Interactions between calcium antagonists and the sympathetic nervous system in various pharmacological models
van der Lee, R.

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GENERAL DISCUSSION AND CONCLUSIONS

In the present thesis several of the newer CA were tested with respect to their indirect and direct interactions with the sympathetic nervous system. The parameters investigated were the time course of action (onset and duration of action), vascular selectivity and calcium channel selectivity (L-, T- and N-type calcium channels, respectively).

The onset of the vasodilator action of CA was investigated in isolated rat and human small arteries as well as in healthy human subjects. In rat isolated small mesenteric arteries amlopidine and lacididine displayed the slowest onset of action of the nine CA investigated. In general, a trend could be observed that with increasing lipophilicity (expressed as logP-values) the onset of action proved to be slower. A dissonant in this context was amlodipine, which has a logP-value comparable with nifedipine, but showed a very slow onset of action. An explanation for this phenomenon might be the protonized tertiary side-chain at a pH of 7.4, resulting in an electrostatically interaction with the negatively charged phospholipid head groups of the cell membrane molecule. This characteristic might slow the diffusion of amlopidine through the membrane in addition to keeping it at the effector site. The persistance of the effects was studied by means of the recovery of the potassium-induced contractile response in these vessels after removing the drugs from the medium, but there was no apparent relationship between the physicochemical profile of the CA investigated and the results obtained in these experiments.

In a study on the vasodilator effect of nifedipine, felodipine and (S)-lercanidipine on potassium-induced contractions in human isolated arteries a clear correlation between increasing lipophilicity and slow onset of action became apparent. It might be noteworthy to mention that these three CA after oral ingestion by hypertensive patients reach peak plasma concentrations within a comparable timespan (i.e. 1-2 hours). Taken together with the results from the study in rat mesenteric arteries, we concluded that the onset of vasodilator action of CA is likely to take place at the site of action via physicochemical interactions between the CA and the plasma membrane.

Contrary to our expectations, there was no difference in onset of vasodilator action between nifedipine and felodipine on basal vascular tone in male healthy human volunteers. Apparently, the 100-fold difference in lipophilicity between these CA was not sufficient to bring about a difference in onset of action in the in vivo situation. Differences in contractile conditions compared to the in vitro studies, presence of a whole functional system with continuous regulation by endocrine, nerve and blood
factors, effects of heart rate, blood pressure and pharmacokinetic and pharmacodynamic interactions with the infused CA may all play a role in the explanation of this finding and warrants further investigation.

It becomes more and more clear that CA are not the exclusively L-type calcium channel blocking agents they were assumed to be. Mibefradil is such an example of a CA with capabilities to block more subtypes of calcium channels than just the L-channels. In a study using rat small isolated arteries from both normotensive and hypertensive rats, it appeared that mibefradil inhibited both the phasic and tonic responses of potassium-induced contractions in the same way as nifedipine, verapamil and diltiazem. We therefore concluded that T-type calcium channels do not play a role in potassium-induced contractions, at least in the type of vessels we have investigated. The vasodilator effect of mibefradil can be explained completely by L-type calcium channel blockade.

Two studies were dedicated to the blockade by mibefradil of N-type calcium channels, a calcium channel involved in the release of neurotransmitters from the sympathetic nerve endings. In the first study, mibefradil was able to block the electrical field stimulation-induced contractions in the rat tail artery. The blockade was complete at the highest dose of mibefradil, in the lower frequency range of electrical field stimulation.

In the pithed rat, where all central regulatory reflexes are absent, mibefradil was able to attenuate the rise in heart rate resulting from sympathetic stimulation only in the lower dose. At the higher dose of mibefradil and verapamil the two CA were equal in their capacity to attenuate the stimulation-induced heart rate. The blockade of L-type calcium channels is likely to be responsible for the latter phenomenon. These two studies show that a CA can display a sympathoinhibitory effect along with a vasodilator effect if both L- and N-type calcium channels are blocked.

In conclusion, CA exert at least two different effects on the sympathetic nervous system: 1. An indirect reflexory stimulating effect, which can be prevented by making the CA very lipophbic or providing the CA in a slow-release formulation and 2. Direct blockade of the N-type calcium channel, involved in the release of neurotransmitter at the sympathetic nerve endings.