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Effects of ouabain on arterial pressure and its modification by tetrodotoxin

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It has been suggested that cardiac glycosides injected intravenously can increase, decrease or have no significant action on the arterial blood pressure (see e.g. Gillis, Quest & Standaert, 1969). These variations in response were not seen when the glycosides were placed in the ventricles of the brain when a consistent sustained pressor response is elicited (Bircher, Kanai & Wang, 1963; Stickney & Lucchesi, 1969). A transient pressor response can also be consistently evoked with intravenous ouabain in cats having the carotid sinus and vagus nerves sectioned or in decapitated pithed cats (Gillis & others, 1969). Whilst examining the central effects of oubain (Peres-Gomes & Ribeiro, unpublished observations) we observed that tetrodotoxin given intraventricularly antagonized the arrhythmia producing doses of ouabain given by continuous intravenous perfusion and also prevented the drug's pressor response. Therefore we have examined this antagonistic effect on arterial pressure.

Adult male cats, 2 to 4 kg were anaesthetized with chloralose, 80 mg kg^{-1}, intravenously. The femoral vein, trachea and femoral artery were exposed for the administration of drugs, artificial respiration and arterial pressure recording respectively. Electrocardiograms (Lead II) and the heart rate (by cardiotachometer connected to the electrocardiogram) were recorded. The technique of Feldberg & Sherwood (1953) was used for intracerebroventricular injections (i.c.v.), the volumes of which never exceeded 0·2 ml. The initial arterial pressure ranged from 150 to 170 mm Hg and the heart rate from 170 to 210 beats min^{-1}. The significance of differences between means was determined by Student's *t*-test.

Fig. 1 illustrates the effect and summarizes the results from 15 experiments, obtained with ouabain (20 μg, i.c.v.) on the blood pressure and heart rate of control and tetrodotoxin-pretreated cats. As can be seen, ouabain raised blood pressure by over 50 mm Hg in the control cats. The effect was abolished by 0·5 μg tetrodotoxin also given intracerebroventricularly. A much higher intravenous dose (4–6 μg kg^{-1}) had little effect on the i.c.v. response to ouabain. By both routes tetrodotoxin reduced the blood pressure (92·5 ± 20·4 mm Hg for the i.c.v. and 92·0 ± 22·4 mm Hg for the i.v.) but the i.c.v. dose was accompanied by a consistent decrease in heart rate (37·0 ± 6·6 beats min^{-1}) which was preceded by a rise on the blood pressure (32·5 ± 3·8 mm Hg) and a small increase on the heart rate sometimes with arrhythmias which reversed spontaneously in 10 min. Ouabain (15–40 μg kg^{-1}, (i.v.)

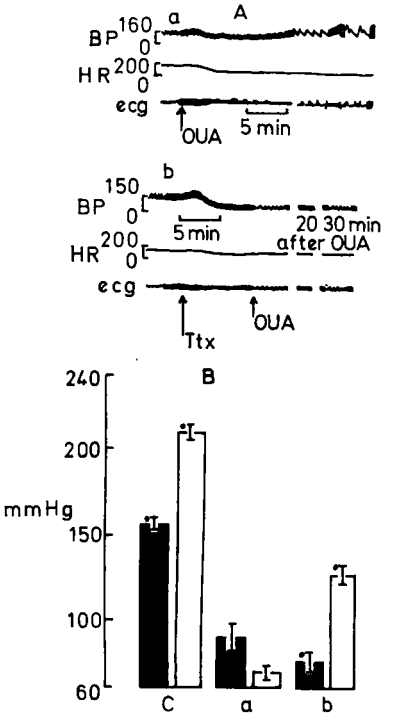

FIG. 1A. Blood pressure responses to ouabain (20 μg, i.c.v.) in a control (a) and in a tetrodotoxin (0·5 μg, i.c.v.) pretreated cat (b). BP (mmHg). HR (beats min^{-1}). OUA Ouabain. Ttx-tetrodotoxin.

