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Effects of calcium channel inhibitors on the hypothermic response to oxotremorine in normo and hypercholinergic rats

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Abstract—The Flinders Sensitive Line of rats (FSL) has been selectively bred to have increased sensitivity to cholinergic drugs. Typically, these rats react with twice as great a hypothermic effect to muscarinic agonists such as oxotremorine, as do similarly bred Flinders Resistant Line rats (FRL). We compared the effects of three chemically different calcium channel inhibitors (diltiazem, nicardipine and verapamil) on the hypothermia induced in FRL and FSL rats by oxotremorine (0·2 mg kg^{-1} s.c.). Each drug was injected i.p. in a dose of 20 μmol kg^{-1} 30 min before oxotremorine. Methylatropine (2 mg kg^{-1} s.c.) was administered 15 min before oxotremorine to block the peripheral effects of the agonist. The hypothermic effect of oxotremorine in FSL rats was antagonized by nicardipine and diltiazem. In contrast, verapamil failed to influence the hypothermic response in FSL rats. Verapamil significantly ($P < 0·05$) augmented oxotremorine hypothermia in FRL rats. Diltiazem and nicardipine were without effect on oxotremorine-induced hypothermia in FRL rats. There were no significant changes in temperature in separate groups of FRL and FSL rats treated with calcium channel inhibitors alone.

Acetylcholine is involved in the central regulation of temperature (Wang & Lee 1989). Although the effects elicited with muscarinic and nicotinic stimulation differ with the species used, in laboratory rodents muscarinic agonists are known to induce hypothermia (Wang & Lee 1989). Cholinergic influences on thermoregulation are thought to be mediated by neurons reaching the posterior hypothalamus which are involved in the regulation of thermic set-point. This occurs via alterations in the calcium/sodium (Ca^{2+}:Na^{+}) ratio (Myers 1980). Perfusion of the posterior hypothalamus with calcium evokes hypothermic effects, whereas depletion of calcium in the above region induces hyperthermia (Myers 1980). Muscarinic mechanisms have been shown to increase synaptosomal free Ca^{2+} concentration by opening voltage sensitive L-type calcium channels (Boess et al 1990) leading to increased intracellular calcium. These channels can be blocked by calcium channel inhibitors (CCIs). The main classes of these compounds include dihydropyridine derivatives (nifedipine, nicardipine, nimodipine), phenylalkylamines (verapamil) and benzothiazepines (diltiazem) (Scriabine 1987).

The influence of various CCIs on spontaneous and evoked thermoregulatory responses has already received some attention. Direct intracerebral injections of verapamil can differentially alter temperature in cats, depending on the injection site. Thus, hypothermia was elicited from the anterior hypothalamus, and hyperthermia from the posterior hypothalamus (Beleslin et al 1985; Rezvani et al 1986a). In rabbits, intracerebroventricular infusion of verapamil, nifedipine and cinnarizine, another CCI from the piperazine group, evoked hyperthermia, whereas Bay K8644, (methyl-1,4-dihydro-2,6-dimethyl-3-nitro-4-(2-trifluoromethyl-phenyl)-pyridine-5-carboxylate) a dihydropyridine calcium channel agonist, elicited a dose-related hypothermic response (Palmi & Sgaragli 1989).

Peripheral injections of various CCIs, in spite of their known vasodilatatory activity, failed to influence core temperature over a wide set of dose ranges (Isaacson et al 1985; Johnston et al 1986; Czyrak et al 1989; Pucilowski et al 1989). The influence of CCIs on pharmacologically induced hypothermia is not uniform. In studies on the hypothermic response to ethanol, CCIs, when administered peripherally, either augmented the response (verapamil, nimodipine) (Isaacson et al 1985; Johnston et al 1986; Rezvani et al 1986b) or were without significant effects (diltiazem, nifedipine, Pucilowski et al 1989). The hypothermic response to apomorphine was significantly reduced by dihydropyridine CCIs and verapamil, while diltiazem was without any effect (Czyrak et al 1989). To our knowledge no attempts have been made to study the possible influence of CCIs on muscarinic receptor-mediated hypothermia.

