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The Effects of Chronic Treatment With a Calcium Channel Antagonist on Two Types of Generalized Epilepsies in Rats

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VAN LUIJTELAAR, E. L. J. M., N. ATES AND F. J. VAN DER STAAY. *The effects of chronic treatment with a calcium channel antagonist on two types of generalized epilepsies in rats.* PHARMACOL BIOCHEM BEHAV **48**(3) 575-579, 1994.—Although calcium antagonists possess antiepileptic properties in various models of epilepsy, their role after chronic administration and in models for generalized absence epilepsy has not been studied. Twenty-four male Wistar rats, aged 84–94 weeks, were chronically provided with EEG electrodes. Two groups received dietary nimodipine (860 ppm) for 14 and 21 weeks, respectively, while a control group received the same rat chow without nimodipine. The EEG was recorded for 3 h to establish the effects of nimodipine on spike-wave discharges. Next, 50 mg/kg pentylenetetrazol (PTZ) was injected to establish the effects on convulsive epilepsy, and the EEG was recorded for 30 min. All animals had spontaneous spike-wave discharges (SWD), but there were no differences between the three groups. However, chronic nimodipine treatment had a significant effect on PTZ-induced seizures: the group that had been treated with nimodipine for 21 weeks showed significantly more and longer-lasting seizures than the control group. The facilitating effects of chronically administered of nimodipine on PTZ-induced seizures are striking and opposite to those reported in the literature. In a second study, nimodipine was administered acutely, but no effects of nimodipine on PTZ-induced epilepsy could be detected. It can be concluded that chronic dietary administration of a calcium antagonist induces different effects on PTZ-induced seizures than acute administration in aged Wistar rats with sponteneous occurring SWD.

Nimodipine Calcium antagonist Pentylenetetrazol-induced seizures Absence epilepsy
Spike-wave discharges Genetic epilepsy model Chronic administration Wistar rats Aging

CALCIUM ions have several modes of action in the central nervous system. These ions play a role in many cellular processes, for instance, in the release of transmitters from presynaptic terminals. It has also been shown that calcium currents are involved in the generation of epileptic activity and that some antiepileptic drugs such as ethosuximide reduce the low-threshold calcium currents (7,22,41). In fact, it has been postulated that the movement of calcium ions into neurons may be the common denominator for triggering and propagating seizure activity.

Drugs that block the influx of calcium ions into the cells by blockade of voltage- or receptor-operated calcium channels are named calcium antagonists. They possess antiepileptic properties in various in vitro and in vivo models of epilepsy (13,14,23). Nimodipine is a centrally active calcium antagonist that blocks the voltage-dependent L-type channels. Its antiepileptic properties are proven in various animal models (9,17, 23). The role of calcium in epileptogenesis was recently confirmed by the demonstration that calcium agonists, such as Bay K 8644, which increases calcium entry into the cells, facilitate convulsions, an effect that is prevented by pretreatment with the calcium antagonist nimodipine (9).

In most studies with calcium antagonists, the drugs have been administered acutely; however, for a putative antiepileptic drug it is imperative that its action is proven in chronic experiments. As far as could be ascertained, there is no information about the antiepileptic action of calcium antagonists in chronic models, we decided to test nimodipine chronically.

The vast majority of models for generalized or focal epilepsy are models, whereby convulsions are induced chemically or pharmacologically. Little is known about the effects of calcium antagonists in genetic models for generalized nonconvulsive epilepsy. Rats with spontaneously occurring SWD in the EEG are an adequate model for human absence epilepsy

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(6,33,35,39). These SWD frequently occur during periods of passive wakefulness and light slow wave sleep and also at transitional phases (10). They can be suppressed by typical antiabsence drugs such as trimethadione and ethosuximide, and by the broad spectrum antiepileptics such as valproate, diazepam, and loreclezole while they are aggravated by carbamazepine and diphenylhydantoin (1,27). Finally, similar cognitive deficits occur in humans and in rats during the presence of SWD, which supports the validity of the epileptic nature of the rat's SWD (36,37). SWD can be found in inbred rat strains (WAG/Rij's), in selection lines (Strasbourg Wistars), but also in outbred rats such as Sprague-Dawley rats (3,16,19,39,42). In all these strains it has been found that the number of rats showing the SWD increases with age (3,5, 40,42). We, therefore, expected that many of the randomly bred Wistar rats aged 2 years that we used would show SWD.

