## Interactions between adenosine and a benzotriazinium salt on guinea pig atria

A.M. FRENCH & N.C. SCOTT

*Pharmacology Section, Department of Pharmacy Heriot-Watt University, Edinburgh.*

A benzotriazine salt, 2-*n*-propyl-4-*p*-tolylamino 1,2,3-benzotriazinium iodide (TnPBI) has been shown to possess considerable antiarrhythmic activity in isolated tissues (French & Scott 1977, 1978a, 1979) and in the whole animal (French & Scott 1978b). The compound has class I and III actions on the action potentials recorded from atrial and ventricular tissues according to the classification of Vaughan Williams (1970). This paper describes some of the interactions between TnPBI and adenosine, a proposed inhibitor of the influx of calcium ions into cardiac tissue (de Gubareff & Sleator, 1965; Schrader, Rubio & Berne, 1975).

In electrically stimulated atrial preparations, adenosine in concentrations of $1–4 \times 10^{-4}$ M reduced the force of contraction to approximately 25% of control values. TnPBI ($1–2 \times 10^{-5}$ M), restored the contractile force to about 80% of the control values. Caffeine, a known promotor of calcium influx, produced a restoration of approximately 90% at concentrations between $3–6 \times 10^{-3}$ M.

This suggests that TnPBI causes an increase in the influx of calcium ions during the atrial action potential. Further evidence for this proposal is shown by the observations that adenosine is much less effective in reducing the force of contraction when applied in the presence of TnPBI. In a separate series of experiments adenosine reduced the force of contraction to about 34% of the control value when applied alone, but in the presence of TnPBI ($1 \times 10^{-5}$ M) the force of contraction was only reduced to 80% of the control value.

Catecholamines, such as noradrenaline are proposed to increase the force of beating of the heart by promoting calcium influx. This mechanism is suggested since noradrenaline has the ability to restore action potentials and contractility to atrial muscle fibres that have been depolarised and made inexcitable by elevation of the external potassium ion concentration. Under such conditions of depolarisation, the inward current is carried by calcium ions as the normal sodium inward currents are inactivated by the lowered membrane potential. Pappano, (1970) has shown that the action potentials can be attributed to calcium inward current as the membrane follows closely theoretical calcium electrode properties. Caffeine and elevated external calcium ion concentration can also restore contractility to depolarised atria by increasing calcium influx. It is interesting, therefore that TnPBI inhibits the restorative effects of caffeine and calcium ions but has no effect at all on the restorative effects of noradrenaline. This suggests that catecholamines cause increased calcium influx by a mechanism different from that induced by caffeine or increased external calcium ion concentration.

Also of interest is the observation that TnPBI increases the maximum rate of depolarisation (MRD) and the overshoot amplitude of the so called 'calcium action potentials' seen in atrial cells depolarised by elevated external potassium and treated with catecholamines. This action indicates increased calcium inward current as the MRD and overshoot amplitude are directly related to the inward flux of calcium.

### References

FRENCH, A.M. & SCOTT, N.C. (1977). A benzotriazinium salt as a potential antiarrhythmic agent. *Br. J. Pharmac.*, **61**, 131–132P.

FRENCH, A.M. & SCOTT, N.C. (1978a). The effects of a benzotriazinium salt on ventricular fibrillation in the guinea pig perfused isolated heart. *Br. J. Pharmac.*, **63**, 379P.

FRENCH, A.M. & SCOTT, N.C. (1978b). The antiarrhythmic effects of a benzotriazinium salt in mice and guinea pigs. *Br. J. Pharmac.*, **64**, 398P.

FRENCH, A.M. & SCOTT, N.C. (1979). Comparison of the effects of a benzotriazinium iodide and quinidine on guinea pig heart. *Br. J. Pharmac.*, (in press).

DE GUBAREFF, T. & SLEATOR, W. (1965). Effects of caffeine on mammalian atrial muscle and its interaction with adenosine and calcium. *J. Pharmac. exp. Ther.*, **148**, 202–214.

PAPPANO, A.J. (1970). Calcium dependent action potentials produced by catecholamines in guinea pig atrial muscle fibres depolarised by potassium, *Circ. Res.*, **27**, 379–389.

SCHRADER, J. RUBIO, R. & BERNE, R.M. (1975). Inhibition of slow action potentials of guinea pig atrial muscle by adenosine: a possible effect on $Ca^{2+}$ influx. *J. Mol. Cell. Cardiol.* **7**, 427–433.

VAUGHAN WILLIAMS, E.M. (1970). The classification of antiarrhythmic drugs. In *Symposium on cardiac arrhythmias*. ed Sandoø, E., Flenstedt-Jansen, E. & Olsen, K.H., A.B. Astra, Sodertalje, Sweden.