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Discriminative and Affective Stimulus Effects of Dihydropyridine Calcium Channel Modulators: Relationship to Antialcohol Effects

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DE VRY, J., R. SCHREIBER AND R. DE BEUN. *Discriminative and affective stimulus effects of dihydropyridine calcium channel modulators: Relationship to antialcohol effects.* PHARMACOL BIOCHEM BEHAV **64**(2) 203–211, 1999.— Voltage-operated calcium channels (VOCCs) have been implicated in alcoholism. Thus, dihydropyridine (DHP) VOCC antagonists, such as nimodipine, reduce ethanol (EtOH) intake and preference in a variety of animal models of alcoholism. Paradoxically, the DHP VOCC agonist BAY k 8644 also demonstrates antialcohol effects in such models. The antialcohol effects of BAY k 8644 are stereoselective [the "agonistic" (−)-enantiomer being more potent than the "antagonistic" (+)-enantiomer], and are not blocked by pretreatment with nimodipine. The present review summarizes studies on the effects of DHPs in drug discrimination (DD), conditioned taste aversion (CTA), and conditioned place preference (CPP) paradigms, and discusses the possibility that the apparent antialcohol effect of these compounds is related to their discriminative and/or affective stimulus effects. In rats trained to discriminate nimodipine from vehicle, (−)-BAY k 8644 completely generalizes to the nimodipine cue; whereas, in rats trained to discriminate (−)-BAY k 8644, nimodipine completely generalizes to, and is unable to block, the (−)-BAY k 8644 cue. The same stereoselectivity is obtained for BAY k 8644 in DD paradigms and models of alcoholism. The apparent similarity of these profiles of activity suggests that a common neurobiological mechanism underlies the discriminative stimulus and antialcohol effects of DHPs. It appears unlikely, however, that the antialcohol effects of DHPs are based on substitution for, or blockade of, the EtOH cue, as these compounds were not found to generalize to, or block, the EtOH cue. Comparison of the effects of DHPs in CTA and CPP paradigms suggests that the affective stimulus effects of these compounds are dissimilar, and that the mechanism underlying the latter effects is probably not related to the mechanism underlying the antialcohol effects of DHP VOCC modulators. © 1999 Elsevier Science Inc.

(Animal model of) alcoholism BAY k 8644 Conditioned place preference Conditioned taste aversion Drug discrimination Ethanol Isradipine Nimodipine Stereoselectivity

CENTRAL dihydropyridine (DHP)-sensitive voltage-operated calcium channels (VOCCs) have been implicated in the neurobiological adaptations resulting from repeated exposure to ethanol (EtOH) and, therefore, may be involved in the development and expression of alcoholism (24,31). During the last decade, several DHP calcium channel antagonists were reported to reduce EtOH consumption in animal models of alcoholism [for references, see (13)]. As these effects of DHPs showed a certain degree of behavioral selectivity and specificity [e.g., (13)], and were not merely the result of a pharmacokinetic interaction with EtOH [e.g., (3)], they may indicate that pharmacological blockade of VOCCs leads to a reduction of EtOH intake (further referred to as "antialcohol effects"), offering a therapeutic approach for the treatment of alcoholism. In the case of the DHP nimodipine, antialcohol effects have been demonstrated in different species, including mice, rats, and primates, and a variety of models, including operant oral or intravenous self-administration of EtOH and nonoperant consumption in a two-bottle procedure with limited or continuous access to relatively high EtOH concentrations (≥10% v/v) or water (13,19,28,30,37,41) (Table 1). Nimodipine was found to have antialcohol effects in nongenetic as well as genetic models of alcoholism, including the alcohol-preferring P rats and AA rats. In addition, the antialcohol effects of nimodipine appear to be relatively robust, as repeated treatment with the compound remained effective in reducing EtOH intake (Table 1). Thus far, the antialcohol effects of nimodipine have not yet been verified in alcoholics, but a clini-

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cal trial with the DHP VOCC antagonist isradipine (which shows similar efficacy to nimodipine in animal models of alcoholism (13), confirmed that this compound is effective in reducing craving for, and consumption of, alcohol in alcoholic patients (17).

