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The cellular mechanism of action of nimodipine (BAY e 9736), a new calcium antagonist

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Nimodipine (BAY e 9736, isopropyl (2-methoxyethyl) 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate) is a new agent which prevents the sequelae of, and reduces the mortality after cerebral ischaemia in several animal models (Kazda & Hoffmeister, 1979; Hoffmeister, Kazda, & Krause, 1979). These actions appear to be due to a predilective vasodilatation of the cerebral vasculature (Kazda, Hoffmeister, Garthoff & Towart, 1979). We have investigated the effects of nimodipine on peripheral and cerebral vascular smooth muscle.

Contractions of the isolated rabbit aortic strip (Furchgott & Bhadrakom, 1953) were induced with cumulative doses of KCl (20–50 mM) or of noradrenaline (1.7×10^{-8} M–1.7×10^{-5} M), either alone, or in the presence of increasing doses of nimodipine or phentolamine. Phentolamine competitively inhibited the noradrenaline-induced contractions, but had no effect (up to a dose of 2.6×10^{-6} M) on KCl-induced contractions, showing that neuronally released noradrenaline did not contribute to the contractions induced by KCl. Nimodipine in contrast inhibited only the contractions induced by KCl ($ID_{50} = 5 \times 10^{-9}$ M), and had (up to a dose of 10^{-5} M) no effect on the contractions induced by noradrenaline. As there is good evidence that KCl-induced depolarization increases the transmembrane influx of Ca^{2+} into the rabbit aorta, but that noradrenaline produces contractions by release of internally stored Ca^{2+} (Peiper, Griebel, & Wende, 1971; Massingham, 1973), these results suggest that nimodipine acts by blocking KCl-induced Ca^{2+} influx, and can therefore be classed as a 'calcium antagonist' (Fleckenstein, Tritthart, Fleckenstein, Herbst, & Grün, 1969).

Ring segments of rabbit basilar artery were depolarized by incubation with Ca^{2+}-free Tyrode solution containing K^+ (40 mM). Addition of Ca^{2+} (2–5 mM) produced reproducible contractions. Preincubation of the tissue in nimodipine dose-dependently inhibited these contractions ($ID_{50} = 8 \times 10^{-9}$ M).

We conclude that nimodipine is a potent inhibitor of Ca^{2+} influx into isolated peripheral and cerebral vascular smooth muscle. Allen & Banghart (1979) have shown that pathological spasm of the cerebral vasculature is more dependent on extracellular Ca^{2+} than is the tone of peripheral vessels.

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Electrophysiological effects of bunaphtine on guinea pig myocardium

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Bunaphtine (N-(2-Diethylaminoethyl)-N-(n-butyl)-α-naphthamide has been found effective in the treatment of both ventricular and supraventricular arrhythmias, either chronic or paroxysmal (Vegis, 1975). On the basis of its cardiac electrophysiological effects on guinea-pig and rabbit heart bunaphtine (BNA) has been considered as a membrane stabilizer (Ferroni & Monticelli, 1973). However, recent experiments on human atria using bipolar suction electrodes considered the BNA as a class 3 antiarrhythmic drug (Fenici, Marchei, Bellocci & Zecchi, 1977) according to the classification of Vaughan Williams (1970). The present study has been devoted to determining which of these actions is exhibited by bunaphtine.

Right ventricular guinea-pig papillary muscles were perfused with warmed (34°C) and oxygenated Tyrode solution and stimulated at a basal rate of 1 Hz. Intracellular action potential were recorded with glass microelectrodes filled with KCl solution (3 M). Preparations were observed both under control conditions and during exposure to BNA in concentrations from 1×10^{-7} M to 1×10^{-4} M (0.36–36.5 mg/l). Spontaneous activity was induced by adding $BaCl_2$ (0.2 mM) to the normal Tyrode solution. Ca-action potentials were elicited by adding isoprenaline (0.2 mg/l) to high K (27 mM) Tyrode solution.

At concentrations between 1×10^{-7} M and 5×10^{-6} M BNA exerted no significant effect on resting membrane potential or overshoot and thus no change in total amplitude of the action potential occurred. At higher concentrations BNA produced a dose-dependent decrease on the amplitude, overshoot and maximum upstroke velocity of the action potential but no change was observed in resting membrane potential. Reduction of maximum upstroke velocity was more pronounced at lower membrane potentials and the inactivation curves were shifted to more negative membrane potentials. At all concentrations used in this study BNA prolonged the total action potential duration. This effect was due predominantly to a decreased slope of phase 3 and was accompanied by an increase in the effective refractory period of the ventricle. BNA (1×10^{-5} M—5×10^{-5} M) reduced the maximum following frequency and almost suppressed the pacemaker activity elicited by Ba ions in ventricular fibers, while it had no effect on the Ca-mediated action potentials. It is concluded that BNA is an antiarrhythmic drug of the first class and within this group is more closely related to quinidine than to lidocaine.

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