Nifedipine-insensitive vasoconstriction of pressurised rat basilar arteries

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Cerebrovascular constriction depends on influx of calcium through voltage dependent calcium channels (VDCCs). Although L-type channels are often attributed to this process, we have previously identified a role for nifedipine-insensitive VDCCs in regulating cerebrovascular tone in juvenile rats (Navarro-Gonzalez *et al.*, 2009). Here we have extended these studies to adult rat basilar arteries, in which the effect of VDCC blockers was tested against vasoconstriction induced by intraluminal pressure, receptor activation (thromboxane mimetic, U46619; 0.11μM) and depolarisation (10-120mM $[K^+]_o$). The selective L-type channel blocker, nifedipine (0.1, 1μM), substantially inhibited pressure-induced constriction, whereas the putative T-type channel blocker, mibefradil, inhibited myogenic tone at low concentration (1μM) but produced paradoxical constriction at high concentration (10μM). A mibefradil analogue, NNC-550396 (3, 10μM), inhibited constriction at both concentrations. However, effects of either mibefradil or NNC-550396 showed considerable overlap with nifedipine, indicating dual L and T actions of both inhibitors. Consequently, experiments were performed with sequential application of nifedipine (1μM) followed by mibefradil (1μM). Under these conditions, mibefradil caused additional relaxation over that produced by nifedipine ($n=5$, $P<0.001$), suggesting a component of tone that is resistant to L-type VDCC inhibition but sensitive to T-type channel inhibition. While U46619-induced constrictions were insensitive to nifedipine or mibefradil, constrictions to high $[K^+]_o$, that were not reliant on intracellular calcium (blocked by 10μM U73122), were reduced by nifedipine, leaving a small but significant residual component. We conclude that rat cerebral arteries employ both L- and T-type calcium channels to regulate vascular tone, however the non-specific actions of putative T-type channel blockers necessitate caution in their use when arguing for a role in vascular function.

Navarro-Gonzalez, MF *et al.* (2009) *Clin. Exp. Physiol. Pharmacol.* **36**: 55-66.