ANTAGONISM OF THE POSITIVE INOTROPIC EFFECT OF DPI 201-106 BY ITS METHYL-INDOLE DERIVATIVE (BDF 8784)

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DPI 201-106 (4-3(4-diphenyl-methyl-1-piperazinyl)-2-hydroxypropyl-1H-indole-2-carbonitrile; DPI) is a novel cardiotonic agent which activates cardiac Na^+-channels (Scholtysik et al., 1985). Kohlhardt et al. have demonstrated that DPI modulates cardiac Na^+-channels in a voltage-dependent manner.
In the course of studying chemical derivatives of DPI we synthetized the methyl-indole analogue which carries a methylgroup in place of the cyano in the indole moiety of DPI, which for purposes of clearity has been named BDF 8784.

In the isolated, electrically driven (1 Hz) right ventricular papillary muscle of the guinea pig, BDF 8784 itself was inactive at 0.1 - 3 µmol/l, but caused a slight negative inotropic effect at 10 µmol/l. Preincubation of untreated organs with BDF 8784 resulted in a rightward shift of the concentration-effect curves of DPI in a parallel fashion.
In electrophysiological studies BDF 8784 antagonized the positive inotropic actions of DPI and also inhibited the DPI-induced prolongation of action potential (AP) duration. BDF 8784 itself at 10 µmol/l slightly reduced the force of contraction and shortened the action potential duration in control preparations.

For further differentiation of the interaction between DPI and BDF 8784 we studied the influence of chlorpromazine and pindolol on the cardiotropic actions of DPI. Chlorpromazin, which is known to accumulate in the lipid moiety of cell membranes, antagonized the DPI-induced changes in electrical and mechanical activity. In contrast, pindolol that has some structural resemblance to DPI, reduced the inotropic effect of DPI without influencing the AP-prolongation.
Our results suggest that BDF 8784 and DPI may not only interact at a common binding site on Na^+-channels, but that these compounds could also interfere unselectively with membrane function. The antagonism of DPI by such a closely related derivative like BDF 8784 is similar to that found for effectors of the voltage-dependent Ca^{++}-channel in the 1,4-dihydropyridine family.

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Scholtysik, G. et al. (1985) Naunyn Schmied.Arch.Pharmacol. 329, 316-325