distance a few millimetres from the denervated zone. This growth can apparently be initiated by several seemingly nonspecific mechanical disturbances of these nerves. Axonal growth from the fimbria may provide an opportunity to study the factors that effect initiation, stimulation and guidance of growing nerve fibres in the mature mammalian brain.

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Positive inotropism of vanadate in cat papillary muscle

MANY samples hf 'Sigma grade' ATP from Sigma Chemical Co. reportedly contained an impurity which induces anomalous kinetics of (Na, K)-ATPase activity[1–3]. This impurity has recently been identified as vanadate[4], and shown to inhibit (Na, K)–ATPase from kidney[4] and red blood cells[5]. These findings have received considerable interest because of a possible physiological role of vanadate as an endogenous regulator of (Na, K)–ATPase activity[3–5]. We now report that vanadate is capable of producing positive inotropic effects in electrically driven papillary muscles isolated from cats.

Cats (0.5–1.6 kg) were anaesthetised with sodium pentobarbital (30 mg per kg i.p.) and papillary muscles (mean cross-sectional area 0.62 ± 0.05 mm^2, $n = 17$) were dissected from the right ventricles. The preparations were attached to a platinum stimulating electrode and mounted individually in glass tissue chambers for recording isometric contractions as described previously[6]. The bathing solution (5 ml) containing (mM) NaCl 136.9, KCl 5.4, $CaCl_2$ 1.8, $MgCl_2$ 1.05, NaH_2PO_4 0.42, $NaHCO_3$ 11.9, glucose 5.5 was equilibrated with 95% O_2 + 5% CO_2 and maintained at 35 °C. The preparations were driven electrically at a frequency of 0.2 Hz (duration 5 ms, intensity about 10% above threshold). Drugs used were ammonium vanadate anhydrous (NH_4VO_3), sodium vanadate anhydrous ($NaVO_3$; both from Merck, Darmstadt) and (±)propranolol HCl (ICI). The compounds were freshly dissolved in bathing medium and injected into the tissue chamber in volumes of 300 μl or less. NH_4VO_3 and $NaVO_3$ did not contain any measurable calcium and did not change the *p*H (7.4) of the bathing solution.

The effects of NH_4VO_3 on force of contraction are illustrated by the representative experiment shown in Fig. 1. NH_4VO_3 (20–500 μM) was added cumulatively, and the time of exposure

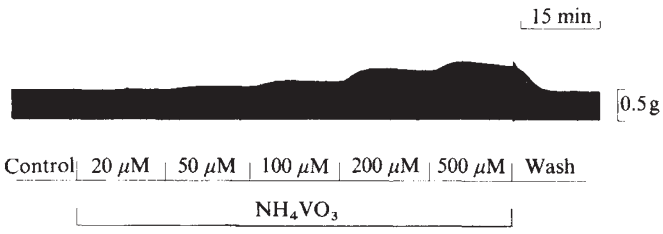

Fig. 1 Effect of NH_4VO_3 on isometric force of contraction of a cat isolated papillary muscle driven electrically at a frequency of 0.2 Hz. NH_4VO_3 was applied cumulatively at concentrations of 20–500 μN as indicated. The time of exposure to each concentration of NH_4VO_3 aas about 15 min. After exposure to 500 μM NH_4VO_3, the preparation was washed three times with drug-free bathing solution. Temperature 35 °C. Extracellular Ca^{2+} concentration 1.8 mM. Preparation diameter 0.7 mm. Experiment 13 06 784. Similar results were obtained in each of nine other preparations.

to each concentration was about 15 min. NH_4VO_3 produced a chncentration-dependent increase in force of contraction. The effect became clearly visible at 50 μM and was maximal at 500 μM. These concentrations correspond to those of Na_3VO_4 required to inhibit rubidium uptake in intact red cells by 50 to 80%[5]. The typical time course of action is also well shown. An increase in force of contraction was detectable after about 1 min, and a peak effect was attained after 6–8 min. The effect of NH_4VO_3 was readily reversible within less than 15 min on washing with drug-free bathing solution. Higher concentrations of NH_4VO_3 (1 mM) produced arrhythmias as a sign of toxicity.

The mechanism of the positive inotropic effect of NH_4VO_3 remains to be elucidated. Similar results as with NH_4VO_3 were odained with $NaVO_3$ and, moreover, the effect of NH_4VO_3 was also observed in the presence of 1 μM of the β-adrenoceptor blocking agent propranolol (data not shown). This indicates that the positive inotropic action of NH_4VO_3 was neither due to an effect of the NH_4^+ ion nor to a stimulation of β-adrenoceptors. Experiments are in progress to determine whether the positive inotropic effect of vanadate is accompanied by an inhibition of myocardial (Na, K)–ATPase, and, if so, whether both effects occur at similar concentrations of vanadate.

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