Paradoxically, it was recently found that the highly selective and potent DHP VOCC agonist, BAY k 8644 [methyl-1,4-dihydro-2,6-dimethyl-3-nitro-4-(2-trifluoro-methyl-phenyl)-pyridine-5-carboxylate] (1) was also able to reduce EtOH consumption and preference (14). The antialcohol effects of BAY k 8644 were found to be stereoselective (14); the (−)-enantiomer, which behaves as a high affinity VOCC agonist (1), being more potent and effective than the (+)-enantiomer, which has been characterized as a low-affinity VOCC antagonist (1). Moreover, the antialcohol effects of (−)-BAY k 8644 could not be blocked by the antagonist nimodipine (14). These findings suggest that a common neurobiological mechanism (which may be related to an agonistic or an antagonistic interaction with VOCCs, or with a mechanism unrelated to VOCCs) underlies the antialcohol effects of DHPs [(14); for discussion, see further]. Antialcohol effects of (−)- or (±)-BAY k 8644 have now been reported in several genetic animal models of alcoholism, including the alcohol-preferring AA rats, P rats, and HEP rats, as well as in operant models of alcoholism [for review, see (14,28,42); Table 1]. As assessed in the genetic models of alcoholism, the antialcohol effects of (−)- or (±)-BAY k 8644 are considered to be relatively selective, as reductions in EtOH intake could be demonstrated at doses that did not affect general consummatory behavior or body weight, and that appeared to be devoid of behavioral side effects. The remainder of this article will discuss behavioral mechanisms possibly related to or underlying the antialcohol effects of DHP calcium channel agonists and antagonists. Particular emphasis will be given on the discriminative and affective stimulus effects of DHPs, and on the possible relationship between these effects and the antialcohol effects.

MECHANISMS UNDERLYING THE ANTIALCOHOL EFFECTS OF DHPS

Although it has been reported that a number of behavioral effects of BAY k 8644 can be blocked by the protypical DHP VOCC antagonist nifedipine [e.g., (4,5,34,38)], such an antagonism has generally been demonstrated only in the case of those behavioral effects that occur at relatively high doses of BAY k 8644 (i.e., doses that are higher than those effective in the animal models of alcoholism and that may be more related to side effects), and it was generally not tested whether other DHP VOCC antagonists were also able to block the effects of BAY k 8644. In those rare instances where it was tested whether antagonism of the behavioral effects of BAY k 8644 could be extended to other antagonists, unsuccessful attempts have been reported [i.e., (7)], indicating that DHP VOCC antagonists may differ in their ability to block certain behavioral effects of BAY k 8644. Thus, Cohen et al. (7) found that pretreatment with nimodipine or nicardipine did not block the BAY k 8644 cue in rats trained to discriminate BAY k 8644 from vehicle, under the same conditions where nifedipine was able to do so. Moreover, besides the antialcohol effects, other instances have been been published where

TABLE 1

EFFECTS OF NIMODIPINE AND BAY K 8644, AND THEIR ENANTIOMERS, IN ANIMAL MODELS OF ALCOHOLISM

Drug	Doses,* Application†	Model, Duration of EtOH Access	Result (MED‡)	Ref.
(±)-Nimodipine	1–30 PO	AA Rat, 18 h	15: ↓	41
	1–30 IP or PO	AA Rat, 12 h	7.5 IP, 10 PO: ↓	13
	20 PO	AA Rat, 12 h × 7 days	20: ↓	§
	4.6–13.8 IP	P Rat, 24 h or 3 days	9.2: ↓	37
	0.3–5.4 SC	Monkey, 24 h	0.9: ↓	¶
	3–30 SC	Operant IV mouse: Acquisition, 0.5 h	10: EtOH concentration/ response curve: →	28
	3–10 IP	Operant PO rat: Maintenance, 0.5 h	10: ↓	19
	2.5–20 IP	Operant IV rat: Acquisition, 2 h	5: ↓	30
	2.5–20 IP	Operant IV rat: Maintenance, 2 h	2.5–5: ↑; 20: ↓	30
(−)-Nimodipine	3–30 IP or PO	AA Rat, 12 h	10 IP, 30 PO: ↓	13
(+)-Nimodipine	3–30 IP or PO	AA Rat, 12 h	30 IP, >30 PO: ↓	13
(±)-BAY k 8644	0.1–2 IP or PO	AA Rat, 12 h	0.5 IP, PO: ↓	14
	0.03–0.3 SC	Operant IV mouse: Acquisition 0.5 h	0.1: EtOH concentration/ response curve: ↓	28
(−)-BAY k 8644	0.1–1 IP or PO	AA rat, 12 h or 12 h × 10 days	0.3 IP, PO: ↓	14
	0.125–0.5 IP	P rat, 24 h × 4 days	0.25: ↓	42
	0.125–0.25 SC	P rat, 2 h × 3 days	0.125: ↓	42
	0.125–0.25 SC	HEP rat, 2 h × 3 days	0.125: ↓	42
	0.3–0.5 IP	Operant PO rat, Maintenance, 0.5 h	10: ↓	#
(+)-BAY k 8644	10–50 IP or PO	AA Rat, 12 h	50 IP, PO: ↓	14

*mg/kg; †route of application; ‡MED: Minimal effective dose in mg/kg: ↓: decrease, ↑: increase in EtOH consumption; →: shift to the right; §De Vry, unpublished; ¶Rezvani, personal communication; #Schreiber and De Vry, unpublished.

