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Effects of phenobarbitone on glucose transport and membrane ATP-ase activities of cerebral cortex

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Phenobarbitone, at anticonvulsant doses, elevates the concentration of glucose in brain (Gilbert, Gray & Heaton, 1971). Stimulation of glucose transport could be a contributing factor and this would be compatible with the observation that phenobarbitone stimulates xylose transport in cerebral cortex slices (Gilbert, Ortiz & Millichap, 1966). Direct evidence that the drug influences glucose transport has been lacking and the object of the present work was to test this possibility.

Guinea-pig cerebral cortex slices were incubated in oxygenated Krebs-Ringer bicarbonate or phosphate media containing pyruvate (4 mM), raffinose (10 mM) and half (1·2 mM) the recommended calcium concentration. Glucose transport was studied under the following conditions in the presence and absence of phenobarbitone sodium.

1. Glucose uptake was determined at 37° C in the bicarbonate medium containing iodoacetamide (1 mM) and glucose (10 mM) after preincubation for 30 min at 37° C in a similar medium lacking glucose.

2. Glucose efflux into the glucose-free bicarbonate medium containing iodoacetamide (1 mM) was determined at 37° C after preincubation for 30 min at 37° C in a similar medium containing glucose (17 mM).

3. Glucose uptake was determined at 1° C in the phosphate medium containing glucose (10 mM) after preincubation for 30 min at 37° C in a similar medium lacking glucose.

Glucose metabolism was negligible in all experiments. At 37° C, glucose uptake by the slices was rapid and its volume of distribution soon exceeded that of raffinose. The kinetics of permeation of glucose into the non-raffinose compartment conformed to carrier transport kinetics and phenobarbitone (2 mM) did not influence the process. At 37° C, glucose efflux from slices was rapid and was not significantly influenced by phenobarbitone. These results are compatible with previous work suggesting that iodoacetamide can prevent stimulation of sugar transport by some drugs. Glucose uptake at 1° C, in the absence of iodoacetamide, was slow and was significantly stimulated by phenobarbitone; the volume of distribution of glucose did not exceed that of raffinose and the kinetics of uptake were compatible with a simple diffusion process.

The sugar transport system in cerebral cortex slices appears to be regulated by local concentrations of sodium ions (Gilbert, 1966) which in turn depend upon the activity of membrane Mg-dependent Na, K-activated ATP-ase. The effects of phenobarbitone on the activities of Mg-activated ATP-ase and Mg-dependent Na, K-activated ATP-ase were therefore determined. The microsomal fraction was prepared from cerebral cortex and ATP-ase activities were determined in Tris-HCl buffer of pH 7·4 using a method similar to that of Samson & Quinn (1967). Phenobarbitone sodium (2 mM) did not significantly alter the activity of either enzyme.

It is concluded that the effect of phenobarbitone on sugar transport is probably mediated by influencing directly the apparent affinity of carrier for sugar rather than indirectly by influencing active sodium efflux from the cell.

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Effect of centrally acting drugs on the uptake of γ-aminobutyric acid by the brain

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The brain has a specific uptake process for γ-aminobutyric acid (GABA) and this may provide an effective mechanism for terminating its inhibitory action on neurones (Iversen & Neal, 1968). Thus, it is possible that some centrally acting drugs might produce their effects by blocking the reuptake of GABA after its release from nerve endings. In the present investigation we have attempted to test this possibility by determining the effect of centrally acting drugs on the uptake of ^{3}H-GABA by brain slices.

Slices of cerebral cortex (10 mg) were preincubated with the drug for 15 min at 25° C in 10 ml of medium. ^{3}H-GABA (5×10^{-8} M) was added and the incubation was continued for 10 minutes. The radioactivity in the tissue was then measured by liquid scintillation spectrometry (Iversen & Neal, 1968).

Sixty-five compounds at concentrations of 0·1–1·0 mM were tested for possible inhibitory effects on the uptake of ^{3}H-GABA. More than half of the drugs tested produced a significant reduction in the uptake of ^{3}H-GABA by the cortex, but the only groups of centrally acting drugs in which all members consistently produced inhibition of uptake were the phenothiazines and the tricyclic antidepressants. Other compounds which had a relatively powerful inhibitory effect on uptake of ^{3}H-GABA were: *p*-chloromercuriphenylsulphonate, L-2,4-diaminobutyric acid, haloperidol, apomorphine and diphenhydramine. The concentrations of some of these drugs which reduced the uptake of ^{3}H-GABA by 50% (IC_{50}) are presented in Table 1, which also shows the effect of these drugs on the uptake by cortex of: ^{3}H-alanine, ^{14}C-glycine, ^{3}H-5-hydroxytryptamine and ^{3}H-noradrenaline. With the exception of L-2,4-diaminobutyric acid, all the drugs at the IC_{50} for GABA, also significantly reduced the uptake of ^{14}C-glycine and ^{3}H-alanine and were often much more effective