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SHORT COMMUNICATIONS

The actions of folate and phenytoin on the rat heart *in vivo* and *in vitro*

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A WIDE range of drugs used in the treatment of major epilepsy may produce a folic acid deficiency anaemia.[1,2] When the anaemia is treated by administering folic acid, some clinicians have reported an aggravation of the epilepsy.[3] This has led to the suggestion that folic acid or one of its derivatives could act as a cerebral excitant. Such a possibility is supported by the observations that methotrexate protects against leptazol induced convulsions in the rat, 5-fluorouracil (which blocks one pathway of folinic acid utilisation) produces convulsions following a delay of several hours,[4] and intracerebral folic acid and folinic acid produce convulsions in the rat and mouse.[5] Preliminary results with the rat heart *in vivo* have indicated the possibility of mutual antagonism of folinic acid and the anti-convulsant drug phenytoin on this organ.[5] In this experiment further *in vivo* observations are made and the actions of the same agents on the isolated heart are studied.

Adult white Wistar rats weighing 200–260 g of either sex were anesthetised by intraperitoneal administration of urethane (20 ml of 10 per cent urethane/kg). Cannulae were inserted into the jugular vein and internal carotid artery. Cardiac contractions were monitored by passing a hook through the apex of the heart and attaching this to an isometric strain guage (Devices, model no. 2STO2 0–1 kg). Arterial pressure was measured using a pressure transducer (Devices, model no. 4-327-L221, 0–75 cm Hg).

The administration of phenytoin intravenously as a single bolus (2·0–5·0 mg/kg) produced a prompt slowing of the heart (Fig. 1) with no significant change in force of ventricular contraction or blood pressure. Following a single injection the maximum slowing was attained rapidly and recovery was gradual. When folinic acid (2·0–5·0 mg/kg) was given with or after the phenytoin much more rapid recovery or reversal of the bradycardia occurred (Fig. 2). Folic acid (5–30 mg/kg) also reversed

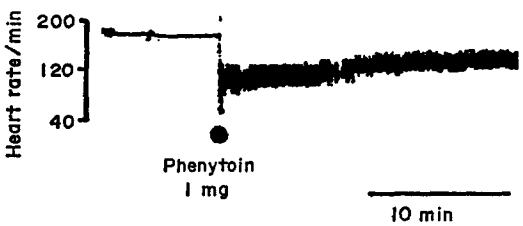

FIG. 1.

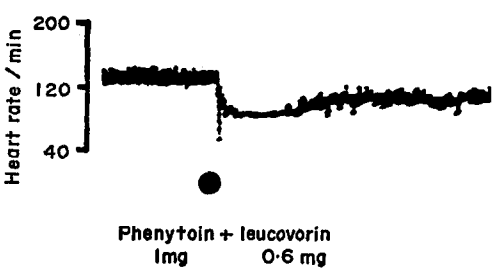

FIG. 2.

phenytoin induced bradycardia. Larger doses of phenytoin (25 mg/kg) given as a bolus produced a reduction of systolic and diastolic blood pressure and force of cardiac contraction (Fig. 3). These recovered within 5 min, but bradycardia accompanied these changes and persisted for at least 30 min.

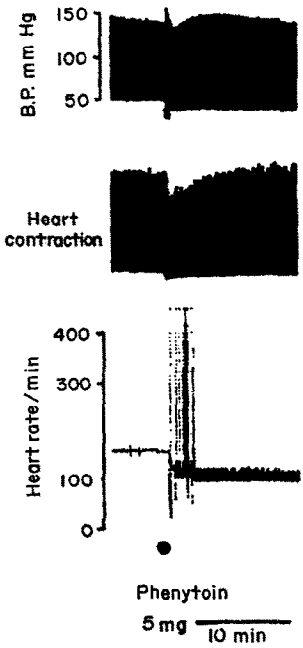

FIG. 3.

When the same dose of phenytoin was given as a continuous intravenous infusion (25 mg/kg over 23·5 min) during the period of administration there was a progressive fall in the heart rate with no change in blood pressure or cardiac contraction (Fig. 4).

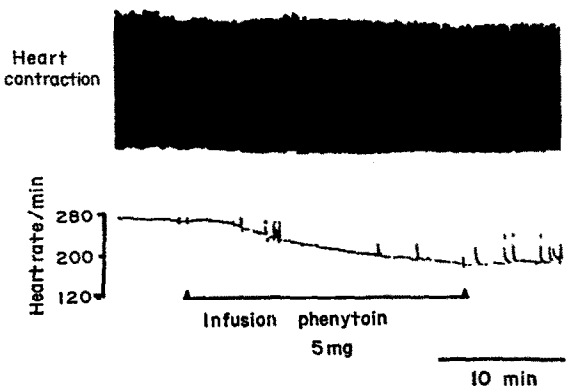

FIG. 4.

Folinic acid (5·0 mg/kg) and folic acid (30 mg/kg) alone, each produced an increase in systolic blood pressure and in force of cardiac contraction (Fig. 5). A further feature of the effects of these agents on the heart was a diminution in diastolic relaxation of the heart.