BAY k 8644 induced similar pharmacological effects as antagonists. Thus, behavioral changes associated with naloxone-precipitated withdrawal (8), analgesic effects of sufentanyl (23), and local cerebral glucose utilization (27) were all similarly affected by nimodipine and BAY k 8644. It has been shown in vitro that, under particular conditions, DHP VOCC antagonists may have agonistic effects on Ca^{2+} flux (1,16), whereas agonists may have antagonistic effects on VOCCs (1). Therefore, it is conceivable that the antialcohol effets of DHPs, as well as some of the other effects induced by these compounds, are due to a similar effect (either agonistic or antagonistic) on VOCCs (14).

Similar to the molecular mechanism, the behavioral mechanism(s) underlying the apparent antialcohol effects of DHPs is currently unclear. In the light of the high comorbidity of alcoholism with mood and anxiety disorders, it can be speculated that the antialcohol effects of DHPs are a secondary effect of possible antidepressant or anxiolytic effects of such compounds. Indeed, alcohol-preferring rats, such as the AA rat strain, have been found to show "emotional" disturbances, as assessed in animal models of anxiety and depression (15), and DHPs possess antidepressive and, possibly, anxiolytic properties [(33); for reviews, see (21,36)]. However, several lines of evidence argue against this possibility as being the behavioral mechanism underlying the antialcohol effects of DHPs. First, antidepressant and anxiolytic properties have only been found in the case of antagonists, whereas BAY k 8644 appears to have no such properties, and is able to antagonize the antidepressant-like effects of DHP VOCC antagonists [e.g., (34); De Vry unpublished]. Some of the animal models of alcoholism in which BAY k 8644 was tested, such as the alcohol-preferring AA rat model, have been extensively validated with respect to pharmacological specificity, and were found to be sensitive to a number of compounds lacking antidepressive or anxiolytic properties [i.e., (18)]. Second, the shape of the dose–response curve for the antialcohol and antidepressant-like effects of DHPs appears to be different. Thus, whereas the former curve has a monotonous shape, the latter seems to be an inverted U-shape (13,41). Third, the impact of repeated treatment on the anti-alcohol and antidepressant-like effects of DHPs appears to be different. In the former case, a slight reduction in efficacy has been found [e.g., (14)], whereas in the latter case, a pronounced sensitization was obtained [for review, see (21)].

An alternative mechanism responsible for the antialcohol effects of DHPs may be a possible hypophagic or hypodipsic effect of such compounds. This appears to be unlikely, however, as it was shown that in those models of alcoholism in which general consummatory behavior was simultaneously measured with EtOH intake, antialcohol effects could be dissociated from effects on fluid or food intake [for discussion, see (13,14)]. Although it remains possible that the antialcohol effects are the result of a general attenuating effect of such compounds on the palatability or hedonic value of stimuli (not necessarily with a caloric value), nimodipine was found to be ineffective in an intracranial self-stimulation paradigm (26), suggesting that DHPs do not interfere with the functional status of the brain reward system. In the light of the antidepressive properties of nimodipine (21), the possibility that such compounds possess anhedonic effects would also be rather unlikely.

Because it is well established that EtOH can serve as a discriminative and affective (positive reinforcing or rewarding)

TABLE 2

EFFECTS OF DIHYDROPYRIDINE CALCIUM CHANNEL MODULATORS IN DRUG DISCRIMINATION PARADIGMS

Training Drug (*†)	Test Drug (*†)	Test Result (‡*†)	Ref
(±)-Nimodipine (15 PO)	(±)-Nimodipine (0.1–60 PO, 1–10 IP)	Full Gen. (15 PO, 3 IP)	16
	(−)-Nimodipine (0.3–20 PO)	Partial Gen. (10)	22
	(+)-Nimodipine (0.1–20 PO, 0.3–10 IP)	Full Gen. (1 PO, 5 IP)	22
	Nifedipine (5–40 PO)	Full Gen. (20)	16
	(±)-BAY k 8644 (0.3–1 PO)	Partial Gen. (1)	22
	(−)-BAY k 8644 (0.1–1 PO)	Full Gen. (1)	22
	(+)-BAY k 8644 (1–5, PO)	Full Gen. (5)	22
Isradipine (10 IP)	Isradipine (5–10 IP)	Full Gen. (10)	39
	Nifedipine (5–50 IP)	Partial Gen. (40)	39
	Nicardipine (0.5–3 IP)	Partial Gen. (1)	39
(±)-BAY k 8644 (2.5 PO)	(±)-BAY k 8644 (0.16–2.5 PO)	Full Gen. (2.5)	25
	(−)-BAY k 8644 (0.3–2.5 PO)	Full Gen. (2.5)	25
	(+)-BAY k 8644 (2.5–10 PO)	Partial Gen. (10)	25
	Nifedipine (2.5–20 PO)	Partial Antag. (20)	25
(±)-Bay k 8644 (0.5 IP)	(±)-BAY k 8644 (0.12–0.75 IP)	Full Gen. (0.5–0.75)	7
	Nifedipine (2.5–10 IP)	Full Antag. (10)	7
	Nicardipine (1.25–5, IP)	Partial Antag. (2.5)	7
	(±)-Nimodipine (0.6–10, IP)	Partial Antag. (1.25–2.5)	7
(−)-BAY k 8644 (0.3 IP)	(−)-BAY k 8644 (0.06–1 IP)	Full Gen. (0.1)	11
	(±)-BAY k 8644 (0.01–1 IP)	Full Gen. (1)	11
	(+)-BAY k 8644 (0.1–10 IP)	Full Gen. (1)	11
	(±)-Nimodipine (0.3–1 IP)	Full Gen. (1), No Antag.	22

