Cardiac effects of strychnine and their mechanism

Several reports indicate that strychnine affects various neural functions, including not only the post-synaptic inhibitory system but also neuromuscular and ganglionic transmission, as well as the cholinergic and adrenergic post-ganglionic conduction (Alving, 1961; Chieppa & Siro Brigiani, 1965; Chieppa, 1966; Lanari & Luco, 1939).

In view of these pharmacological properties, it seems conceivable that the cardiac effects of strychnine might be related to an interference with the regulation of the autonomic intrinsic system of the heart. However, although myocardial activities of strychnine were described many years ago (Burridge, 1928; Kakovsky, 1905; Mezey & Staub, 1936), present knowledge on their mechanisms appears unsatisfactory; an attempt to correlate the cardiac to the neural actions of the drug appears to be the only recent report (Paoletti, 1966).

In this paper are reported experiments *in vivo* and *in vitro* on the effects of strychnine on heart rate, made to evaluate the degree of activity of the drug and to elucidate the basic mechanisms involved in its actions.

The *in vitro* experiments were made on frog isolated heart and guinea-pig isolated atria. The effects *in vivo* were examined according to James & Nadau (1963), on the open-chest dog under pentobarbitone narcosis (30 mg/kg, i.v.), by injecting the drug into the artery supplying the sino-auricular node. Myocardial isometric contractile force was recorded by means of a calibrated strain gauge arch, according to Boniface, Brodie & Walton (1953).

The results of the experiments on frog heart indicate that strychnine exerts a clear, dose-related negative chronotropic activity; the decrease of heart rate ranges from 20 to 60%, depending on the drug concentration (5–10–20 μg/ml). Heart contractility was slightly enhanced by the lowest concentrations and transiently depressed by the highest one. The negative chronotropic effects of strychnine proved to be unaffected by atropine (2×10^{-6} w/v), prostaglandin E_1 (10^{-8}–10^{-7}), $CaCl_2$ (4×10^{-4}), GABA (10^{-4}) and glycine (10^{-4}). Only adrenaline exerted (at high concentration, 10^{-6}) a weak, transient antagonism, without restoring the normal heart rate. The degree of activity of strychnine was much greater on guinea-pig atria, where the chronotropic effect was clearly detectable at concentrations as low as 10^{-8}–10^{-7}: this last concentration currently induced in 20–30 min a 40–50% decrease of the frequency, without significantly affecting the amplitude of the contraction. As observed on the frog heart, this effect was not prevented by atropine-(2×10^{-6}). Furthermore, unlike quinidine, the action of strychnine remained unaffected by a reduction of potassium concentration in the bathing medium to 25% of normal value. At high concentration (5×10^{-6}), strychnine proved to prevent the chronotropic effect of adrenaline (10^{-7}), but not the inotropic one. Both on guinea-pig atria and on frog heart, eserine failed to enhance the negative chronotropic activity of strychnine. The experiments on the open-chest dog demonstrated that strychnine retained its activity *in vivo* also. After intracoronary injection (5–50–100 μg), the drug elicited a sinusal bradycardia, without any impairment of conduction or contraction. The degree of activity appeared high, since the lowest dose employed induced an evident decrease of the rate, reaching the maximum value (−20·5%, mean of 4 experiments) 30–60 s after the injection and lasting 2–3 min.

The results of present investigations indicate that strychnine exerts a remarkable negative chronotropic activity, not only on isolated heart preparations but also *in vivo*. The mechanism of action appears independent of a cholinergic or a quinidine-like activity and deserves further research.

Institute of Pharmacology,
University of Padua, Italy.

February 28, 1970

C. BORTIGNON
F. CARPENEDO
I. MARAGNO
E. SANTI SONCIN
G. D. STELLA
M. FERRARI

REFERENCES

ALVING, B. O. (1961). *Archs int. Pharmacodyn. Thér.*, **131**, 123–150.
BONIFACE, K. J., BRODIE, O. J. & WALTON, R. P. (1953). *Proc. Soc. exp. Biol. Med.*, **84**, 263–266.
BURRIDGE, W. (1928). *Archs int. Pharmacodyn. Thér.*, **34**, 105–112.
CHIEPPA, D. & SIRO-BRIGIANI, G. (1965). *Arch. Sci. Biol.*, **49**, 217–222.
CHIEPPA, D. (1966). *Ibid.*, **50**, 55–62.
JAMES, T. N. & NADEAU, R. A. (1963). *Am. J. Physiol.*, **204**, 9–15.
KAKOVSKY (1905). *Archs int. Pharmacodyn. Thér.*, **15**, 21–139.
LANARI, A. & LUCO, J. V. (1939). *Am. J. Physiol.*, **126**, 277–282.
MEZEY, K. & STAUB, H. (1936). *Arch. exp. Path. Pharmak.*, **182**, 183–204.
PAOLETTI, G. (1966). *Boll. Soc. it. Biol. Sper.*, **42**, 1722–1725.

The action of desipramine on noradrenaline depletion by reserpine in the vas deferens of the rat *in vivo*

The interaction between reserpine and desipramine at the level of adrenergic neurons (both in the central and in the peripheral nervous system) has been investigated by many authors. Although desipramine does not block the reserpine-induced depletion of endogenous noradrenaline in brain or heart (Brodie, Bickel & Sulser, 1961; Garattini, Giachetti & others, 1962; Pletscher & Gay, 1962; Sulser, Watts & Brodie, 1962; Stone, Porter & others, 1964), it does significantly reduce the rate at which reserpine releases noradrenaline from these tissues (Manara, Sestini & others, 1966; Manara, Algeri & Sestini, 1967; Sulser, Owens & others, 1969). Desipramine was also shown to inhibit the release of tritiated noradrenaline by small doses of reserpine from prelabelled mice hearts (Titus, Matussek & others, 1966).

In the present study, another peripheral organ, the vas deferens, was used because of its rich adrenergic innervation and its high noradrenaline content (Sjöstrand, 1965). Sprague Dawley rats, 200 g, were given desipramine 15 mg/kg, i.p. 1 h before reserpine and the animals were killed at selected times after reserpine. Noradrenaline measurements were made in the heart and in the vas deferens (Shore & Olin, 1958).

Four vasa deferentia were pooled for each sample. The releasing action of reserpine is not very much affected by the pretreatment with desipramine (Table 1). However, at some times and doses, desipramine pretreated animals show a lower concentration of noradrenaline in the vas deferens compared with controls given only reserpine. Fig. 1 shows noradrenaline levels determined simultaneously in the heart and in the vas deferens of the same animals. It is evident that while in the heart, as previously reported (Manara & others, 1966), desipramine counteracts the noradrenaline releasing action of reserpine, in the vas deferens desipramine rather facilitates the depletion of noradrenaline.