

**Tuesday, August 22****1 Drugs and Membranes. Introductory Remarks.** C. A. M. HOGGEN (U.S.A.).**2 The Molecular Architecture of Cell Membrane and Cytoplasmic Membranes.** F. S. SJÖSTRAND (U.S.A.).

Indirect methods revealing certain properties of the cell membrane combined with direct morphological analysis of the structure of various types of membranes by means of high resolution electron microscopy have allowed proposing models for the molecular architecture of these membranes. Electron microscopy, furthermore, can demonstrate structural changes in the membranes that can be correlated to variations in functional condition. The hypothesis will be discussed according to which the membranes represent enzymatically active structures involved in, for instance, oxidative phosphorylation in mitochondria and protein synthesis in certain other cytoplasmic membranes.

Membranes of various types represent the most common and spectacular structural components of the cytoplasm of cells and might be of great importance for co-ordination and regulation of the enzymatic activities of cells. The hypothesis regarding their functional importance can be tested. The role of the various membranes in connection with the action of drugs could be further explored by combined biochemical and morphological analysis. Possible approaches to this problem will be discussed.

**3 Passage of Materials across Biological Membranes.** H. H. USSING (Denmark).

A survey of current research on cell permeability indicates the lipid-pore concept of the membrane as originally advanced by Collander and Bärklund is still tenable if it is supplemented by the concepts of active transport and facilitated diffusion.

The evidence for the existence of pores in the cell membranes or surfaces is of two kinds: (1) The dependence of diffusion rates on molecular diameter (Collander *et al.*, Pappenheimer *et al.*, Solomon *et al.*); and (2) The existence of "solvent drag" on molecules diffusing in an osmotic water stream through the membrane, a phenomenon which requires a continuous water phase (Ussing; Koefoed Johnsen and Ussing; Andersen and Ussing).

It is pointed out that "sandwich-membranes" consisting of two or more layers with different pore-sizes and different solubility properties may obtain a very high degree of specificity.

The concept of active transport as well as that of facilitated diffusion constitute transport phenomena which cannot be predicted on the basis of the lipid-pore theory. They differ in that the active transport processes consume metabolic energy whereas the facilitated diffusion processes do not. Kinetically, both types of transport can often be described satisfactorily on the basis of specific mem-

branes carriers, but it is better for the time being to consider the carriers only as abstractions. Despite our lack of detailed information concerning the molecular basis of these processes, the two concepts have proved themselves exceedingly useful in organizing a confusing array of observations into a framework from which predictions can be made.

Finally, it is pointed out that although the phenomenon of pinocytosis may be of importance in special cases, it is extremely unlikely to be among the main vehicles of membrane transport.

**4 Biochemical Aspects of Transport.** L. E. HOKIN and M. R. HOKIN (U.S.A.).

Evidence will be reviewed favouring the phosphatidic acid cycle as the mechanism of the Na<sup>+</sup>-pump. In this cycle lipid soluble disodium phosphatidate is formed at the inner surface of the membrane from ATP, diglyceride, and 2 Na<sup>+</sup>. Disodium phosphatidate crosses the membrane where it is hydrolyzed by phosphatidate phosphatase, releasing 2 Na<sup>+</sup> into the aqueous phase bounding the outer surface of the membrane. Diglyceride returns to the inner surface of the membrane where the cycle is repeated. There is no direct evidence on the mechanism of return of phosphate to the cytoplasm but it is postulated that in those cells which pump Na<sup>+</sup> in exchange for K<sup>+</sup> the phosphate returns with 2 K<sup>+</sup>, and in those cells which pump NaCl the phosphate returns in exchange for two Cl<sup>-</sup>. The following will be discussed in support of the cycle: (1) the increased renewal of phosphate in phosphatidate on stimulation of the avian salt gland with acetylcholine; (2) the time course of this increased renewal; (3) evidence that the phosphatidic acid effect is in secretory membranes; (4) evidence that the stimulated renewal of phosphate in phosphatidate is catalyzed by diglyceride kinase and phosphatidic acid phosphatase, both situated in the membrane; (5) the requirement of the cycle for Na<sup>+</sup>; and (6) the presence of the phosphatidic acid cycle enzymes in the erythrocyte membrane and the evidence that the cycle enzymes may be components of the Na<sup>+</sup> and K<sup>+</sup> dependent membrane ATPase which appears to be closely related to the Na<sup>+</sup> and K<sup>+</sup> pumps.

**5 Enzymatic Aspect of Active Transport of Na<sup>+</sup> and K<sup>+</sup> across the Cell Membrane.** J. SKOT (DENMARK).

From peripheral crab nerves a submicroscopic particle has been isolated which contains a system fulfilling a number of the requirements for a system involved in the active linked transport of Na<sup>+</sup> and K<sup>+</sup> across the cell membrane.

- (1) It contains an enzyme which catalyses the transfer of energy from ATP to the system as an energy-rich phosphate bond.
- (2) It has one site where there is an affinity for Na<sup>+</sup> which is higher than for any other monovalent ion and another site where the affinity for K<sup>+</sup> is highest.