*Dose (range) in mg/kg; †Route of application; ‡Maximal level of generalization/antagonism: full Gen./Antag.: >80% generalization/antagonism, Partial Gen./Antag.: >20% and <80% generalization/antagonism, No Gen./Antag.: <20% generalization/antagonism.

stimulus and because such stimulus effects are thought to play a role in alcohol abuse/dependence, the possibility that DHPs have such stimulus effects, as well as the possibility that these compounds are able to interact with the discriminative and affective stimulus effects of EtOH is reviewed in the next chapters.

DISCRIMINATIVE STIMULUS EFFECTS OF DHPS: DRUG DISCRIMINATION PARADIGMS

Thus far, only a few studies have characterized the discriminative stimulus effects of DHPs. As reviewed in Table 2, rats have been successfully trained to discriminate either an antagonist, such as nimodipine (16,20) or isradipine (39), or an agonist, such as (±)- or (−)-BAY k 8644 (7,11,22,25) from vehicle. The pharmacological specificity of the cue produced by a DHP [i.e., isradipine (39) and (±)-BAY k 8644 (7)] was investigated to a limited extent and appeared to be relatively high. The time dependency of the cue was studied for isradipine (39) and nimodipine (16)] and was found to be very similar ($T_{1/2}$ value about 90 min). Interestingly, the shape of the dose–response curve obtained with nimodipine (1–60 mg/kg) in rats trained to discriminate this compound (15 mg/kg) from vehicle was an inverted U-shape. The occurrence of such a dose–response curve in a dose range that was devoid of behavioral toxicity (i.e., all rats tested selected a lever) is quite unique in drug discrimination studies, and suggests that the discriminative stimulus effects of the training dose are different from those of higher doses. In the case of the (−)-BAY k 8644 cue, the same stereoselectivity as in the AA rat model of alcoholism (14) was found [i.e., (−)-BAY k 8644 ≤ (±)-BAY

