

MODEL FOR POTASSIUM EFFECTS ON ELECTROLYTE AND OXIDATIVE METABOLISM IN GLIA

DARRELL D. FANESTIL

*Division of Nephrology, M-023, Department of Medicine,
University of California, San Diego, La Jolla, California 92093, U.S.A.*

(Received June 1, 1984)

Neuronal activity releases K^+ into the surrounding extracellular solution (ECS). Glia are believed to be involved in "buffering" this increase in K^+ concentration, since the increase in K^+ concentration initiates a series of ion transport and metabolic events in glial cells. Studies on transport of K^+ in primary cultures of glia (Walz and Hertz, 1983b) and in a glial cell line (Johnson *et al.*, 1982) provide evidence for the activity of the bumetanide-sensitive, electroneutral NaCl-KCl symport mechanism. A model is presented that incorporates the primary activation of the NaCl-KCl symport, followed by increased turnover of the Na-K pump, into a rational explanation for the electrolyte and metabolic alterations produced in glia by an increase in the concentration of potassium in the ECS.

Neurons and glia are surrounded by an aqueous extracellular solution (ECS) that constitutes about 20% of the volume of the central nervous system and has a K^+ concentration of about 3.0 mM. Neuronal activation releases K^+ into the ECS, the increase in concentration of K^+ being probably no more than 0.3 mM with spontaneous neuronal activity, but may amount to a 7-10 mM increase following repetitive stimulation. (For general review of K^+ and glia see Walz and Hertz, 1983a).

Glia have been postulated to accumulate some of this K^+ and, because of their large and dispersed surface area, to function as a "spatial buffer" to affect geographical dispersion of the K^+ . (Eventually, of course, the K^+ must be released from glia and re-accumulated by the neurons.) An increase in K^+ concentration in the ECS initiates or is accompanied by a number of events in glial cells: (i) depolarization of the glial cell membrane; (ii) a diminution in the volume of the ECS (up to a 50% decrease occurs with 20-30 seconds of repetitive electrical stimulation of neurons) (Dietzel *et al.*, 1980); (iii) a decrease in the concentration of Na^+ in the ECS (of up to 5-8 mM from about 150 mM with the 20-30 second stimulus) (Dietzel *et al.*, 1980); (iv) a decrease in the quantity of Cl^- in the ECS (this must occur to maintain charge balance, if the volume of the ECS decreases and the sum of the concentrations of Na^+ and K^+ is about constant); (v) a deviation of the glial potential from the potassium equilibrium potential such that the cell membrane becomes hyperpolarized (Tang *et al.*, 1980); (vi) a burst of oxidative activity (reflected by a decrease in NADH reduction) that quantitatively correlates with the initial magnitude of an induced increase in the K^+ concentration in the ECS (Lewis and Schuete, 1975); (vii) an

