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Pharmacology Biochemistry & Behavior, Vol. 54, No. 4, pp. 657–663, 1996

0091-3057/96 $15.00 + .00

SSDI 0091-3057(95)02232-5

Conditioned Taste Aversion and Place Preference Induced by the Calcium Channel Antagonist Nimodipine in Rats

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Received 14 July 1995; Revised 15 November 1995; Accepted 15 November 1995

DE BEUN, R., A. LOHMANN AND J. DE VRY. *Conditioned taste aversion and place preference induced by the calcium channel antagonist nimodipine in rats.* PHARMACOL BIOCHEM BEHAV **54**(4) 657–663, 1996.—It has become clear that various calcium channel antagonists are able to suppress excessive intake of ethanol in rats. With respect to these findings, it has become of interest whether these drugs can act as rewarding and/or aversive stimulus. Therefore, such affective stimulus effects of the L-type calcium channel antagonist nimodipine and its enantiomers were studied in Wistar rats in a series of conditioned taste aversion (CTA; two-bottle choice procedure) and conditioned place preference (CPP; two-compartment procedure) experiments. Racemic nimodipine (0.95–15 mg/kg IP) was found to induce a dose-dependent CTA, 7.5 mg/kg being the lowest effective dose. Subsequent studies with both enantiomers revealed that the CTA effects of nimodipine are completely dependent on the activity of (−)-nimodipine. With (+)-nimodipine (0.25–90 mg/kg IP), none of the doses tested induced a significant CTA, whereas with (−)-nimodipine clear and dose-dependent CTA effects were noted (0.5–30 mg/kg IP). For this enantiomer, the lowest effective dose was 15 mg/kg. In additional CPP experiments, it was confirmed that (±)-nimodipine and (−)-nimodipine have affective stimulus properties, whereas (+)-nimodipine was again an ineffective stimulus (dose used for all drugs: 15 mg/kg IP). Interestingly, the affective stimulus effects as measured with CPP of (±)- and (−)-nimodipine turned out to be rewarding, as it was found that both drugs produced a significant place preference. It is concluded from these studies that nimodipine possesses intrinsic affective stimulus effects which are rewarding in nature. Furthermore, these stimulus effects are mediated by the activity of the (−)-enantiomer. Possibly, these rewarding effects of nimodipine may play a role in the reported attenuating effects of this drug on voluntary ethanol intake in rats.

Calcium channels Dihydropyridines Nimodipine Stereoselectivity Rewarding stimulus Taste aversion
Place preference Ethanol intake Rats

A considerable number of studies indicate that neuronal calcium (Ca^{2+}) channels are involved in the behavioral actions of ethanol [e.g., (11,21,28,36,53)]. Besides the fact that these ion channels have been proposed to play an important role in the development of ethanol tolerance and dependence [e.g., (8,9,22,23)], it is, at present, also suggested by several studies that Ca^{2+} channels are involved in the regulation of ethanol intake and preference in experimental animals [e.g., (3,5,12,30, 33,35,38)]. With regard to these latter effects, the L-type voltage-gated Ca^{2+} channels have received specific attention. A diversity of Ca^{2+} channel antagonists for which the L-type Ca^{2+} channels are sensitive have been shown to be effective in suppressing ethanol intake and preference in animal models of alcoholism. This, in spite of the fact that L-type Ca^{2+} channel antagonists are derived from different chemical classes. Thus, drugs in the phenylalkylamine group such as verapamil (5,12,33,35) and levemopamil (37), as well as the dihydropyridine derivatives nimodipine (3,5,34), nifedipine (3,5,11,12), isradipine (3,5,12,30), darodipine (12), nicardipine (3,5,30), felodipine (5), nitrendipine (5), and GOE 5438 (29) have all been reported to be effective in decreasing ethanol consumption. The only exception seems to be diltiazem, representing a third class of L-type Ca^{2+} channel antagonists designated as benzothiazepine derivatives. For this drug, either no significant effects could be established on ethanol intake and preference, or, at best, only very weak effects were noticed (5,30,33).