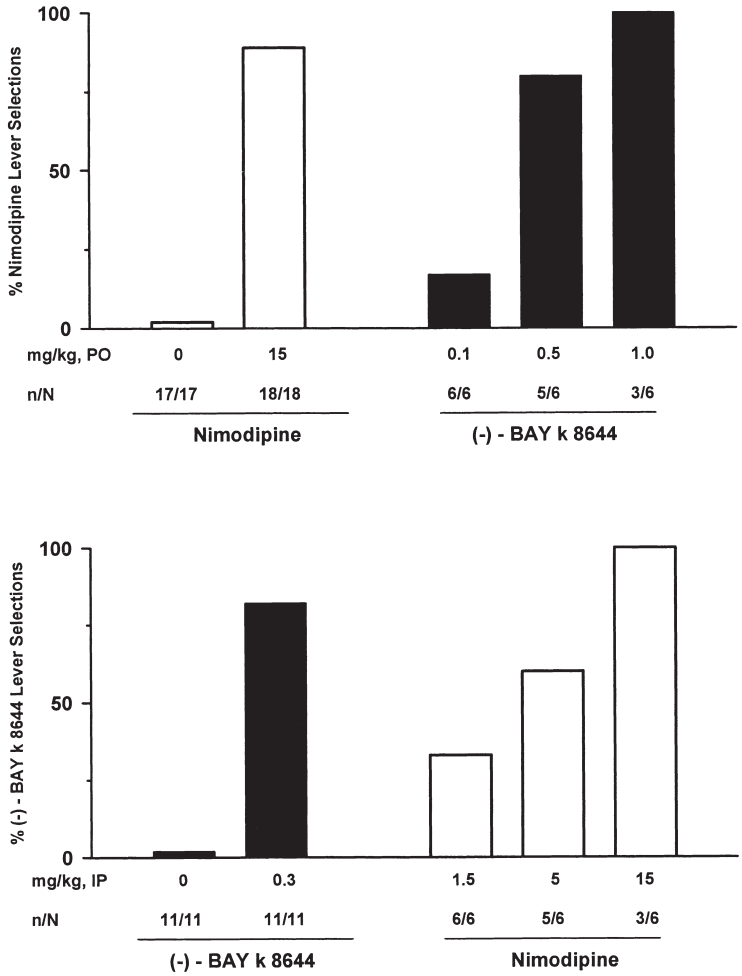

FIG. 1. Effects of nimodipine and (−)-BAY k 8644 in rats trained to discriminate either nimodipine (15 mg/kg, PO, T-30 min, top panel) or (−)-BAY k 8644 (0.3 mg/kg, IP, T-15 min, lower panel) from vehicle in a two-lever, food-reinforced procedure. Rats were trained and tested according to the procedure described in (11). The vehicle and injection-test interval were Tylose® MH 300 P (methylhydroxyethyl cellulose, 1% v/v) plus distilled water, and 30 min, for the nimodipine discrimination, and Solutol® HS 15 (12-hydroxystearic-acid ethoxilate, 5% v/v) plus 5% v/v pure EtOH and saline, and 15 min for the (−)-BAY k 8644 discrimination, respectively. % Lever Selections (y-axis) indicates the percent of rats that selected the drug-appropriate lever. *n/N* indicates the number of rats that selected a lever (*n*) out of the number of rats tested (*N*).

k8644 < (+)-BAY k 8644]. Similar to the finding with nimodipine in rats trained to discriminate nimodipine, the shape of the dose–response curve with the "antagonistic" enantiomer (+)-BAY k 8644 was found to be an inverted U-shape. Interestingly, generalization tests in rats trained to discriminate either nimodipine or (−)-BAY k 8644 from vehicle revealed the occurrence of symmetrical generalization between both compounds (Table 2 and Fig. 1). Moreover, in antagonism tests, it was reported that pretreatment with nimodipine was unable to block the (±)-, or (−)-BAY k 8644 cue (7,22), a finding again reminiscent of the lack of antagonism obtained with both compounds in the AA rat model of alcoholism (14). The close similarity between the profiles obtained with nimodipine and BAY k 8644 in animal models of alcoholism and drug discrimination suggests that a common or close similar molecular mechanism underlies both effects.

Although these findings strongly suggest that the nimodipine and BAY k 8644 cue are qualitatively very similar, some other findings suggest that the discriminative stimulus effects of DHPs may not be identical. First, the antagonists nifedipine and nicardipine were found to induce only partial generalization in rats trained to discriminate the antagonist isradipine (39), whereas nifedipine was found to induce full generalization (again with an inverted U-shaped dose–response curve, however) in rats trained to discriminate nimodipine (16). Although nimodipine was not tested in the former group, and isradipine was not tested in the latter group of rats, these findings suggest that the discriminative stimulus effects of nimodipine and nifedipine may be more similar to each other than to those of isradipine. On the other hand, however, pretreatment with nifedipine was found to block the (±)-BAY k 8644 cue to a larger extent than pretreatment

