THE EFFECT OF A BENZOTRIAZINIUM SALT ON EXTRANEURONAL UPTAKE, (U_2), OF CATECHOLAMINES IN GUINEA-PIG LEFT ATRIA

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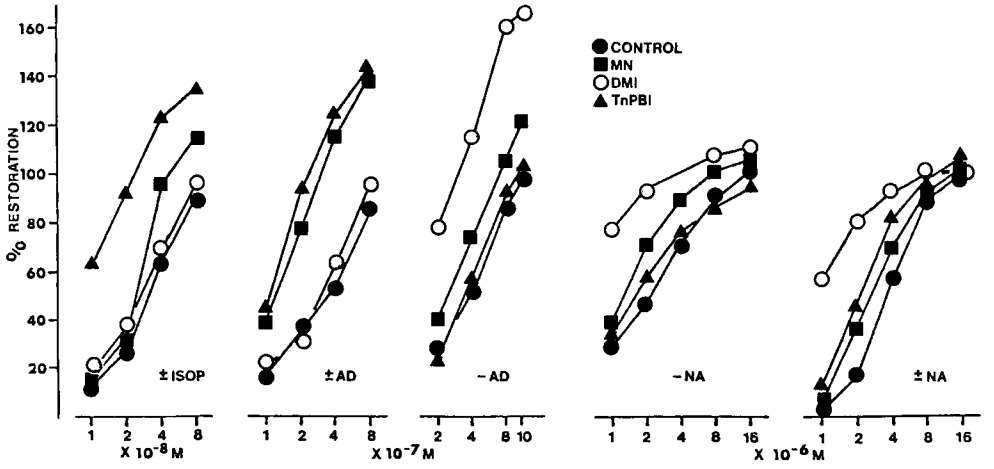
2-n-propyl-4-p-tolylamino-1,2,3-benzotriazinium iodide (TnPBI) possesses antiarrhythmic activity in a number of different models of experimental arrhythmia, (French & Scott, 1978a,b; Scott & French, 1980). It also potentiates the vasopressor responses of the pithed rat to noradrenaline (NA) and tyramine (Abdullah et al, 1980). TnPBI fails to restore contractions in guinea pig depolarised left atria, unless the tissue has been pretreated with desipramine (DMI). Such restored contractions are inhibited by propranolol, suggesting the involvement of β-receptors and/or catecholamines. This study reports further investigations into the interactions between TnPBI and sympathomimetic amines.

Guinea pig left atria were driven at 0.5Hz (1ms, 10-15mA, punctate electrodes) in oxygenated Locke solution. Increasing the potassium concentration to 22mM rendered tissues inexcitable by the above stimulation parameters. Contractions were restored by the addition of (±)-isoprenaline (±)-ISOP, 1 - 10 x 10^{-8}M; (±)-adrenaline (±)-AD, 1 - 10 x 10^{-7}M; (-)-noradrenaline (-)-NA, 1 - 16 x 10^{-6}M; or (-)adrenaline (±)-AD, 2 - 10 x 10^{-7}M, either alone or in the presence of other agents.

Responses to (±)-ISOP were potentiated by TnPBI (1 x 10^{-5}M) to a greater extent than by dl-metanephrine (MN, 2 x 10^{-5}M). Since ISOP is a specific substrate for extraneuronal (U_2) uptake mechanisms, this result suggests that TnPBI inhibits the U_2 process. This is verified by the observation that the responses to (±)-AD, which is also a proven substrate for U_2, were also potentiated by TnPBI. However, the responses to (-)-AD and (-)-NA were not significantly potentiated by TnPBI, presumably since these isomers are preferentially removed by the neuronal (U_1) uptake processes, as suggested by the potentiating effects of DMI, especially at low concentrations. The actions of (±)-NA were slightly potentiated by TnPBI and by MN, suggesting that the racemic form may also be removed by the U_2 process to some extent.

These results suggest that TnPBI inhibits the extraneuronal uptake of catecholamines, and its potency is similar to that of dl-metanephrine.



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