For the present study, nimodipine was selected as one of the aforementioned successfully applied drugs in tests for ethanol

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intake reduction, to examine its affective stimulus properties. Although it has already been found that nimodipine possesses discriminative stimulus properties in rats (4,6,7), no systematic investigations have been carried out yet to reveal whether or not nimodipine can also act as an affective stimulus. Thus far, only preliminary but promising data on this subject have been presented by our lab [see (4,7)]. However, evaluating such stimulus effects of nimodipine in more detail seems of significance because characterization of this drug as a rewarding or aversive stimulus may provide more insight in the mechanism of action with respect to the reported efficacy of nimodipine in attenuating ethanol intake. For this purpose, a conditioned taste aversion (CTA) as well as a conditioned place preference (CPP) procedure were used.

In a typical CTA design, subjects are presented a fluid with a novel (and assumed palatable) taste and immediately after consumption of this liquid injected with a drug, whose effects the animals have not experienced before. Subsequently, on a later occasion and under nondrug conditions, avoidance of the taste associated with the drug effect is measured [cf. (15,41,47)]. In a characteristic CPP setting, subjects are exposed to distinct environmental stimuli after being injected with a drug. After administration of the drug vehicle, they are exposed to clearly dissimilar environmental stimuli. This pairing of drug state with a specific environment is repeated several times and thereafter approach towards, or avoidance of, the drug-associated environment is measured under nondrug conditions [cf. (16,26,51)].

Initially, in a series of CTA experiments with male Wistar rats, dose-dependent effects of racemic nimodipine and both its enantiomers were established in a two-bottle choice procedure. Both enantiomers were tested, as it was previously reported that the ethanol intake reducing effects of nimodipine are mediated mainly by the (−)-enantiomer (3,7), whereas the discriminative stimulus properties of nimodipine appear to reside mainly in the (+)-enantiomer (4,7). Subsequently, a two-compartment CPP study was conducted with a single dose of all three drugs to corroborate the affective stimulus effects as found with CTA, and to determine the quality of the affective stimulus effect, for instance, rewarding or aversive.

METHOD

Subjects

A total of 232 male Wistar rats were used (Harlan–Winkelmann; Hsd/Win:WU, Borchen, Germany), 8 animals for each experimental group. All rats weighed 220–230 g upon arrival at our laboratory and were throughout the studies maintained in groups of four per cage (Macrolon type 3) under a normal 12 L:12 D regime (conditioned taste aversion (CTA) experiments, lights on at 0700 h), or under a reversed 12:12 cycle (conditioned place preference (CPP) experiments, lights on at 1900 h). The animals were allowed to adapt to the respective laboratory conditions for 1 week prior to the experimental sessions. Food (standard pellets; Snniff Spezialdiäten GmbH, Soest, Germany) and tap water were supplied ad lib during the adaptation period. Room temperature was kept constant at 22–23°C. At the start of the behavioral tests, the body weight of the animals was around 250 g.

Apparatus

Conditioned Taste Aversion. CTA sessions were conducted in a standard Macrolon type 3 cage (37 × 25 × 16 cm) bedded with sawdust. Two bottles (of 300 ml content each) were placed next to each other on top of the cage, near the front wall. The drinking spouts (fitted with double stoppers) protruded about 3 cm into the cage. The distance between the drinking spouts was approximately 15 cm. Fluid consumption was measured by weighing the bottles manually. All sessions were conducted under white light conditions.

Conditioned Place Preference. CPP equipment consisted of a two-compartment preference box (91 × 41.5 × 38 cm) made of polyvinyl chloride (PVC). The walls of one-half of the box were black, whereas the other half had white walls. The black and white parts of the box were of equal size (41.5 × 41.5 × 38 cm) and were separated by a small area of 8 × 41.5 × 38 cm with gray walls. The floor of all parts of the box was gray. Frequencies of entrance and duration of time spent on the three different locations were registered by infrared beam interruption, and via a house-made interface automatically recorded on an IBM personal computer running house-made acquisition software. To prevent direct contact with the infrared beam equipment, a transparent Plexiglas inner box was fitted within the preference box. Conditioning sessions were run in separate association boxes (41.5 × 41.5 × 38 cm), which were similar to the black or white compartment of the preference box. Preference and conditioning boxes were open on top and all sessions were conducted under monochromatic red light conditions.

