SELECTIVE K^+ TRANSPORT THROUGH SYNTHETIC MEMBRANES USING ANTIBIOTICS IN A POTENTIAL GRADIENT

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Received February 5, 1969

SUMMARY

A selective transport of potassium ions in the presence of an equal amount of sodium ions is obtained by applying a potential difference across a synthetic membrane impregnated with a macrotetrolide antibiotic. An analogous selective transport is suggested for biological systems.

Certain antibiotics (1) (2) (3) (4)[1] show a high degree of cation specificity in metabolic behaviour (5) (6) and are probably linked with the transport of certain cations across biological membranes (5). EMF measurements on synthetic membranes consisting of such antibiotics supported on inert materials show an analogous cation specificity (7) (8) (9) (10). Similar results are obtained by conductance measurements on synthetic phospholipid membranes (11). These effects are consistent with the complex formation of the antibiotics in question with alkali metal salts (7) (8) (12) (13).

Through the isolation of crystalline 1 : 1 complexes of these antibiotics with sodium, potassium and ammonium salts (8) (9) (12) and the X-ray analysis (14) (15) of some of these the molecular basis of the complex formation has been elucidated (14) (15) (16) (see also (17) (18)).

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[1] Macrotetrolides such as nonactin and monactin (1), cyclohexadepsipeptides such as enniatins (2), cyclododecadepsipeptides such as valinomycin (3), gramicidins (4).

All the antibiotics mentioned[1] show a preferred complex formation with potassium as compared to sodium ions (7) (8) (12) (13) consistent with the selective K^+ transport in biological systems (5). In a synthetic membrane consisting of an agent complexing preferably potassium ions, a selective transport is to be expected if a potential is applied across the membrane (19) in the presence of equal molalities of sodium and potassium ions. In this communication it will be shown that such a selective transport of potassium ions is obtained using a porous PVC membrane impregnated with macrotetrolides in octanol-2.

EXPERIMENTAL

The porous polyvinylchloride membranes used (Porvic S, Porous Plastics Ltd., Dagenham Dock, Essex, England) as inert support were treated with a solution of 6 mg/ml macrotetrolide mixture (28% monactin, 72% nonactin) in octanol-2 previously saturated with dilute hydrochloric acid of pH 3.5. An area of 80 mm^2 (10 mm diameter) of the membrane with a total diameter of 19 mm and 0.75 mm thickness was exposed to the solutions to be electrolyzed. These membranes were mounted as described earlier (9) and placed in aqueous 0.1 M alkali chloride solutions of pH 3.5, the outer solution containing K^{42} or Na^{24} as tracer, the inner compartment containing unlabelled potassium and/or sodium chlorides. For the electrolysis a platinum electrode was inserted in each of the compartments and a voltage of 30 V applied. The current for a typical electrolysis carried out at room temperature (23^{o} C) was in the range of 2 - 10 µA.[2]

During a period of one hour the current/time integral was taken. The transport of sodium and potassium respectively was deter-

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[2] The total current is by a factor of about 5 smaller for sodium compared to potassium chloride solutions of equal concentration. For a 0.1 M solution of KCl the current decreases by an order of magnitude if the membrane is impregnated with octanol free of antibiotics. These facts are in qualitative agreement with conductance measurements (11) carried out on lipid bilayers formed from beef brain lipid.

mined by measuring the activity of the inner solution using a Geiger-Müller counter ("1000" Scaler, Tracerlab Inc., Boston, USA).

RESULTS AND DISCUSSION

The percentage of the current transported by alkali metal cations is given in the table. The results show clearly that the macrotetrolide impregnated membranes lead to an almost exclusive transport of potassium ions in the presence of equal concentrations of sodium ions.[3] By analogy the selective transports in biological systems may readily be imagined to be caused by potential differences across membranes (20) in the presence of these and/or other similar complexing agents. Preliminary studies of the complex formation of such complexing agents with alkali metal cations suggest that the selectivity order may change with environment.

TABLE 1

Percentage of Current Transported Through the Membrane in Direction of the Inner Electrode by Sodium and Potassium Ions

Electrolyte	% of the Current Transported by		Inner Electrode
	Na^+	K^+	
0.1 M NaCl	15±4	--	cathode
0.1 M NaCl	0	--	anode
0.1 M KCl	--	42±5	cathode
0.1 M KCl	--	0	anode
0.05 M KCl 0.05 M NaCl	0.6±0.3	42±5	cathode

[3] In the absence of antibiotics no selectivity in the cation transport is observed.

At present electrolysis experiments with labelled nonactin are in progress to decide whether the transport of potassium ions occurs by migration of the complex or by a transfer of the uncomplexed ion from molecule to molecule of the complexing agent.