The current work was aimed at the assessment of the effect of selected CCIs on oxotremorine-induced hypothermia in two strains of rats selectively bred for differences in sensitivity of cholinergic mechanisms (Overstreet et al 1988). The Flinders Sensitive Line (FSL) of rats has been developed to have increased sensitivity to cholinomimetic drugs. Typically, FSL rats react to oxotremorine with twice as great a decrease in temperature as do similarly bred Flinders Resistant Line (FRL) rats. The thermoregulatory mechanisms in the FLS rats appear to be deeply altered, as these rats are consistently supersensitive to various pharmacological hypothermia-inducing treatments such as apomorphine, quinpirole, m-chlorophenylpiperazine, buspirone, and ethanol (Overstreet et al 1988, 1990; Wallis et al 1988).

Materials and methods

Male FRL and FSL rats, 340–380 g, were bred at the Center for Alcohol Studies, University of North Carolina School of Medicine. At the age of 10 weeks, all rats were screened for cholinergic sensitivity by measuring their hypothermic response to an oxotremorine challenge (Russell & Overstreet 1987).

The rats were kept two or three per cage (25 × 45 × 20 cm), under reversed phase 12:12 h light:dark cycles (lights off at 1000 h) and a controlled room temperature of 21 ± 1°C, with free access to commercial laboratory chow and tap water.

As handling stress can markedly influence temperature response (Gordon 1990), all rats were handled for at least 5 days before the experiments. The experiments were carried out between 1100 and 1500 h in an experimental room under the same light and temperature conditions as in the animal room.

On the day of the experiment, the rats were moved to the experimental room and left undisturbed for 60 min before the first temperature measurement. Colonic temperature was recorded with a BAT-12 digital thermometer (Sensortek, Clifton, NJ), with a resolution of 0·1°C. Each rat was removed from its home cage, placed on a table, and a lubricated thermistor probe was inserted 5 cm into the rectum for approximately 1 min. The rats were returned to their home cages between temperature measurements.

The experiment evaluating the influence of CCIs on the hypothermic response to oxotremorine was carried out in 7 FRL and 7 FSL rats. Each rat received each of the following CCIs: diltiazem HCl (Sigma), nicardipine HCl (Yamanouchi), verapamil HCl (Sigma) (20 μmol kg^{-1} each) and distilled water (a solvent for all CCIs). All injections were given i.p. in a volume of 2 mL kg^{-1}. The dose, corresponding to approximately 9 mg

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kg^{-1} of diltiazem, 10 mg kg^{-1} of verapamil and 13 mg kg^{-1} of nicardipine, was chosen on the basis of previous studies (Rezvani et al 1986b; Czyrak et al 1989; Pucilowski et al 1989) as the highest equimolar dose not likely to affect core temperature on its own. In a pilot study for another experiment we observed that 30 μmol of verapamil induced hypothermia in Sprague-Dawley rats.

At least 1 week elapsed between injections and their sequence was randomized for each rat according to a Latin square design. Fifteen minutes after CCI or water injection, each rat was administered 2 mg kg^{-1} methylatropine nitrate (Sigma) s.c. and following another 15 min, 0·2 mg kg^{-1} oxotremorine sesquifumarate (Sigma) s.c. All drugs were prepared extemporaneously, and their doses refer to the salt form. Nicardipine handling was done under protective sodium light. Rectal temperatures were recorded before all injections, immediately before methylatropine (T_1) at 15 min after CCI or water injection, and then after oxotremorine at 30 min intervals for 2 h (T_2-T_5).

In a separate group of 5 FRL and 5 FSL rats, the effect of CCIs as such on colonic temperature was assessed. After determination of the baseline temperature (T_0) the rats were injected i.p. with an individual CCI (20 μmol kg^{-1}), or water, and the temperature measurements were taken at 30 min intervals for the subsequent 180 min. This experiment was carried out according to the Latin square design so that each rat received each drug or water during 4 sessions, spaced 7 days apart.

From the raw temperature recordings the temperature difference from the baseline (T_0) was calculated for each rat and for each treatment. The total area under the temperature curve was integrated for each rat, according to Simpson's rule (Tallarida & Murray 1987). The data were analysed with a one way ANOVA, followed by Dunnett's test for multiple comparisons with the control group (Tallarida & Murray 1987). All results are expressed as means ± s.e. and a confidence limit of $P < 0.05$ was considered as statistically significant.