Drugs

Racemic nimodipine (BAY e 9736), (−)-nimodipine (BAY n 5248), and (+)-nimodipine (BAY n 5247) were synthesized by Bayer AG; Leverkusen, Germany. All drugs were dissolved in a solvent containing 5% v/v Solutol HS 15 (12-hydroxystearic-acid ethoxilate, purchased from BASF AG; Ludwigshafen), 5 % v/v pure ethanol and 90 % v/v saline. Drugs were injected IP in a volume of 1 ml/kg. The saccharin (2,3-dihydro-3-oxobenz-isosulfonazole sodium salt) used for the CTA experiments was purchased from the Sigma Chemical Company (St. Louis, MO) and dissolved in tap water.

Procedure

Conditioned Taste Aversion. Twenty-four hours before the first CTA session (day 0), the animals were water deprived and fluid access was from then on restricted to daily experimental sessions of 15 min, which took place individually in a Macrolon type 3 test cage. After each session, the animals returned to their respective home cages. Food was freely available in the home cages throughout the procedure, but was not available during the sessions. For a given subject, all six sessions required to complete a CTA took place in the same test cage and the cages were not cleaned between sessions. Animals designated to the same experimental group were run in parallel. During the first four sessions (day 1 through day 4), both bottles contained plain tap water. During this phase of the procedure, the animal learns to drink a reasonable amount of fluid in a short period of time. For the 5th session (day 5, conditioning session), both bottles were filled with a saccharin solution (0.1% w/v) and immediately after completion of this session the animals were injected with either the vehicle (the three respective control groups), (±)-nimodipine (0.95, 1.875, 3.75, 7.5, 15 mg/kg), (−)-nimodipine (0.5, 0.95, 1.875, 3.75, 7.5, 15, 30 mg/kg), or (+)-nimodipine (0.25, 0.5, 0.95, 1.875, 3.75, 7.5, 15, 30, 60, 90 mg/kg). Per animal, only one dose (or the vehicle) of a particular drug was tested, making up a total of 25 experimental groups (N = 8 per group). On days 6 and 7,

no sessions were conducted (washout period) and the animals had free access to tap water in their home cages from the end of day 5 until the morning of day 7, when the animals were again deprived of water, 24 h prior to the final 6th session (day 8, test session). During this last session, one bottle contained the saccharin solution and the other bottle was filled with tap water. To control for location bias, the saccharin was presented in the left bottle for half of the animals in each group and in the right bottle for the other half. By measuring the amount of fluid consumed from both bottles separately, drug-induced CTA could be determined by comparison of the relative saccharin intake in the drug treated groups and their vehicle-treated controls.

Conditioned Place Preference. The first session (day 1) was conducted in the two-compartment preference box under nondrug condition, to establish the baseline preference of the animals. The rats were placed in the gray starting area of the box and allowed free access to the black and the white compartment of the box for 60 min. The box was cleaned between each individual session. From the next day onwards, subjects were treated daily with either the drug of interest or its vehicle and subsequently placed in one of the two distinct association boxes (black or white). The injection session interval was always 10 min and a conditioning session lasted for 30 min. CPP effects of the vehicle (control group), 15 mg/kg (±)-nimodipine, 15 mg/kg (−)-nimodipine, and 15 mg/kg (+)-nimodipine were investigated in four different groups of animals (N = 8 per group). Drug and vehicle treatment were alternated during eight sessions (day 2 through day 5, and day 8 through day 11. No sessions were conducted on days 6 and 7), drug treatment being paired four times with one of the association boxes and vehicle treatment being paired four times with the other association box. The design was fully balanced in that for half of the animals of each experimental group drug treatment was paired with placement in the black association box; for the other half it was paired with the white box without conditioning against initial preference. In addition, half of the animals in each subgroup started their conditioning sessions in the white association box (and, consequently, finished in the black box), whereas the other animals in the respective subgroup were treated first in the black box and, thus, finished in the white box. Twenty-four hours after the last conditioning session the animals were tested again in the two-compartment preference box (10th session, day 12). Similar to the baseline session, the animals were tested under nondrug condition and were allowed free access to the black and white compartment for 60 min. CPP could be determined by comparing the time spent on the drug-associated side before (1st session) and after (10th session) conditioning for the four drug conditions tested (including the vehicle condition in the control group).