Beside the effects of chronic administration of calcium antagonists on absences, we were also interested in the effects of chronically administered nimodipine on pentylenetetrazol (PTZ)-induced seizures. High dosages of PTZ induce a tonic-clonic type of seizure, and nimodipine has been reported to antagonize the effects of PTZ in mice (14), as well as in rabbits in acute experiments (24). The purpose of the present study is to investigate in rats the effects of chronic administration of nimodipine on two types of generalized epilepsy.

METHOD

Animals

Twenty-four male random bred Wistar rats, purchased from Winkelmann (Borchen, Germany), served as subjects for the chronic study. At the time of surgery they were between 84 and 94 weeks old and weighed between 385 and 512 g. Thirty-two male rats, age between 100 and 104 weeks and with a body weight from 360 and 540 g and otherwise identical to the rats used for the chronic study, were used for the acute experiment. All rats had no prior drug history. The rats were maintained on a 12 L : 12 D regime, with white lights on at 2000 h, and were housed in groups until surgery, when they were singly housed.

The rats were divided into three groups for the chronic experiment: group 1 (n = 8), group 2 (n = 5), and group 3 (n = 11). The rats of the first group served as controls and the rats of the two latter groups received nimodipine in the diet for 14 and 21 weeks prior to testing, respectively. The animals received food pellets that contained 860 ppm nimodipine, which corresponds to a daily intake of about 30 mg/kg body weight (Bayer, Leverkusen, Germany). This drug regime was successful in reducing age-related changed in locomotor activity (28) and it will yield more constant and slowly changing plasma levels than what can be obtained by two times per day IP administration. Finally, oral administration mimics more closely human antiepileptic drug intake. The animals from group 1 received food pellets of the same size without the drug. The nimodipine and control diets were started at Troponwerke in Cologne and continued at the University of Nijmegen. At the times of testing, the three groups did not differ in body weight or in age.

The rats for the acute experiment were divided into four groups, three drug groups and a control group. The four groups did not differ in age or in body weight.

Material

Animals were chronically provided with standard EEG electrodes (Plastics One, MS 333/2-A) under complete Nembutal anaesthesia. Electrodes were placed on the surface of the cortex, one in the frontal region (coordinates with skull surface flat and bregma zero-zero: A 2.0, L 3.5) and a second one in the parietal region (A −6.0, L 4.0). The earth electrode was placed in the cerebellum. The animals were allowed to recover for 1 week after surgery, were then moved to a transparent recording cage (25 × 25 × 35 cm), connected to the EEG leads, and habituated to the leads for 6 h. The EEG was registered on an Elema-Schönander polygraph, with a paper speed of 1 cm/s. Only the EEG frequencies between 1 and 70 Hz were allowed to pass.

Procedure

First, the EEG was registered for 3 h in the dark period of the rats for the chronic experiment, between 1000 and 1300 h [(during this phase of the dark cycle rats show the highest number of SWD, (34)] to evaluate the effects of nimodipine on the number of spontaneous occurring SWD. This procedure was chosen to make sure that the effects of nimodipine on SWD could be evaluated independently from its effects on PTZ-induced seizures. Next, a dose of PTZ (50 mg/kg) was injected intraperitoneally and then the EEG was recorded for another 30 min.

A spike-wave discharge was identified from the EEG paper as such if it included a train of sharp spikes and slow waves with an amplitude of at least twice the background EEG amplitude and a duration of at least 1 s [for more details, see (33)]. The number and the mean duration of the SWD in the 3-h period were determined. The effects of PTZ were also quantified from the EEG paper. The rats showed tonic or generalized convulsions with afterdischarges. The latency to the first aberrant EEG sign, the number of full blown seizures, and the convulsion time, i.e., the duration from the start of the first convulsion until the end of the last convulsion, were determined.

