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The Effects of Ether on Potassium Flux in Skeletal Muscle Preparations

SIR,—In anaesthetic concentrations, ether increases and in higher concentrations, decreases the response of striated muscle to potassium (Torda, 1944). Lorkovic (1959) has noted that in potassium-stimulated frog muscle, ether depresses the twitch fibres and potentiates the response of the slow fibres. Ether also alters the blood potassium levels. It decreases serum potassium in the dog (Gerschman and Marenzi, 1933), an effect preceded by an initial rise (Kiersz, 1948) and confirmed in man (Goodman and Gilman, 1955). Using cat erythrocytes, Davson and Reiner (1942) showed that ether increased the rate of efflux of potassium and decreased the inward movement of sodium. The effects of ether upon serum sodium levels are, however, irregular, and small (Kiersz, 1948; Gerschman and Marenzi, 1933). The ether-induced depolarisation of nervous elements (Lorente de Nó, 1947) and the suggestion that ether had a depolarising action at the neuromuscular synapse (Secher, 1951) led us to re-investigate the effects of ether and some volatile anaesthetics on potassium flux in skeletal muscle preparations.

Saturated solutions of the volatile liquids were freshly prepared by shaking with the appropriate saline for 15 min. at room temperature. The clear, anaesthetic-saturated layer was decanted and used.

Uptake and release of potassium-42 ($^{42}K^+$) from paired frog sartorius muscles and from rectangular strips of rat diaphragm were measured by a method similar to that of Lister and Lewis (1959) and Ahmad and Lewis (1962).

The effects of ether upon the twitch height, in response to both direct and indirect stimulation, in the isolated rat phrenic-nerve diaphragm preparation (Bülbring, 1946) and, using this preparation the actions of ether and tubocurarine (1 to 3 μg./ml.) on the $^{42}K^+$ efflux from $^{42}K^+$-loaded rats were observed.

In pentobarbitone-anaesthetised cats, the effects of adrenaline (50–100 μg./kg.), neostigmine (0·25 mg./kg.) and tubocurarine (100–200 μg./kg.) on ether-induced neuromuscular block and at the same time on blood serum levels of $^{42}K^+$ were studied.

The effects of ether, methyl n-propyl ether, chloroform and halothane upon acetylcholine-induced contractions of the isolated frog rectus abdominis muscle were also investigated.

In the isolated frog sartorius muscle and isolated strips of rat diaphragm, ether decreased the uptake ($P < 0{\cdot}001$) and increased the release of $^{42}K^+$. Qualitatively similar results were obtained using saturated solutions of chloroform, halothane and methyl n-propyl ether. Methyl n-propyl ether and ether also increased the release of $^{42}K^+$ from the frog rectus abdominis muscle. Ether

increased the blood levels of $^{42}K^+$ in pentobarbitone-anaesthetised cats. Neither on this preparation nor on the isolated rat phrenic nerve-diaphragm preparation did tubocurarine (0·2–0·5 mg./kg. and 1–2 μg./ml. respectively) alter the release of $^{42}K^+$. On the rat diaphragm-phrenic nerve preparation, ether reduced or abolished the response to indirect stimulation and increased the block produced by tubocurarine (1–2 μg./ml.) or decamethonium (10–20 μg./ml.). The latter effect confirms the findings of Secher (1951). The effects of ether were antagonised by 2–10 μg./ml. of neostigmine. Qualitatively similar results were obtained on the cat gastrocnemius muscle-sciatic nerve preparation. Inhalation of the vapour of from 5–10 ml. of ether reduced the magnitude of contractions of the muscle elicited by sciatic nerve stimulation. Adrenaline (20–50 μg./kg.) and neostigmine (0·25 mg./kg.) both antagonised the action of ether and at the same time, increased serum $^{42}K^+$ levels.

Ether solution (2–10 ml.) caused a contraction of the isolated frog rectus abdominis muscle, confirming the findings of Torda (1943). This was followed by a decline in sensitivity to acetylcholine (0·1–1·0 μg./ml.). Repeated exposure to ether further reduced the response to acetylcholine. Soaking in Ringer's fluid containing three times the normal quantity of potassium did not reverse this effect.

Solutions of methyl n-propyl ether (2–10 ml.), halothane (2–5 ml.) and chloroform (2–5 ml.) also depressed the response of the frog rectus abdominis muscle to acetylcholine. Methyl n-propyl ether had in addition a direct stimulant effect accompanied by an increase in the release of potassium-42.

Although ether and the other anaesthetics increase potassium release from skeletal muscle preparations in a similar manner to depolarising muscle relaxants (Ahmad and Lewis, 1961), ether potentiates non-depolarising (Foldes, 1957) more consistently than depolarising drugs (Paton, 1953). Synergism between ether and decamethonium is not difficult to interpret on this basis, but it seems very unlikely that the ether-potentiation of tubocurarine is due to a high local concentration of potassium causing intense depolarisation sufficient to override the competitive effects of tubocurarine and then exert a depolarising block of its own. On the other hand, loss of large amounts of intracellular potassium may weaken the contractile mechanism of the cell. A further possibility is that ether-induced potassium loss may render more easy the access of tubocurarine to receptor sites.

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BOOK REVIEWS

BENTLEY'S TEXTBOOK OF PHARMACEUTICS. 7th Edition. By Harold Davis. Pp. xiii + 1091 (including 309 illustrations and Index). Baillière, Tindall and Cox, London, 1961. 52s. 6d.

Bentley's Textbook of Pharmaceutics has been a standard reference book on pharmacists' bookshelves for over 35 years and during that time has been the vade mecum of countless pharmacy students.

In his preface to the first edition. Bentley remarked that no book had then been published on this aspect of the training of a pharmacist. It now seems remarkable that the whole field of Pharmaceutics should be included within the covers of one volume. The fact that the book is now in its seventh edition shows that it is in demand and that there is a need for frequent revision; this revision would surely be simplified if the work were in three or four volumes. In this manner justice would be done to each section of the subject.

The present edition has been extensively revised by Dr. Davis in co-operation with academic and industrial specialists who have been able to effect the revision with only a slight increase in the overall size. A new section on Radio-activity is included and there is a very welcome chapter on Containers and Packaging. Certain rearrangements have also been effected although they do not always assist in the use of the book. Containers, preservatives and incompatibilities which are dealt with in widely separated sections are all facets of the one problem —*formulation*—which warrants a complete section of its own. Similarly eye drops and eye lotions (neither of which appear in the index) should not be separated by 80 pages.

The introduction of a specific section on Unit Dosage Forms for Oral use is welcome but it seems a pity that it is restricted to tablets and capsules. Pills and cachets are dealt with elsewhere, the former occupying almost as much space as tablets; some of this space could well have been devoted to delayed action formulations and the associated processes for producing them.

The present edition contains an increased number of line diagrams which are most helpful, but there is still a need for further diagrams—the two illustrations of a steamer which appeared in the first edition might well be replaced by diagrams of an ethylene oxide steriliser, pre-vacuum autoclave system and spray cooling autoclave for bulk injections. Although there are five pictures of tablet machines there is none which illustrates how a simple tablet machine works.

The authors are to be congratulated in having placed between the covers of one book the present state of a rapidly developing subject and the publishers have done well to produce it so well at a very reasonable price. The above comments are made in the hope that they will help to keep this important work abreast with modern trends.

The inclusion of an increased number of references to other works and to original publications is very commendable, but the usefulness of "Bentley" as a book of reference could be enhanced by the amplification of its own index.

J. C. PARKINSON.