Statistics

Conditioned Taste Aversion. Data of (±)-nimodipine, (−)-nimodipine, and (+)-nimodipine were submitted separately to one-way analyses of variance (ANOVA), with the between-subjects factor DOSE (6, 8, and 11 levels, respectively). The dependent variable was the ratio of (saccharin solution)/(saccharin solution + tap water) intake. Fluid intake scores were calculated in grams. Post hoc analyses took place with Tukey HSD multiple comparisons. Results were considered significant when $p < 0.05$.

Conditioned Place Preference. Data were submitted to a three-way analysis of variance (ANOVA) with repeated measures with the between-subjects factors drug (four levels; vehicle, (±)-nimodipine, (−)-nimodipine, and (+)-nimodipine) and side (two levels; putative conditioning in black or white compartment). The within-subjects factor was conditioning (two levels; pre- and postconditioning data). Time spent in the drug-associated compartment (calculated in minutes) was the dependent variable. Where appropriate, pre- vs. postconditioning comparisons were made with two-tailed paired-samples t-tests. Significance level was set at $p < 0.05$.

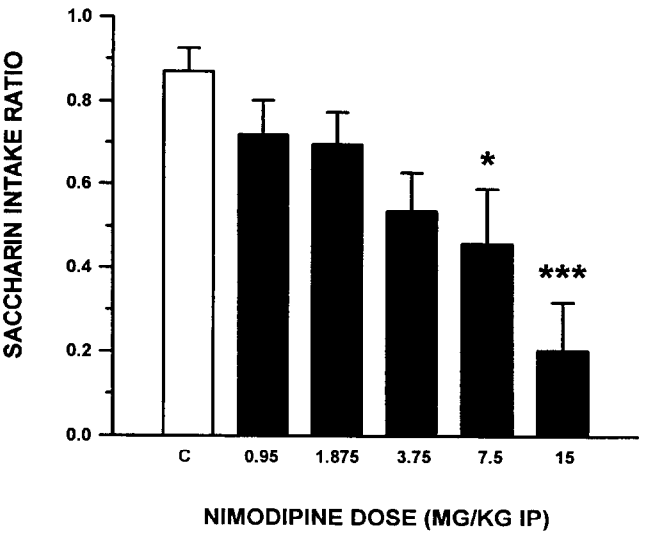

FIG. 1. Saccharin solution intake expressed as the ratio of (saccharin bottle)/(saccharin bottle + water bottle) consumption during the final test session, after conditioning with nimodipine. Depicted are the mean (+ SEM) scores for five doses of racemic nimodipine, administered IP (filled bars), and the controls (C, open bar). N = 8 per group. Significant differences from controls are indicated by asterisks (*$p <$ 0.05, ***$p < 0.001$; Tukey HSD multiple comparisons).

RESULTS

Conditioned Taste Aversion

No differences in saccharin preference could be noted between the control groups used for the separate (±)-, (−)-, and (+)-nimodipine analyses, $F(2, 21) = 0.53$, NS.

Figure 1 presents the preference for saccharin during the final test session, for five experimental groups treated with (±)-nimodipine and the control group. Pairing saccharin intake with nimodipine injections resulted in clear and dose-dependent taste aversion learning (CTA). A significant main effect of dose was found, $F(5, 42) = 6.02, p < 0.001$. Additional group-wise comparisons revealed that the 7.5 mg/kg ($p < 0.05$) and 15 mg/kg ($p < 0.001$) doses of nimodipine induced a significant CTA, as compared with the control group. In absolute amounts, mean total fluid intake for the six groups of animal used was 12.67 ± 0.37 g (range: 11.75–13.75 g). The control group consumed 12.00 g of the saccharin solution and 1.75 g of water. In the 15 mg/kg nimodipine group, saccharin intake was only 2.62 g, whereas water intake was 9.13 g.

Figure 2 shows the results obtained with (−)-nimodipine, depicting seven experimental groups plus the corresponding control group. As with racemic nimodipine, this enantiomer produced a solid and dose-dependent CTA: The factor DOSE showed a significant main effect: $F(7, 56) = 7.96$, $p < 0.001$.