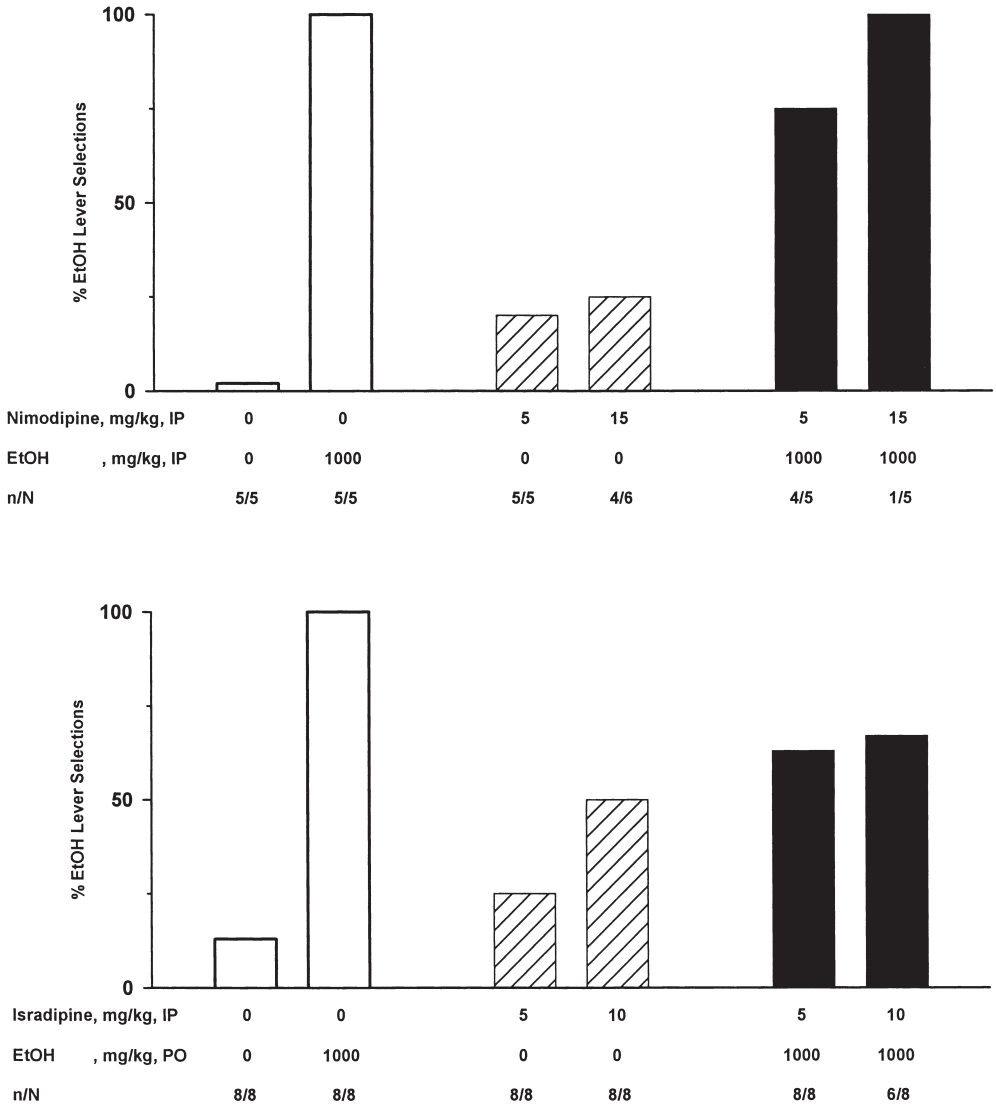

FIG. 2. Effects of nimodipine (upper panel) and isradipine (lower panel), tested as an agonist or as an antagonist, in rats trained to discriminate EtOH (1000 mg/kg, T-15 min) from saline in a two-lever, food-reinforced procedure (12). Nimodipine, isradipine, or vehicle [Solutol® HS 15 (12-hydroxystearic-acid ethoxilate, 5% v/v) plus 5 % v/v pure EtOH and saline] pretreatment was given 15 min before EtOH or saline treatment.

with nimodipine (7,25), suggesting that there may also be subtle differences between the discriminative stimulus effects of nifedipine and nimodipine. Further comparative studies are clearly needed to characterize in more detail the nature of the discriminative stimulus effects of diverse DHP VOCC modulators, and to clarify to which extent training dose and training drug are determinants of such characterization.

INTERACTION OF DHPS WITH THE DISCRIMINATIVE STIMULUS EFFECTS OF ETHANOL

The finding that DHPs have discriminative stimulus effects that share certain qualitative properties opens the possibility that the antialcohol effects of these compounds are due to an interaction with the discriminative stimulus effects of EtOH. Indeed, it is conceivable that the discriminative stimulus effects of these compounds are qualitatively similar to those of EtOH, and that the antialcohol effects of DHPs are based on stimulus substitution [for discussion, see (12)]. On the other hand, it is possible that pretreatment with a DHP masks, attenuates, or antagonizes the discriminative stimulus effects of EtOH, and that such a mechanism underlies the antialcohol effects of these compounds. Indeed, such a possibility was raised by Colombo et al. (9), as they found that pretreatment with isradipine was able to antagonize discriminative responding induced by EtOH, as assessed in a T-maze procedure. In rats trained to discriminate EtOH in a standard operant two-lever procedure, we were unable to find evidence for such an antagonism in the case of nimodipine, and isradipine only patially blocked the EtOH cue (Fig. 2). In addition, generalization tests with nimodipine and (−)-BAY k 8644 failed to show generalization to the EtOH cue, whereas isradipine induced partial generalization (Figs. 2 and 3). Although not tested in a human drug discrimination paradigm, it may be interesting to note that nimodipine did not affect subjective effects induced by EtOH in healthy volunteers (43). Taken together, it therefore appears to be unlikely that the antialcohol effects of DHPs are due to an interaction with the discriminative stimulus effects of EtOH (12).