Results

The baseline core temperatures did not differ between groups; their mean values fell within the range of 38·0–38·2 for saline or drug-treated FSL rats, and within 38·3–38·5 for FRL rats, respectively. ANOVA revealed that there was a significant overall effect of treatment on the oxotremorine-induced hypothermia which occurred in both the FRL ($F(3,24) = 3.67$, $P < 0.05$) and the FSL rats ($F(3,24) = 6.09$, $P < 0.01$). In the FRL rats, oxotremorine-induced hypothermia was significantly ($P < 0.05$) augmented by pretreatment with verapamil, with nicardipine acting in the same direction at 90 and 120 min (Figs 1, 2). In the FSL rats, the opposite picture was observed, in that hypothermia was significantly attenuated by nicardipine and diltiazem (Figs 1, 3). Verapamil failed to influence the effect of oxotremorine in FSL rats.

There was no significant change in colonic temperature after CCIs alone as revealed by ANOVA [$F(3,16) = 0.89$ for FRL rats, and 1·62 for FSL rats], although verapamil tended to decrease body temperature in FSL rats (Fig. 4).

Discussion

Calcium ions appear to play a significant role in hypothalamic thermoregulatory control. An increase in the $Na^+ : Ca^{2+}$ ratio in the posterior hypothalamus is associated with elevation in body temperature (Myers 1980). Muscarinic receptor activation has been demonstrated to result in prolonged elevation of cytostolic free Ca^{2+}, due to the stimulation of the ion release from intracellular storage sites by inositol trisphosphate (Kudo et al

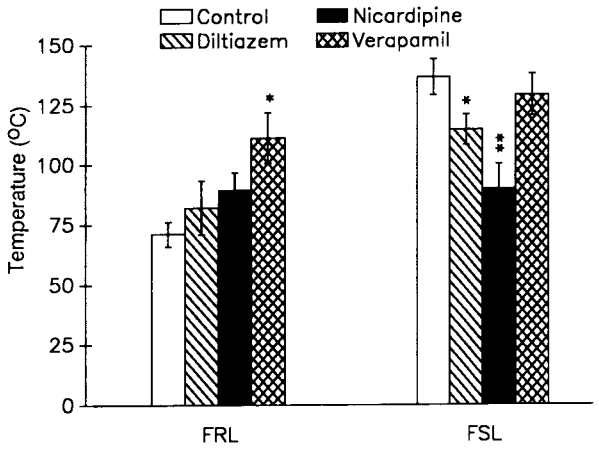

FIG. 1. Integrated area under the temperature response curve (mean + s.e., 7 rats per group). * $P < 0.05$, ** $P < 0.01$ vs control (Dunnett's test).

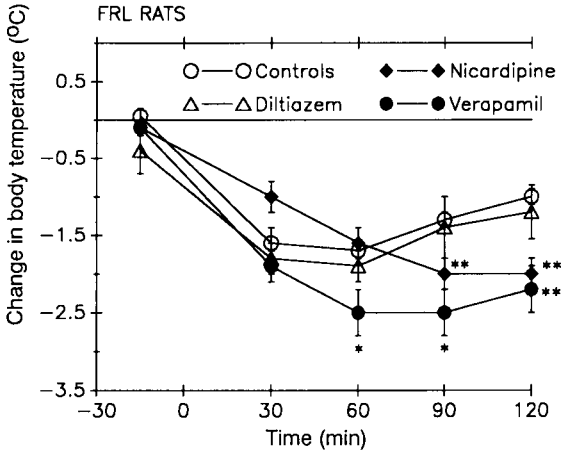

FIG. 2. Effect of calcium channel inhibitors on oxotremorine-induced hypothermia in FRL rats. * $P < 0.05$, ** $P < 0.01$ vs control (Dunnett's test).