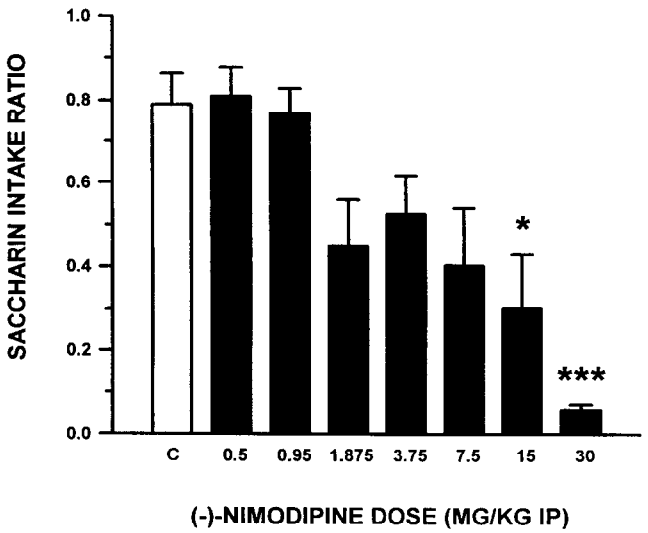

FIG. 2. Saccharin solution intake expressed as the ratio of (saccharin bottle)/(saccharin bottle + water bottle) consumption during the final test session, after conditioning with (−)-nimodipine. Depicted are the mean (+ SEM) scores for seven doses of (−)-nimodipine, administered IP (filled bars), and the controls (C, open bar). $N = 8$ per group. Significant differences from controls are indicated by asterisks (*$p < 0.05$, ***$p < 0.001$; Tukey HSD multiple comparisons).

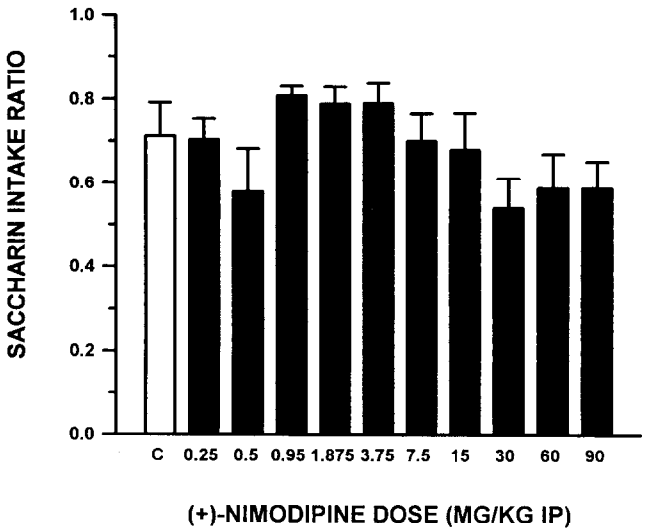

FIG. 3. Saccharin solution intake expressed as the ratio of (saccharin bottle)/(saccharin bottle + water bottle) consumption during the final test session, after conditioning with (+)-nimodipine. Depicted are the mean (+ SEM) scores for 10 doses of (+)-nimodipine, administered IP (filled bars), and the controls (C, open bar). $N = 8$ per group. A significant difference from controls was for none of the doses noted.

Subsequent group-wise comparisons revealed that the 15 mg/kg ($p < 0.05$) and 30 mg/kg ($p < 0.001$) doses were effective in inducing a CTA, as compared to the control group. In absolute amounts, mean total fluid intake for the eight groups of animal used was 13.46 ± 0.36 g (range: 12.13–15.25 g). The control group consumed 9.88 g of the saccharin solution and 2.75 g of water. In the 30 mg/kg (−)-nimodipine group, saccharin intake was limited to 0.75 g, whereas water intake was found to be 12.13 g.

As can be seen in Fig. 3, representing the data of 10 experimental groups submitted to (+)-nimodipine treatment and their control group, the (+)-enantiomer of nimodipine did not produce CTA. No significant main effect of dose was observed, $F(10, 77) = 1.74$, NS, and none of the experimental groups was found to be different from the control group with regard to saccharin preference. In absolute amounts, mean total fluid intake for the 11 groups of animal used was 13.86 ± 0.53 g (range: 11.75–16.63 g). The control group consumed 11.88 g of the saccharin solution and 4.13 g of water. In the 90 mg/kg (+)-nimodipine group, saccharin and water intake were 8.00 and 5.63 g, respectively.