AFFECTIVE STIMULUS EFFECTS OF DHPS: CONDITIONED TASTE AVERSION AND CONDITIONED PLACE PREFERENCE PARADIGMS

As in the case of the discriminative stimulus effects, only a few reports have documented the affective stimulus effects of DHPs, as assessed in conditioned taste aversion (CTA) or conditioned place-preference (CPP) paradigms. With respect to the CTA paradigm, all DHPs tested thus far [i.e., isradipine, nimodipine and its (−)-enantiomer, and BAY k 8644 and its enantiomers], with the exception of (+)-nimodipine, induced a significant effect (for references, see: Table 3). Although it can be argued that a postive outcome in a CTA paradigm merely indicates that a compound has (affective) stimulus effects, and, therefore, does not allow for a conclusion on the nature (either aversive or rewarding) of the stimulus [for discussion, see (10,11)], some authors have concluded that the apparent antialcohol effects of a DHP are a confound, and due to their ability to induce aversive effects in a CTA paradigm [i.e., (35)]. Even if the nature of the affective stimulus should be aversive (as indicated by a place avoidance in a CPP paradigm, see further), it remains difficult, however, to ascribe the antialcohol effect of a DHP to this presumed property of the compound, as, in general, subjects used in the animal models of alcoholism have had extensive experience with EtOH (for which they have developed a preference), and therefore, the EtOH is no longer a novel taste to which an aversion is conditioned by treatment with a DHP. In the case that a positive CTA outcome is interpreted as merely an indication that the treatment induces aversion in the sense of sickness, it should be expected that the animals will show a general decrease in consummatory behavior (food and/or fluid intake). As discussed previously, this appears to be not the case if assessed in appropriate models of alcoholism. In addition, the fact that (+)-nimodipine was not able to induce a CTA [even at the very high dose of 90 mg/kg; (10)]; whereas it was clearly effective at lower doses in the AA rat model of alcoholism (13), also suggests that the property to induce CTA is not required for an antialcohol effect, and therefore, appears not to be the underlying mechanism responsible for the antialcohol effects of DHPs in general.

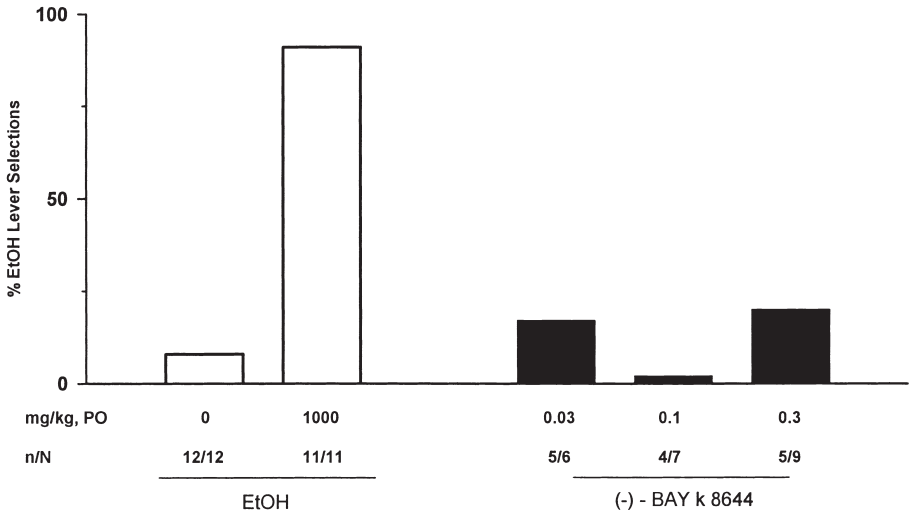

FIG. 3. Effects of (−)-BAY k 8644 in rats trained to discriminate EtOH (1000 mg/kg, T-15 min) from saline in a two-lever, food-reinforced procedure (12). (−)-BAY k 8644 or vehicle [Tylose® MH 300 P (methylhydroxyethyl cellulose, 1% v/v) plus distilled water] was given 30 min before test.

A limited number of DHPs have also been tested in diverse CPP paradigms (for references, see Table 4). Interestingly, however, different outcomes were obtained with different compounds and procedures. In particular, whereas the affective stimulus induced by the agonist (±)-BAY k 8644 appeared to be neutral [i.e., no place preference or avoidance; (11)], both rewarding (as indicated by induction of place preference), neutral, and aversive (as indicated by induction of place avoidance), stimulus effects have been obtained with the antagonists, even for the same compound (Table 4). This suggests that the nature of the affective stimulus of DHPs is highly dependent on particular characteristics of the experimental procedure, and therefore, may not be very pronounced (compared with the rewarding stimulus induced by the majority of compounds with abuse potential, or the aversive stimulus induced by lithium), and probably not relevant for the mechanism underlying the antialcohol effects of DHPs.

