital was given at 40 mg/kg IP in each case. The addition of nitrendipine to the chronic treatment did not significantly alter the effects of pentobarbital after either vehicle or barbital chronic treatment ($p > 0.1$). Values are means ± SE.

ment was less than in the previous work, we repeated the tests on the general anaesthetic action of pentobarbital after 12 days treatment with barbital. Nitrendipine was given twice daily, as before, with the last injection 24 h before cessation of the barbital diet. Figure 4b shows that concurrent administration of nitrendipine did not alter the tolerance to the action of pentobarbital.

## DISCUSSION

Some protective effect of acutely administered nitrendipine was seen on the barbiturate withdrawal syndrome, but this was less than that seen in our earlier studies on the ethanol withdrawal syndrome (16) and was of short duration. The compound also had little anticonvulsant action against seizures due to bicuculline during barbital withdrawal, although there was a significant effect on the convulsions produced by the partial inverse agonist FG7142. Dihydropyridine calcium channel antagonists have been reported to have some anticonvulsant actions, mainly against seizures due to pentylenetetrazol, but we have found this effect to be small compared with their actions against seizures induced by withdrawal from ethanol (16) or from nitrous oxide (6). We have found little anticonvulsant action against other types of seizures (3). We have not seen any protective effects against the actions of bicuculline in control mice, but this convulsant was included to see whether nitrendipine affected the potentiation of its actions that is seen during barbiturate withdrawal.

When given chronically, concurrently with the barbital, nitrendipine had a protective effect on the barbital withdrawal syndrome. We showed previously that such treatment completely prevented the occurrence of convulsive behaviour on handling during ethanol withdrawal (27). The effect on the barbiturate withdrawal syndrome was not as complete as in the latter study, but was consistent in both experiments. The pattern was also consistent in that the effect of the concurrent chronic nitrendipine treatment was evident throughout the withdrawal testing periods, in contrast to the acute action. The nitrendipine injections were stopped at least 24 h before the testing began, and we have shown previously that the brain concentrations of nitrendipine at this time interval after two weeks treatment with the dose schedule used in the present study were too low to have any acute action on the ethanol withdrawal syndrome (27). In view of the very small acute action of nitrendipine on barbiturate withdrawal (see above), it is unlikely that the effects seen in the present experiments were due to such an acute effect. Nitrendipine therefore appears to act on the development of the adaptive responses that result in the withdrawal syndrome.

The tolerance studies, however, did not show any effects of chronic nitrendipine on the development of tolerance to either the ataxic or the general anaesthetic actions of barbiturates. These results were complicated by an effect of chronic nitrendipine, when given in the absence of barbital, that increased the actions of pentobarbital. We have not previously seen any effects of such treatment, either on the actions of ethanol (5), on the convulsant properties of bicuculline (27), or when measuring behaviour in the absence of acute drug administration. The interaction may have been due to an effect of the nitrendipine treatment on pentobarbital metabolism. This was supported by the fact that it was not seen when barbital was used as the challenge drug, as barbital undergoes little metabolism (17).

The dose of nitrendipine used in this work, 50 mg/kg, was the same as that in our earlier studies on ethanol physical dependence (16,27). During this earlier work we measured the brain concentrations of this compound after acute injection (using the same strain of mice as the present study) and found that 2 h after injection the mean concentration was 1.4 $\mu$M and by 8 h after administration it had fallen to 400 nM. These values are in the same range as those found to be required for effects on neurones. Nitrendipine at 0.1–10 $\mu$M had a selective effect on calcium currents in dorsal root ganglion cells (24). Mogul and Fox reported that nimodipine, at 2 $\mu$M, selectively affected a slowly inactivating calcium current in acutely isolated hippocampal CA3 neurones (19). The selectivity of dihydropyridines in blocking the L subtype of calcium channel reported in cultured cells (20) may not be as clear in brain tissue; Takahashi et al. reported that in CA1 hippocampal pyramidal cells nicardipine had more effect on T-type currents ($IC_{50}$ value 3 $\mu$M) than on those resembling the N or L subtypes (25). However, some selectivity may be seen when calcium currents are activated by the dihydropyridine Bay K 8644 (28), and the level of depolarisation will affect the results, as blockade by dihydropyridines was decreased by hyperpolarisation (9). The latter effect may account for the greater sensitivity of cardiac and muscle cells to dihydropyridines. Concentrations of nitrendipine of 10 $\mu$M and above are not considered to be selective for calcium currents in neurones (24).

We have previously reported increased density of dihydropyridine binding after chronic ethanol treatment, but little change in affinity (23). Increases in calcium channel activity after barbital treatment were also demonstrated by an increase

in $^{45}Ca^{2+}$ uptake (13). In the latter study, the increase in calcium uptake into hippocampal slices after the barbital treatment was blocked by a dihydropyridine calcium channel antagonist, while the dihydropyridines had no effect on uptake into synaptosomes. In both these studies the same chronic treatment schedule was used as in the present work, and the results suggested that increases may occur in both dihydropyridine-sensitive and dihydropyridine-insensitive calcium channels.

These results support the concept that withdrawal syndromes caused by ethanol and by barbiturates, whilst superficially similar, are not produced by the same mechanisms. This is consistent with the results of Okamoto et al. (21), who came to a similar conclusion following their demonstration that diazepam was more effective in protecting against barbiturate withdrawal than against ethanol withdrawal.

In summary, acute administration of a calcium channel antagonist gave a small amount of protection against the behavioural signs of withdrawal from barbital. The effects were less pronounced than those against ethanol withdrawal. Concurrent chronic administration of nitrendipine was more effective, and the calcium antagonist appears to decrease the adaptive changes responsible for the withdrawal syndrome. There was no effect, however, of concurrent administration of nitrendipine on the development of tolerance to barbiturates. These results suggest that dihydropyridine-sensitive calcium channels may be involved to a small degree in the adaptations to chronic barbiturate treatment, but to a considerably less extent than in ethanol dependence.

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