Conditioned Place Preference

Differences in baseline preference for the putative side of conditioning were not seen between the four groups of animals used, $F(3, 28) = 0.27$, NS. Furthermore, there was no initial preference for one of the compartments of the preference box, $F(1, 30) = 0.08$, NS. During the baseline session, animals spent 27.17 ± 2.94 and 25.99 ± 2.94 min on their respective black and white side of putative conditioning. Nimodipine produced a significant conditioned place preference (CPP), as can be seen in Fig. 4. This figure shows the time spent in the drug-associated compartment of the preference box before and after treatment with either racemic nimodipine or one of its enantiomers (each drug in a dose of 15 mg/kg). For the three experimental groups, extended with the control group, a main effect of conditioning was found, $F(1, 24) = 7.83$, $p < 0.01$. This CPP effect was dependent on the drug tested, a significant interaction effect of drug × conditioning was noted, $F(3, 24) = 5.01$, $p < 0.01$. The CPP effect was independent of side of putative conditioning as no interaction effects were found for side × conditioning and for drug × side × conditioning, $F(1, 24) = 0.13$ and $F(3, 24) = 0.43$, respectively, both NS.

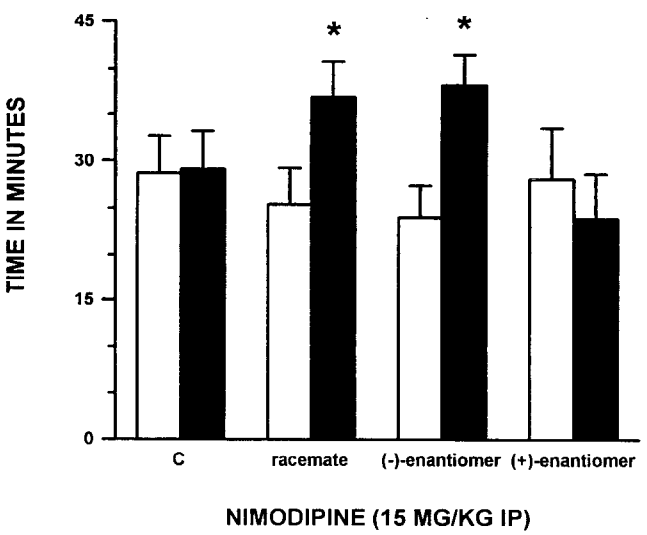

FIG. 4. Time spent in the drug-associated compartment of the preference box during the initial baseline session (open bars) and final test session (filled bars) after conditioning with nimodipine. Depicted are the mean (+ SEM) scores for racemic nimodipine, (−)-nimodipine, (+)-nimodipine, and the controls (C). $N = 8$ per group. Significant shifts in time (within-group baseline vs. test) are indicated by asterisks (*$p < 0.05$).

By comparing for each group the pre- and posttreatment scores, it was revealed that, similar to the CTA studies, only (±)- and (−)-nimodipine were effective compounds in producing a CPP. A significant shift in preference was noticed after conditioning with 15 mg/kg (±)-nimodipine [from 25.41 to 36.91 min: $t(7) = -2.44$] and after conditioning with 15 mg/kg (−)-nimodipine [from 24.08 to 38.33 min: $t(7) = -2.94$]. For both t-values, $p < 0.05$. In the control group (vehicle conditioning, shift from 28.69 to 29.12 min) and the 15 mg/kg (+)-nimodipine group (shift from 28.13 to 23.94 min), no significant CPP effects could be detected.

DISCUSSION

The present data provide evidence that the dihydropyridine calcium (Ca^{2+}) channel antagonist nimodipine possesses affective stimulus properties in rats. Clear and dose-dependent conditioned taste aversion (CTA) effects were found with racemic nimodipine, 7.5 mg/kg being the lowest dose producing a significant aversion towards the associated saccharin taste. The CTA results obtained with both enantiomers of nimodipine confirm the notion that this Ca^{2+} channel antagonist can act as an aversive stimulus. More important, however, is the observation that significant effects could only be noted with (−)-nimodipine, whereas (+)-nimodipine was completely ineffective within the dose range tested. These findings indicate that CTA effects induced by nimodipine are mainly, if not exclusively, mediated by the activity of (−)-nimodipine. Thus, (−)-nimodipine showed dose-dependent aversive stimulus properties, being effective for doses from 15 mg/kg to 30 mg/kg (the highest dose tested). In contrast to the effectiveness of (−)-nimodipine in producing a CTA, there was not a single dose of (+)-nimodipine that induced a significant CTA, despite the fact that a broad range of doses was tested, starting off with 0.25 mg/kg and ending up with a massive dose of 90 mg/kg. The fact that (+)-nimodipine does not induce a CTA cannot be attributed to the compound being pharmacologically inactive, as it was found that this enantiomer produced full generalization in rats trained to discriminate racemic nimodipine from vehicle (4,7). Furthermore, although clearly less potent than the (−)-enantiomer, this compound was still able to reduce ethanol intake and preference in ethanol preferring AA rats (3,5). Therefore, from these data it can be concluded that (+)-nimodipine probably has no aversive stimulus properties and, as most rewarding stimuli also induce a CTA (the so-called paradoxical CTA effect) [cf. (15,18)], is likely to lack affective stimulus effects at all. This assumption is supported by the additional conditioned place preference (CPP) studies conducted with this compound.

