DEMONSTRATIONS

Studies of the actions of drugs affecting the central nervous system and of the relationship between nerve terminal ATPase activities and neurotransmitter release

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A centrally-acting drug may mediate its action by altering neurotransmitter release. This effect could, in turn, result from inhibition or stimulation of enzymes in nerve terminals of the central nervous system.

The demonstration shows techniques which may be used to prepare nerve terminals (synaptosomes) from rat brain (homogenization, differential and density gradient centrifugation), a technique to measure the release of neurotransmitters from these terminals in the presence and absence of drugs *in vitro*, and the results of experiments to determine the effects of the same drugs on the activities of enzymes in the terminals. The enzymes principally studied here are ATP-hydrolyzing enzymes (ATPases) which are activated to different extents by sodium, potassium and magnesium ions. When synaptosomes are burst by osmotic shock it is possible to separate the mitochondria, membranes and vesicles from them and to study the effects of the drugs on the enzymes in these fractions independently. Some results are shown. A number of centrally-acting drugs inhibit ATPases in different components of the synaptosome but of the drugs tested so far only those with anticonvulsant activity inhibit the magnesium-ATPase located in the vesicles.

The effects of the drugs on the enzymes can be compared with their effects on the basal and evoked release of neurotransmitters from intact synaptosomes maintained *in vitro*. This comparison may throw light on the roles of the enzymes in neurotransmitter uptake and release processes.

On-line computation of peripheral resistance and stroke volume in the conscious cat obtained by the use of a chronically-implanted electro-magnetic flow transducer

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The use of electromagnetic flow transducers to determine cardiovascular parameters in conscious dogs has not proved totally successful in the chronic situation because of the occurrence of aortic rupture (Stone & Sawyer, 1966; Folts & Rowe, 1973). We therefore decided to investigate the use of the cat as an alternative species since the cat has been shown to be particularly useful for cardiovascular measurements in the conscious state (Poyser, Shorter & Whiting, 1974). Aortic blood flow in the conscious cat was determined using an electromagnetic flow transducer placed around the ascending aorta. In addition, arterial blood pressure was measured using an indwelling aortic cannula (Day & Whiting, 1972).

The interpretation of drug-induced changes of the cardiovascular system is improved if determinations of peripheral resistance and stroke volume are made in addition to those of blood pressure and aortic flow. The assessment of these changes over periods of up to 8 h can be greatly simplified by using the on-line computer shown, in block diagram form, in Figure 1.

With this circuit the inputs, arterial blood pressure, aortic blood flow and heart rate, are first averaged using filters with a time constant of 15 seconds. This time constant was chosen as it provides an accurate representation of the effects upon peripheral resistance and stroke volume of both short and long-acting compounds whilst removing beat-to-beat variations. Subsequent to this averaging, mean arterial blood pressure is divided by mean aortic flow (this quantity is taken to be a reasonable approximation to cardiac output neglecting the 5% or so loss via the coronary arteries) to yield peripheral resistance, and mean aortic flow is divided by mean heart rate to give stroke volume. The units of peripheral resistance are presented in $kPa\,l^{-1}$ minute. This use of mixed SI and traditional units has been recommended (Kappagoda & Linden, 1976) in situations where changes in flow rate are mainly consequent upon