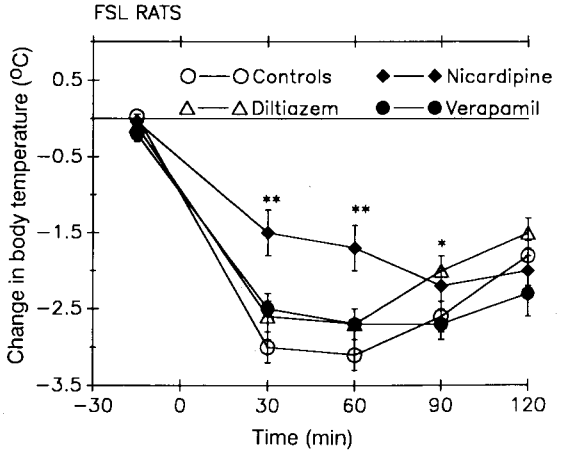

FIG. 3. Effect of calcium channel inhibitors on oxotremorine-induced hypothermia in FSL rats. * $P < 0.05$, ** $P < 0.01$ vs control (Dunnett's test).

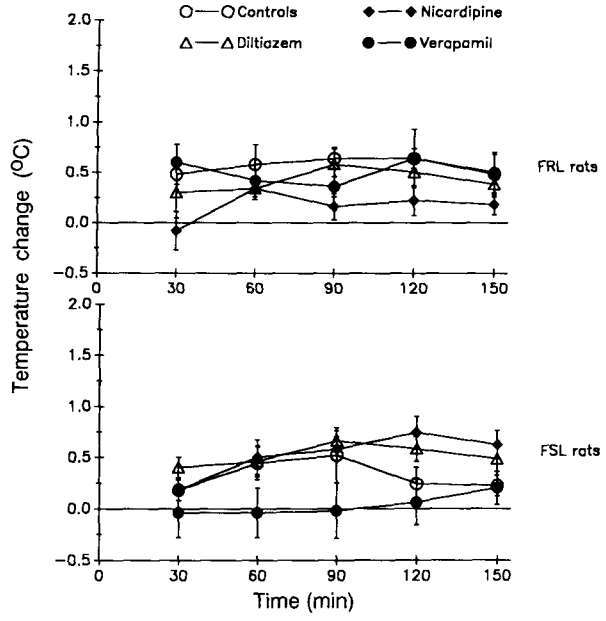

FIG. 4. Effect of calcium channel inhibitors on body temperature in FRL and FSL rats.

1988), as well as by diacylglycerol-activated protein kinase C-dependent opening of slow Ca^{2+} channels (Boess et al 1990). Through such mechanisms, muscarinic agonists such as oxotremorine can decrease the $Na^+:Ca^{2+}$ ratio, thereby decreasing body temperature. CCIs induce the opposite effect, hyperthermia, when applied centrally (Beleslin et al 1985; Rezvani et al 1986a, 1990a; Palmi & Sgaragli 1989). However, peripheral administration of various CCIs does not seem as such to influence the basal body temperature (Isaacson et al 1985; Johnston et al 1986; Czyrak et al 1989; Pucilowski et al 1989), an observation confirmed in the present study using diltiazem and nicardipine. However, verapamil tended to decrease basal temperature in hypercholinergic FSL rats. This appears to indicate that peripherally injected CCIs do not reach the CNS in sufficiently high concentrations to influence temperature regulatory mechanisms on their own. Alternatively, peripheral effects of CCIs (vasodilatation) seem to antagonize the centrally mediated hyperthermia.

Nevertheless, the effectiveness of CCIs in elevating temperature becomes manifest when a hypothermic response is induced by other means. Thus, CCIs were shown to antagonize (with the exception of diltiazem) the hypothermic effects of the dopaminergic agonist, apomorphine (Czyrak et al 1989). As the FSL rats are hyperresponsive to the hypothermia inducing effects of apomorphine, and the more selective D_2-agonist, quinpirole (Crocker & Overstreet 1991), we expected that CCIs would be similarly effective against oxotremorine-induced hypothermia. However, the present results appear to indicate that such a protective action is observed only in FSL rats. Moreover, it can be manifest after nicardipine and diltiazem, but not verapamil. The latter drug was ineffective in FSL rats and even potentiated the hypothermic response in normocholinergic FRL rats. We have recently reported similar effects of verapamil (facilitation) and nicardipine (suppression) on ethanol-induced hypothermic response in FRL and FSL rats (Rezvani et al 1990b). Consequently, we suspect that the primary effect of peripherally administered verapamil is a hypothermic one, and that the lack of a further increase of hypothermic response in FSL rats was due to the "ceiling effect", as hypothermia in these rats after oxotremorine challenge was already very profound.