ACKNOWLEDGMENTS

The present work has been supported by the Schweizerischer Nationalfonds zur Förderung der wissenschaftlichen Forschung (Research Projects Nr. 4312 and 5188.2). We thank Privatdozent Dr. P. Jordan and Mr. P. Köberle, ETH, for their help in the application of the tracer technique.

REFERENCES

(1) Corbaz, R., Ettlinger, L., Gäumann, E., Keller-Schierlein, W., Kradolfer, F., Neipp, L., Prelog, V. and Zähner, H., Helv. Chim. Acta 38, 1445 (1955);
Keller-Schierlein, W. and Gerlach, H., Fortschr. Chem. org. Naturstoffe 26, 161 (1968).

(2) Plattner, P. A., Vogler, K., Studer, R. O., Quitt, P. and Keller-Schierlein, W., Helv. Chim. Acta 46, 927 (1963);
Quitt, P., Studer, R. O. and Vogler, K., Helv. Chim. Acta 46, 1715 (1963); 47, 166 (1964).

(3) Brockmann, H., Springorum, M., Träxler, G. and Höfer, I., Naturwiss. 50, 689 (1963);
Shemyakin, M. M., Aldanova, N. A., Vinogradova, E. I. and Feigina, M.Yu., Tetrahedron Letters No. 28, 1921 (1963).

(4) Schwyzer, R. and Sieber, P., Helv. Chim. Acta 40, 624 (1957);
Sarges, R. and Witkop, B., J. Amer. Chem. Soc. 87, 2027 (1965).

(5) Moore, C. and Pressman, B.C., Biochem. Biophys. Res. Comm. 15, 562 (1964);
Pressman, B. C., Proc. Nat. Acad. Sci. U.S.A., 53, 1076 (1965);
Graven, S. N., Lardy, H. A., Johnson, D. and Rutter, A., Biochemistry 5, 1729 (1966);
Chappell, J. B. and Crofts, A. R., Biochem. J. 95, 393 (1965);
Tosteson, D. C., Andreoli, T. E., Tieffenberg, M. and Cook, P., J. Gen. Physiol. 51, 373 (1968).

(6) Cockrell, R. S., Harris, E. J. and Pressman, B. C., Biochemistry 5, 2326 (1966);
Höfer, M. and Pressman, B. C., Biochemistry 5, 3919 (1966);
Pressman, B. C., Harris, E. J., Jagger, W. S. and Johnson, J. H. Proc. Nat. Acad. Sci. U. S. A., 58, 1949 (1967);
Graven, S. N., Lardy, H. A. and Rutter, A., Biochemistry 5, 1735 (1966).

(7) Štefanac, Z. and Simon, W., Chimia (Switz.) 20, 436 (1966); Štefanac, Z. and Simon, W., Microchem. J. 12, 125 (1967).
(8) Wipf, H.-K., Pioda, L. A. R., Štefanac, Z. and Simon, W., Helv. Chim. Acta 51, 377 (1968).
(9) Pioda, L. A. R., Wipf, H.-K. and Simon, W., Chimia (Switz.) 22, 189 (1968).
(10) Pioda, L. A. R. and Simon, W., Chimia (Switz.) 23, 72 (1969).
(11) Mueller, P. and Rudin, D. O., Biochem. Biophys. Res. Comm. 26, 398 (1967).
(12) Pioda, L. A. R., Wachter, H. A., Dohner, R. E. and Simon, W., Helv. Chim. Acta 50, 1373 (1967).
(13) Shemyakin, M. M., Ovchinnikov, Yu. A., Ivanov, V. T., Antonov, V. K., Shkrob, A. M., Mikhaleva, I. I., Evstratov, A. V. and Malenkov, G. G., Biochem. Biophys. Res. Comm. 29, 834 (1967).
(14) Kilbourn, B. T., Dunitz, J. D., Pioda, L. A. R. and Simon, W., J. Mol. Biol. 30, 559 (1967).
(15) Dobler, M., Dunitz, J. D. and Krajewski, J., unpublished work; Healy, M. and Dunitz, J. D., unpublished work.
(16) Dunitz, J. D. and McLachlan, A. D., unpublished work.
(17) Agtarap, A., Chamberlin, J. W., Pinkerton, M. and Steinrauf, L. K., J. Amer. Chem. Soc. 89, 5737 (1967).
(18) Steinrauf, L. K., Pinkerton, M. and Chamberlin, J. W., Biochem. Biophys. Res. Comm. 33, 29 (1968).
(19) Eisenman, G., Sandblom, J. P., Walker, J. L., Jr., Science 155, 965 (1967); Bloch, R., Katchalsky, A., Kedem, O. and Vofsi, D., Brit. Pat., No. 1,049,041.
(20) Mitchell, P., Nature 191, 144 (1961); Mitchell, P., Moyle, J. and Smith, L., European J. Biochem. 4, 9 (1968); Mitchell, P., Fed. Proc. 26, 1370 (1967).