INTERACTION OF DHPS WITH THE REWARDING OR POSITIVE REINFORCING STIMULUS EFFECTS OF ETHANOL

To the best of our knowledge, only one study has been published investigating the effects of a DHP on the rewarding stimulus effects of EtOH, as assessed in a CPP paradigm (2). In that study it was found that daily nifedipine pretreatment did not affect the acquisition of a CPP with EtOH in rats (although such pretreatment was able to attenuate the acquisition of a CPP with cocaine or morphine). Further studies are needed to test whether this finding can be generalized to other DHPs, and whether the same conclusion can be drawn with respect to the expression of an established CPP with EtOH. Effects of a DHP on the acquisition and maintenance of operant self-administration of EtOH, and thus, by inference, on the positive reinforcing stimulus effects of EtOH, have been investigated both with nimodipine and BAY k 8644 (for references, see Table 1). In rats or mice, nimodipine was able to affect the acquisition and maintenance of operant self-administration, although the nature of the effect appeared to be dependent on the concentration of the EtOH unit dose and on the dose of nimodipine. The profile of effects obtained with nimodipine in these studies appeared to be relatively selective (i.e., not merely the result of behavioral toxicity), and was thought to reflect an attenuation of the magnitude of the positive reinforcing stimulus effects of EtOH (19,28,30). In mice and rats, (±)- or (−)-BAY k 8644 was reported to inhibit self-administration of EtOH during the acquisition and maintenance of the experiment [(28); Schreiber and De Vry, unpublished]. The profile of effects induced by BAY k 8644 and its (−)-enantiomer suggested, however, that the effects were at least partly confounded by behavioral toxicity of the pretreatment. It remains unclear, therefore, to what extent a DHP VOCC agonist is able to interact with the positive reinforcing stimulus effects of EtOH.

TABLE 3

EFFECTS OF DIHYDROPYRIDINE CALCIUM CHANNEL MODULATORS IN CONDITIONED TASTE AVERSION PARADIGMS

Training Drug	Dose (*†)	Test Result (MED‡)	Reference
Isradipine	1–30 IP	Aversion (3)	35
	30 PO	No effect	35
(±)-Nimodipine	0.95–15 IP	Aversion (7.5)	10
(−)-Nimodipine	0.5–30 IP	Aversion (15)	10
(+)-Nimodipine	0.25–90 IP	No effect	10
(±)-BAY k 8644	0.06–1 IP	Aversion (0.25)	11
(−)-BAY k 8644	0.12–1 IP	Aversion (0.25)	11
(+)-BAY k 8644	2.5–20 IP	Aversion (10)	11

*Dose (range) in mg/kg; †Route of application; ‡MED: Minimal effective dose in mg/kg.

TABLE 4

EFFECTS OF DIHYDROPYRIDINE CALCIUM CHANNEL MODULATORS IN CONDITIONED PLACE PREFERENCE PARADIGMS

Training Drug	Dose (*†)	Test Result (MED‡)	Reference
Isradipine	2.5 SC	No effect	29
	2.5–10 IP	No effect	6
Nifedipine	20 SC	No effect	40
	5–10 IP	Preference (5)	2
(±)-Nimodipine	15 IP	Preference	10
	0.1–10 SC	Avoidance (10)	32
(−)-Nimodipine	15 IP	Preference	10
(+)-Nimodipine	15 IP	No effect	10
(±)-BAY k 8644	0.25–2 IP	No effect	11

*Dose (range) in mg/kg; †Route of application; ‡MED: Minimal effective dose in mg/kg.

CONCLUSION: RELATIONSHIP BETWEEN ANTI-ALCOHOL AND STIMULUS EFFECTS OF EFFECTS OF DHPS

Characterization of the discriminative and affective stimulus effects of DHPs points to similarities as well as differences between the diverse DHPs. Interestingly, however, there appears to be a relatively close similarity between the profiles obtained with nimodipine and BAY k 8644 in animal models of alcoholism and in drug discrimination, suggesting that the antialcohol and discriminative stimulus effects of these compounds share a common molecular mechanism. Although it is unlikely that the antialcohol effects of DHPs are due to an interaction (either generalization or antagonism) with the discriminative stimulus effects of EtOH, the possibility that DHPs affect the reinforcing stimulus properties of EtOH is an option that should be further evaluated. The finding that inverted U-shaped curves are frequently obtained with DHP VOCC antagonists in drug discrimination paradigms suggests that the discriminative stimulus effects induced by relatively high doses of these compounds is qualitatively different from those induced by relatively low doses. As DHP VOCC antagonists may have agonistic properties at low concentrations (1), it is conceivable that the similarity between the discriminative and antialcohol effects of DHP agonists and antagonists (and the failure to find mutual antagonism) reflects such agonistic interactions with VOCCs. It is speculated that further elucidation of the molecular mechanisms underlying the discriminative stimulus effects of DHP VOCC modulators will be instrumental in understanding the mechanism underlying the antialcohol effects and possibly other central effects of these compounds.

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