FRL rats, when tested under various conditions, do not differ from the parent strain, Sprague-Dawley rats (Overstreet et al 1988). Thus nicardipine and diltiazem do not affect muscarinic receptor-mediated hypothermia. The same holds true for the hypothermia induced by reserpine and by clonidine (Czyrak et al 1989). Interestingly, FSL rats do not differ from FRLs with respect to clonidine-induced hypothermia (Overstreet et al 1988). It thus seems that the possibility that noradrenergic mechanisms mediate the observed effects of CCIs on body temperature can be ruled out.

The present results show that the effects of various CCIs on oxotremorine-induced hypothermia in FRL and hypercholinergic FSL rats differ. There is already some evidence of different or even opposite effects of various CCIs in pharmacological tests (Grebb 1986; Czyrak et al 1989; Pucilowski et al 1989; Bidzinski et al 1990; Kostowski et al 1990). This observation seems to indicate that the blockade of calcium channels, a feature common to all three drugs studied, is not responsible for the observed effects, and consequently, that the differences in their effects in the present and other studies are probably related to other non-specific pharmacological properties of various CCIs. Even though we have already learned about several of these characteristics of CCIs, it remains difficult to explain the present and previously observed differences in the effects brought about by various CCIs. Verapamil can act as a competitive antagonist of 5-HT_2, histamine H_2, α and α_2 adrenoceptors and dopaminergic D_2 receptors, and inhibit high affinity uptake systems for 5-HT, dopamine, noradrenaline, GABA, or choline (Brown et al 1986; DeFeudis 1987; Fairhurst et al 1980; Galzin & Langer 1983). Diltiazem does not interact with central noradrenergic transmission, 5-HT_1 and 5-HT_2 receptors or choline uptake (Galzin & Langer 1983; Adachi & Shoji 1986), and only weakly inhibits 5-HT synaptosomal uptake (Brown et al 1986). Dihydropyridines seem to be devoid of any direct interaction with the central noradrenergic or 5-HT receptors (Andersson 1986; DeFeudis 1987). They do however, influence monoamine turnover (Pileblad & Carlsson 1986; Bolger et al 1988; Fadda et al 1989). Nicardipine was also recently demonstrated to be a potent competitive inhibitor of high affinity choline uptake (Bidzinski & Pucilowski upublished data), which however, does not explain its presently observed suppressant effect on the hypothermia induced by a direct muscarinic agonist in FSL rats. It may be of some importance to note the time effect of the drug in both groups of rats. Not only did nicardipine antagonize the hypothermic effect of oxotremorine in FSL rats at 30 and 60 min, but it tended to decrease the early hypothermic effect in FRL rats as well (Figs 2, 3). Nicardipine appeared to lose its antihypothermic effect or even augment hypothermia in FRL rats. The nature of this double response to the drug is hard to understand at this point, but may indicate that two distinct, and to some extent opposite, components exist with respect to the drug's action.

Another possible explanation of the present findings can include pharmacokinetic interactions between CCIs and oxotremorine. It is known that diltiazem (Yamaguchi et al 1974) and nicardipine (Abe et al 1983), but not verapamil (Dietz et al 1983), increase the glomerular filtration rate, and thereby can possibly influence excretion rate of oxotremorine. The well known vasodilatatory action of CCIs, likely to occur at the dose used in the present study, cannot be conducive to explanation of the differences between the effects brought about by these drugs. Vasodilatation is likely to facilitate heat loss and thus could potentiate the hypothermic effect of oxotremorine. However, all three CCIs used in the study cause vasodilatation, and nicardipine, which attenuated hypothermia, appears to be most potent in that respect (Chaffman & Brogden 1985; Sorkin & Clissold 1987).

Although there appears to exist an opposite interaction

between certain CCIs and oxotremorine with respect to the thermic effect of the latter drug, apparently this is manifest only in the rats with supersensitive muscarinic mechanisms (e.g. FSL). The exact nature of these interactions remains to be resolved.

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