The effects caused by nimodipine were statistically evaluated with a one-factor analysis of variance with number of weeks of nimodipine treatment (groups) as factor with three levels and subsequent conservative post hoc tests according to Scheffé ($p < 0.05$) to evaluate differences between groups.

In order to investigate whether acutely administered nimodipine has comparable effects on PTZ-induced convulsions, the four groups were given intraperitoneally the solvent or 2.2, 8.8, or 35,2 mg/kg nimodipine in a freshly ultrasonicated solution containing a mixture of solutol/ethanol/0.9% NaCl (5 : 5 : 90). The solutions were prepared in a dark room and shielded from light otherwise. One hour after the administration of nimodipine the rats were injected with 50 mg/kg PTZ. Measured were the seizure onset latency, the number of seizures, total seizure time, and offset latency. The data were analyzed with a analysis of variance with dose as factor (four levels).

RESULTS

The results of the 3-h recording periods from the chronic experiment are presented in Table 1. Analyses of variance did not show any difference between the three groups concerning the number and mean duration of the SWD. However, a difference emerged after PTZ administration: the number of seizures appeared to differ significantly between the three groups, $F(2, 21) = 6.69, p < 0.01$. Post hoc analysis revealed that the group that had received nimodipine for 21 weeks had a significantly higher number of seizures than the control group. The convulsion time, i.e., the duration from the start

TABLE 1

EFFECTS OF DIETARY NIMODIPINE TREATMENT (860 ppm) ON ABSENCE AND PTZ (50 mg/kg)-INDUCED SEIZURES

Condition	Number of Spike-Wave Discharges	Mean Duration of Spike-Wave Discharges in s	Mean Number of Convulsions	Convulsion Time in s
Group 1 control	56.3 ± 12.3	8.7 ± 2.4	.62 ± .18	46.1 ± 7.8
Group 2 14 weeks' nimodipine	51.5 ± 8.9	9.3 ± 2.3	1.20 ± .37	221.2 ± 114.9
Group 3 21 weeks' nimodipine	54.8 ± 11.2	8.3 ± 3.4	1.73 ± .19*	443.0 ± 132.4*

Means and standard deviations are presented of the number and mean duration in seconds of spike-wave discharges measured over 3 h (absence epilepsy), mean number of PTZ-induced convulsions, and mean convulsion time in seconds.

*Significantly different from group 1.

of the first convulsion until the end of the last convulsion, was also different in the three groups, $F(2, 21) = 3.55$, $p < 0.05$. Post hoc tests confirmed that this group with nimodipine for 21 weeks had a significantly longer convulsion time than the control group. Finally, the onset latency showed a marginally significant difference ($p < 0.1$): the latency tended to be shorter for group 3 compared to the other groups.

Acutely administered nimodipine did not result in statistical differences between the four groups on any of the dependent variables. The convulsion time (mean and SEM) in seconds was 110 ± 38, 97 ± 12, 106 ± 30, and 63 ± 16, respectively, for the solvent and the 2.2, 8.8, and 35.5 mg/kg nimodipine groups.

DISCUSSION

It has not previously been reported that old Wistar rats from Winkelmann show SWD, although it was to be expected as it is established that at a certain age many inbred and outbred rat strains show this nonconvulsive type of epilepsy, although to different extents (6,16,39,42). In addition, various authors have described an increase in the number of spike wave discharges with age (5,40,42). The number of SWD per hour found in the present study is similar to the number found in WAG/Rij rats aged 6 months; the mean duration of the SWD of the Wistar Winkelmann rats was longer than that of WAG/Rij rats.