For the CPP study, a single dose of 15 mg/kg was chosen for nimodipine and both its enantiomers, based on the significant CTA effects of this dose with racemic nimodipine. In accordance with the CTA findings, for both nimodipine and the (−)-enantiomer affective stimulus properties were found. A significant shift in preference towards the drug-associated environment was noted after conditioning, providing evidence that both compounds have rewarding stimulus properties in rats. Because there was no substantial unconditioned preference for one of the compartments, the observed shifts in preference cannot be explained by nimodipine reducing aversiveness for one of the sides, due to anxiolytic- or antidepressive-like activity of this compound. This notion is strengthened by the finding that the magnitude of the CPP effect was about equal for both sides (black or white) of conditioning. As with CTA, no affective stimulus effects could be detected for (+)-nimodipine. As far as we know, these are the first studies showing that a Ca^{2+} antagonist can function as a rewarding stimulus in a CPP procedure. In the scarce literature dealing with CPP effects of Ca^{2+} antagonists, it was thus far reported that isradipine (20), nifedipine (50), flunarizine (50), diltiazem (50), and verapamil (27) were all ineffective in producing a CPP effect (either rewarding or aversive). However, because the aim of all these studies was to show possible attenuating effects of Ca^{2+} channel antagonists on CPP effects induced by various drugs of abuse, the experimental designs were not optimized for measuring possible effects of the respective Ca^{2+} channel antagonists alone, with respect to injection-session intervals (i.e., relatively long), number of doses (i.e., only one dose tested), and dose(s) tested (i.e., relatively low doses). The lack of effect found in these studies is, therefore, not necessarily in contradiction with the positive CPP results obtained in the present study with nimodipine. Moreover, it might still be the case that nimodipine has affective stimulus effects somewhat different from the Ca^{2+} channel antagonists used in the above-mentioned studies. Although this possibility seems not very probable (though not impossible) for the dihydropyridine derivatives isradipine and nifedipine, this might well be the case for flunarizine, diltiazem, and verapamil which are all nondihydropyridines.

Collectively, the current data could be interpreted as nimodipine being an affective stimulus that is rewarding in nature, with (−)-nimodipine as the essential enantiomer responsible for this kind of stimulus effect. Such an interpretation is not necessarily challenged by the CTA results, as it is a well-known phenomenon that most (if not all) drugs that are regarded to be a rewarding stimulus or positive reinforcer (as measured with CPP and operant self-administration, respectively), also readily induce a CTA [cf. (15,18)]. It could well be the case that nimodipine, as an intrinsic rewarding stimulus, is also able to act as an aversive stimulus under the specific one-trial CTA circumstances, simply due to a neophobic reaction (drug shyness) against the psychotrophic activity of the drug [cf. (15,18)]. It should, however, be clear that an alternative explanation for the concurrent CTA and CPP effects of nimodipine is not ruled out, in that it is possible that the affective stimulus produced by nimodipine has both aversive and rewarding components in it (in parallel or in succession). Dependent on the particular behavioral paradigm used, expression of either the rewarding or the aversive constituents of the drug effect may be more favored. Obviously, additional studies will be required to be able to characterize nimodipine more firmly as a drug with rewarding, but no inherent aversive stimulus properties.