B. Mean pressor responses elicited by two intraventricular injections of ouabain, 20 μg each, at an interval of 20 min. The central bars represent the standard error of the mean. (a) Ttx i.c.v.—group pretreated by intraventricular route with 0·5 μg tetrodotoxin. (b)-Ttx i.v.—group pretreated intravenously with 4–6 μg kg^{-1} tetrodotoxin. ■ Before ouabain, □ Ouabain response, n = 5. $P < 0.01$. C—control. y axis—arterial pressure (mm Hg).

did not consistently change the blood pressure in normal cats. This is in agreement with many results (see e.g. Goodman & Gilman, 1970). However a rapid and transient, but consistent, pressor response, 25·0 ± 6·5 mm Hg corresponding to a mean 33% increase, could be elicited by a single injection of 15 to 40 μg kg^{-1} (i.v.) ouabain in cats previously treated with 0·5 μg tetrodotoxin given i.c.v. (Fig. 2). The effect appeared in the first 2 min after the injection and, unlike the response evoked by ouabain i.c.v., it was transient and always reproducible until ventricular fibrillation occurred. The effect is of peripheral origin and did not result from sympathetic activation. No modification was seen in the ouabain pressor response after treatment with dibenamine (10 mg kg^{-1}, i.v.) (Fig. 2).

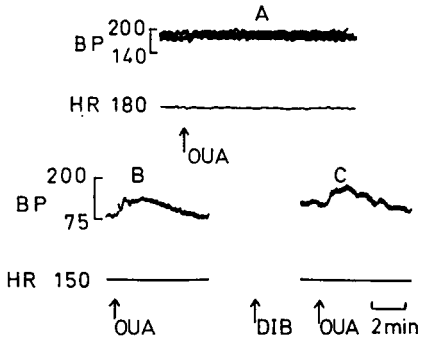

FIG. 2. Blood pressure (BP mm Hg) and heart rate responses (HR beats min^{-1}) to 15 μg kg^{-1} ouabain i.v. in a cat before (A) and after (B and C) pretreatment with 0·5 μg tetrodotoxin i.c.v. Between B and C dibenamine was injected 10 mg kg^{-1} i.v. 30 min separate the responses A and B and 40 min separate B and C.

The points of interest in these results are the prevention by tetrodotoxin of the pressor response to i.c.v. ouabain since intravenous or i.c.v. pretreatment with anticonvulsants (Bircher & others, 1963), hexamethonium (Bircher, Chai & Wang, 1965), reserpine or (±)-propranolol (Stickney & Lucchesi, 1969) did not abolish that effect. Tetrodotoxin blocks the excitation and conduction of nerves (Kao, 1966). On the assumption that the vasomotor centres and the central points of sympathetic and parasympathetic activation were blocked by the toxin, this well known effect explains, at least in part, the marked and sustained fall on blood pressure resulting when the toxin is given i.c.v. in a dose 27 to 30 times smaller than when given intravenously. The blockade inhibited the action of ouabain given i.c.v., which is in agreement with the suggestions of Gillis, Raines & others (1972) has a non-selective excitatory action on those brain centres. The other point is that tetrodotoxin, i.c.v., unmasked the peripheral component of the ouabain pressor response resulting from a direct action of ouabain on vascular smooth muscle as was suggested by Mason & Braunwald (1964) since dibenamine did not change that effect. On the other hand, this increase in arterial pressure was similar to the blood pressure response observed by Gillis & others (1969) in decapitated cats, an effect also not modified by dibenamine. The control blood pressure of decapitated and pretreated cats used in the present experiments was of the same magnitude. Thus it is possible that tetrodotoxin injected into the lateral ventricles of the brain produced a decapitated effect or one resembling the effect on animals with carotid sinus and vagus nerves sectioned and given phentolamine or phenoxybenzamine, which means that tetrodotoxin can produce a pharmacological decapitation.

In conclusion, tetrodotoxin given i.c.v. not only blocked the central but also unmasked the peripheral components of the pressor actions of ouabain. Furthermore this approach could be a way of distinguishing between these components instead of more complicated surgical preparation (cf Gillis & others, 1969).

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