- (3) The splitting of the high-energy phosphate bond of the phosphorylated compound requires  $\text{Na}^+$  in the medium and is highly increased by adding  $\text{K}^+$  when the medium contains  $\text{Na}^+$ , while  $\text{K}^+$  alone has practically no effect.
- (4) G-strophanthin which specifically inhibits the active linked transport of  $\text{Na}^+$  and  $\text{K}^+$  in the intact cell also inhibits the  $\text{Na}^+ + \text{K}^+$  activated splitting of the high-energy bond of the phosphorylated compound.
- (5) There is indirect evidence that the particle studied is derived from the surface membrane of the intact cell.
- (6) A particle which contains a system which has the same specificities for  $\text{Na}^+$  and  $\text{K}^+$  has also been isolated from other tissues where there is an active linked transport of  $\text{Na}^+$  and  $\text{K}^+$ , namely from brain, kidney and heart muscle.

The relationship of the particulate system to the active linked transport of  $\text{Na}^+$  and  $\text{K}^+$  across the cell membrane will be discussed.

#### 6 Pharmacological Control of Release of Hormones Including Antidiabetic Drugs. Introductory Remarks. R. COURRIER (France).

#### 7 Pharmacological Actions of the Hypoglycaemic Arylsulphonamides upon the Histophysiology and the Physiology of the Beta-cells of the Islets of Langerhans of the Pancreas. A. LOUBATIERES (France).

The hypoglycaemic arylsulphonamides (thiadiazole or urea derivatives) have a preferential tropism for the pancreas (pancreatotropism) and especially for the beta-cells of the islets of Langerhans (betacytotropism). The betacytotropism is mainly shown by the degranulation of the beta-cells and by other histological modifications demonstrated with electron microscopy.

Hypoglycaemic sulphonamides are betacytotrophic. They produce a hyperplasia of the islets and stimulate the formation of new insulin secretory beta-cells. There follows an increase in the total amount of the beta-cells and an increased capacity of the endocrine pancreas in blood glucose regulation.

We have at the present time strong evidence showing that hypoglycaemic sulphonamides are insulin-secretory stimulating substances. The venous blood coming from the pancreas is more hypoglycaemically active after administration of these drugs than it was before: its "plasma insulin activity" as well as its endogenous insulin content increases. This is the main reason why these drugs are strongly effective in the treatment of human diabetes characterized by sluggishness or relative depression of insulin-secretory process.

The arylsulphonamides manifest an antidiabetic action against meta-alloxanic, meta-hypophyseal or spontaneous diabetes of moderate intensities. They

counteract the establishment of idio-hypophyseal diabetes in a dog. They exert a preventive action against the exhaustive process which occurs "spontaneously" in the beta-cells of the pancreas remnant of a subtotally depancreatized animal. These phenomena are in direct connexion with the actions (stimulation, neoformation, regeneration) exerted by these sulphonamides upon the apparatus of the beta-cells. Clinical trials plead for the possibility of the use of these drugs as prophylactic agents against the development of full diabetes in human beings predisposed to this illness.

#### 8 Experimental Investigations with Sulphonureas (S.U.). A. BÄNDER (Germany).

The effects of oral hypoglycaemic compounds upon the enzyme-system, the liver and the peripheral carbohydrate metabolism do not sufficiently explain the hypoglycaemic action. Experimental animals and patients deprived of the pancreas do not exhibit any hypoglycaemic reaction, provided that the gland is removed, for several days.

There is agreement that the main action is to be found in releasing insulin from the pancreas. How this liberation is effected constitutes a question of paramount interest.

According to results by Wrenshall *et al.*, a large number of the diabetics who develop the disease when adults have a sufficient amount of insulin in the gland, sometimes even more than non-diabetics. There remains the question why these patients are diabetics. Some evidence has been obtained that in these patients there is an abnormal binding of insulin in the pancreas. Thus, the difference in blood sugar curves between non-diabetics and diabetics could be explained.

Experiments of Aiman *et al.* showed that plasma-bound insulin could be released by S.U.

Our own investigations have demonstrated *in vitro* a degranulation of isolated  $\beta$ -cells under the influence of S.U.

Reviewing these observations one may assume that S.U. are exerting their effects by means of physico-chemical properties. It is suggested that these qualities produce a removal of this abnormal binding; in this way adequate amounts of insulin are released.

#### 9 Pharmacological Effects of Some Chemical Compounds of Biosynthesis and Secretion of Thyroid Hormones. R. MICHEL (France).

The main steps in the biosynthesis and secretion of thyroid hormones are: iodide concentration, iodotyrosines formation, iodotyrosines coupling, thyroglobulin proteolysis, enzymatic deiodination of iodotyrosines followed by iodothyronines secretion.

Various chemical compounds modify thyroidal iodine metabolism. Thiocyanate, perchlorate and other isoelectric anions of about the same volume inhibit iodide concentration. They act competitively with  $\text{I}^-$  which probably fits into some specific