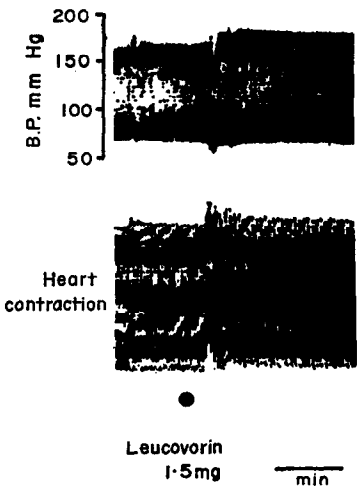

FIG. 5.

Using the isolated rat heart preparation (Langendorff's method), the heart was perfused with oxygenated Lock's solution at 38°. Phenytoin, applied to the heart as a single bolus (10–320 μg; 0·4–12·6 $\times$ 10^{-7} moles) produced a decrease in force of contraction and of heart rate (Fig. 6). Recovery to baseline values usually occurred within 6 min. The dose–response curve was consistent with an adsorption isotherm pattern, with a maximum response at about 12·5 $\times$ 10^{-7} moles. Folic acid (1·0–3·0 mg; 2·3–6·9 $\times$ 10^{-6} moles) and folinic acid (0·3–1·2 mg; 0·5–2·0 $\times$ 10^{-6} moles) produced an increase in rate and force of cardiac contraction (Fig. 7). When phenytoin was applied with the above amounts of folic or folinic acid the rapid onset of decreased force of cardiac contraction was initially prevented and replaced by stimulation (Fig. 8).

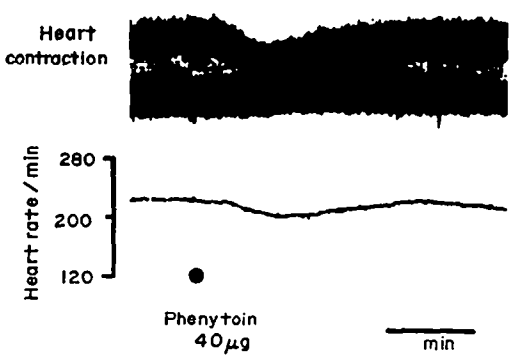

FIG. 6.

The effects of 3·2 $\times$ 10^{-7} moles of phenytoin on the isolated heart were prevented and replaced by stimulation when 1·3 $\times$ 10^{-5} moles of $CaCl_2$ was added simultaneously. $CaCl_2$ alone stimulated the force but decreased the rate of beating of the isolated heart. Maximum effects were obtained when 2·6 $\times$ 10^{-5} moles of $CaCl_2$ were added. Maximum stimulation by folinic acid occurred on the addition of 2 $\times$ 10^{-6} moles alone. The maximum $CaCl_2$ effect (with 2·6 $\times$ 10^{-5} moles) was not enhanced by the addition of 2 $\times$ 10^{-6} moles of folinic acid, however, the $CaCl_2$-induced bradycardia was replaced by a tachycardia. The force of cardiac contraction was also potentiated by the bolus addition of KCl—maximum effects being obtained with 2·2 $\times$ 10^{-5} moles. However, a further

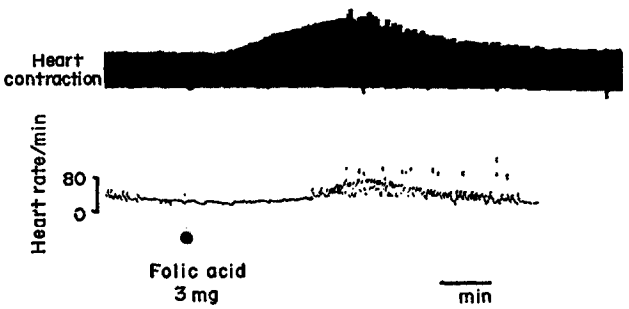

FIG. 7.

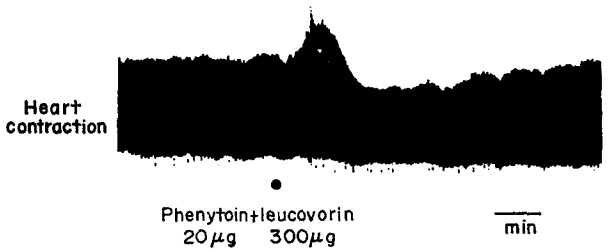

FIG. 8.

increase in contraction force was produced by adding $0{\cdot}5 \times 10^{-6}$ moles of folinic acid to this maximal amount of KCl. Also, when maximal folinic acid effects were obtained (with 2×10^{-6} moles), this was further enhanced with $1{\cdot}6 \times 10^{-5}$ moles of KCl.

Although these experiments demonstrated an antagonism between the actions of folate and phenytoin on the heart no evidence is provided to indicate whether this is a competitive action at receptor level or whether different steps in the excitation–contraction sequence are involved. It has been suggested that structural similarities between folate and antiepileptic drug molecules could indicate the possibility that these agents are competing for similar sites.[6] Excitation of the heart by folate could be via an effect on ionic movements across the cardiac cell membrane. Calcium has several actions on the heart—in this experiment the increase in force of contraction was presumably due to its facilitatory role in excitation–contraction coupling, and the bradycardia was due to its stabilising influence on the pacemaker cell membrane. It is possible that folate could be influencing the availability of Ca^{2+} for the former process, which would be consistent with the observation that folate could not further potentiate maximal inotropic actions of Ca^{2+}. An alternative possibility that folate facilitates plasma membrane depolarisation was rendered less likely by the fact that maximal stimulation by raising the external concentration of K^+ was further enhanced by folate.

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