Independent of whether one should interpret the CTA effects of nimodipine as a neophobic reaction against the (actually rewarding) stimulus effects of this drug or, alternatively, as nimodipine having true aversive stimulus properties, this drug shows in one respect certainly an interesting stimulus profile. The affective stimulus characteristics of nimodipine, as measured with CTA and CPP, are quite similar to those of some drugs of abuse including morphine, amphetamine, cocaine, nicotine, and diazepam (i.e., being able to induce both place preference and taste aversion) and differs from the profile common for drugs generally believed to have no abuse potential, as for example lithium chloride, naloxone, SKF 38393, or cholecystokinin [i.e., place aversion as well as taste aversion; for CTA and CPP reviews, see (16,39,40,45,51). Although this finding might suggest that nimodipine could have some abuse potential, such an assumption is not supported by intracranial self-stimulation data showing that nimodipine

in a dose range up to 100 mg/kg IP does not interfere with the frequency of self-stimulation behavior in rats as one would expect for a drug with abuse potential (17). Moreover, clinical experience with nimodipine in other indications than alcoholism (in which nimodipine has not been tested yet) has been made now for a reasonable time and no signs for abuse potential have thus far been reported. Nevertheless, with regard to the CPP data, it would still be of importance to determine in future studies whether or not nimodipine can serve as a positive reinforcer in a self-administration procedure, a well-suited paradigm to reveal abuse potential of compounds [see (49)].

In light of the apparent rewarding stimulus properties of nimodipine, it is tempting to speculate about the mechanism behind the previously reported effectiveness of this drug in reducing ethanol intake and preference (3,5,34). Curiously as it may seem, it has become clear now that it is extremely difficult (although not impossible) to demonstrate an ethanol-induced CPP in rats. In the majority of CPP studies with ethanol, aversive stimulus effects or a lack of effect are described [cf. (2,46,51)], which is quite different from the ease with which CPP results are obtained for other drugs of abuse [cf. (16,26,51)]. However, notwithstanding the frequent failures to establish rewarding stimulus properties of ethanol, it is a common belief that ethanol, as a major drug of abuse, must have rewarding or positive reinforcing effects. And, indeed, several authors were able to demonstrate CPP effects in rats by applying more atypical CPP designs [e.g., (13,24,31,48,52)], or by using mice instead of rats as experimental subjects [cf. (2)]. In addition, ethanol seems effective in both rats and mice as a positive reinforcer in self-administration paradigms [e.g., (14,42–44)]. If we accept that ethanol has the capacity to be a rewarding stimulus in rats, then the present findings with nimodipine may have implications for the interpretation of the reported ethanol intake-suppressing effects of this Ca^{2+} channel antagonist (3,5,34). It can be speculated that nimodipine reduces ethanol intake and preference by mere stimulus substitution for ethanol. The assumption that the inhibitory action of nimodipine on ethanol consumption may, to a certain extent, result from substitution for ethanol-induced reward seems of particular interest in view of some other studies, describing intake-reducing effects of drugs that were also shown to be rewarding in CPP procedures. Thus, besides nimodipine, the (presumed) serotonergic neurotoxin MDMA (1,32), the dopamine D_2 receptor agonists bromocriptine (25) and quinpirole (10) and the 5-HT_{1A} receptor agonist gepirone (19) have been shown to be effective in both suppressing ethanol consumption and to be able to produce a CPP [cf. (16,45)]. Of particular interest may, therefore, be the observation that the ethanol intake-reducing effects of nimodipine appear to reside mainly in the (−)-enantiomer (3,5), as are its affective stimulus properties as measured with both CTA and CPP. This corresponding stereoselectivity of behavioral effects suggests that both effects may be related to a certain extent. For future studies, a more thorough analysis of affective stimulus properties of drugs that were found to suppress ethanol intake, in comparison with stimulus effects of ethanol itself, may provide a useful tool in the search for a mechanism behind ethanol intake-reducing drug effects. It should, however, be clear that the present findings only leave open the possibility that affective stimulus properties may play some role in the reported antialcohol effects of nimodipine. Other mechanisms of action may well be (or even more) involved. Thus, it can be speculated that, for example, discriminative stimulus effects of nimodipine are interfering with, or generalizing to the ethanol stimulus. Likewise, ethanol-induced reward (or aversion) could be either attenuated or enhanced by nimodipine, influencing drinking behavior.

ACKNOWLEDGEMENTS

The authors would like to express their appreciation to Dr. Thomas Glaser for his valuable support of the project of which the presently described studies are part.

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