A surprising result, given the general antiepileptic action of calcium antagonists, was that chronic administration of a calcium antagonist did not modulate the number and mean duration of SWD. In another genetic model, sound-induced seizures, nimodipine, and other calcium antagonists possess anticonvulsant properties (9). There is another reason why it was expected that nimodipine would decrease the number of SWD. Sleep spindles and SWD are recruited in the lateral parts of the thalamus, and synchronization in thalamic-cortical circuits by the reticular thalamic nucleus forms the basis of these rhythmic oscillations (4). Synchronization of thalamic relay cells occurs by means of hyperpolarization of cells in which a low threshold calcium spike is crucial (4,31). We, therefore, expected that calcium antagonists would reduce calcium currents by reducing the number of calcium channel openings, thereby preventing thalamic and cortical oscillations, including SWD. There is also some evidence, albeit indirect, that calcium ions have a role in rhythmic bursting discharges in the Strasbourg Wistar rats, a similar model of generalized absence epilepsy (2). These authors showed that cadmium, which blocks the calcium-dependent potassium outward current, suppressed the repetitive burst discharges in vitro and the number of SWD in vivo. However, in a preliminary study it was found that acute administration of nimodipine in a higher dose than used in the present experiment in aged Wistar rats facilitates the number of SWD (38).

Therefore, it is likely that dose of nimodipine might have been too small to exert an effect on the number and mean duration of SWD. The lack of effect on SWD might also be due to the way in which nimodipine was administered; namely, in the diet. It is difficult to compare the dose received in the present experiments with the acute ED_{50} of 46 mg/kg in the mouse PTZ model (14). Probably, plasma and brain concentrations of nimodipine were too small to exert an effect on absences. However, the dietary dose of nimodipine was high enough to induce behavioral changes (28) and to facilitate the effects of PTZ in our old rats. The direction of the effects was, again, surprising. The literature on epilepsy and calcium strongly suggests that calcium antagonists, including nimodipine, would decrease the severity and number of seizures (14,15,18,23–25,29,30,43), although a few studies have reported a lack of effect of verapamil (8,22).

There is no simple explanation for the discrepancy between our results on the effect of nimodipine on PTZ-induced epilepsy and the anticonvulsant effects described in the literature, but there are at least two probable explanations. Firstly, the rats were quite old, between 84 and 94 weeks, and they have about 300 SWD per day. It cannot be excluded that the mode of action of calcium antagonists is different in these spontaneous epileptic and old rats and in commonly used juvenile or adult rats. A first indication for an age-dependent action of nimodipine originates from Thompson et al. (32). They found that nimodipine enhanced the spontaneous firing rates of pyramidal neurons in aging rabbits to a greater degree than in young animals. A second indication originates from Schuurman and Traber (28). They found that calcium antagonists improved memory-related functions only in aged rats and not in young animals. This apparent age-specific action of calcium antagonists might be due to age-dependent increase in the level of intracellular calcium concentration (11). Aged rats show a prolongation of the afterhyperpolarizations induced by spike

bursts (20). Membrane hyperpolarization is necessary for thalamic oscillations (31), and this prolongation of the afterdischarges might be related to the age-dependent increase in the number of SWD found in all strains of rats studied so far (3,5,40,42). The presence of SWD during many months may set in motion biochemical changes such as alterations in the number and affinity of receptors, in membrane properties, in biosyntheses, and levels of peptides (21), and these alterations might change the action of the calcium antagonist.

A second discrepancy between the present work and the vast majority of the studies reported in the literature is that the rats were chronically exposed to nimodipine. Our results indicate that the duration of the treatment is critical, as the group treated with the 21 weeks nimodipine diet tended to show more epileptiformic activity after PTZ than the group treated for 14 weeks. In the control study, nimodipine was given acutely and no effects were found on PTZ induced convulsions. This shows that acute administration of nimodipine does not protect these particular animals against PTZ-induced seizures. Moreover, it seems imperative to treat these aged rats chronically to observe a facilitating effect of nimodipine on PTZ-induced convulsions. It is hypothesized that repeated administration may lead to changes in neurotransmitters or neuromodulators, and the result might be that PTZ acts in an opposite way. Some evidence for changes in receptors were already reported following chronic administration: downregulation of [^{3}H] dihydropyridine binding sites in mice has been found following treatment with nifedipine for 28 days (26).

In summary, chronic dietary nimodipine treatment does not influence the number and duration of SWD in a model of absence epilepsy. However, PTZ-induced epilepsy was facilitated in these old Wistar rats. Chronicity of the dietary treatment in these aged and spontaneous epileptic rats is thought to be responsible for the discrepancy between the present results and those reported in the literature.

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