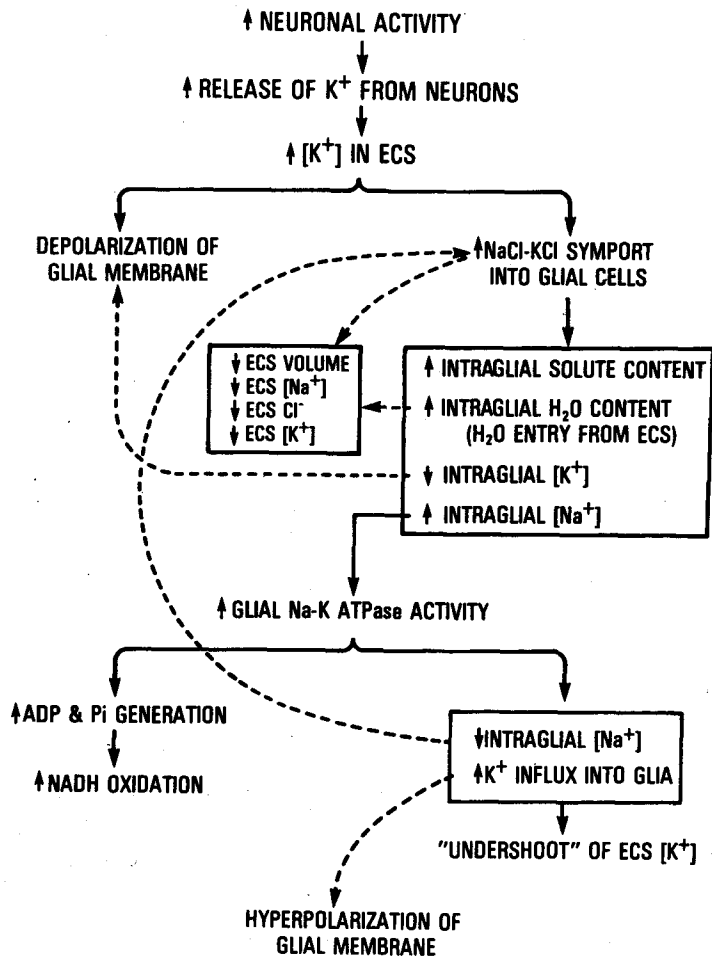


Fig. 1 Model Outlining Effects of K^+ on Electrolyte and Oxidative Metabolism in Glia. The solid arrows indicate sequential effects. The dotted arrows indicate indirect or feed-back effects produced by the more primary sequential effects.

“undershoot” in the ECS K^+ concentration — i.e., the removal of K^+ from the ECS lowers the concentration *below* the initial (resting) concentration by as much as 0.7 mM and lasts 0.5–4 min (Heinemann and Lux, 1975); (viii) the NADH oxidation persists through the end of the “undershoot” in K^+ concentration (Heinemann and Lux, 1975); and (ix) addition of K^+ to the ECS during the “undershoot” period produces a *smaller* increase in the concentration of K^+ in the ECS than occurs when

the same amount of K^+ is added either before or after the undershoot (Dietzel *et al.*, 1980).

These multiple events have led to the description of a number of interesting features of ion transport in glia. Among these are: (i) ion transport in glia is not affected by a direct action of any known neurotransmitter on glia — all known actions of neurotransmitters on glial K^+ transport result secondarily from release of K^+ from neurons (Walz and Hertz, 1983a); (ii) K^+ permeability of glia (primary cultures) is very high with a high unidirectional flux ($\sim 2000 \text{ nmole} \cdot \text{min}^{-1} \cdot \text{mg}^{-1}$) (Walz and Hertz, 1983b), a finding consistent with behaviour that is near to that of a potassium electrode; (iii) about 25% of the K^+ influx in primary glial cultures is inhibited by ouabain (Walz and Hertz, 1983b); (iv) ouabain insensitive uptake of K^+ is inhibited by furosemide or bumetanide in a glial cell line (Johnson *et al.*, 1982) moreover, this uptake of K^+ , which is dependent upon the presence of Na^+ and Cl^- in the extracellular solution (Johnson *et al.*, 1982), produces swelling of the cells (Johnson *et al.*, 1982); and (v) chloride influx in primary glial cultures ($\sim 35 \text{ nmole} \cdot \text{min}^{-1} \cdot \text{mg}^{-1}$) is inhibited about 75–80% by furosemide or bumetanide (Walz and Hertz, 1983b). These last two lines of evidence demonstrate the presence of a bumetanide-sensitive transport system for K^+ , Na^+ and Cl^- that is characteristic of an electroneuronal co-transport system, which facilitates the movement of one Na^+ , one K^+ and two Cl^- across cellular membranes (Saier and Boyden, 1984). This NaCl-KCl symport mechanism operates only when loaded with all four ions and the rate and direction of transport responds to the combined *chemical* gradients for the four ions (Saier and Boyden, 1984). Since the carrier is electroneuronal, the rate of ion symport via the carrier is neither directly affected by the electrical potential nor directly generates a change in electrical potential (Saier and Boyden, 1984).

No current model of glial function incorporates these measured ion transport functions of glia into a cohesive scheme that provides a rational explanation for above nine changes in glial electrolyte and oxidative metabolism that are elicited by K^+ , although interesting and quantitative models have been proposed to explain some of these phenomena (Dietzel *et al.*, 1980). In contrast, the scheme outlined here and shown in Figure 1 provides a rational explanation for the response of glia to an increase in ECS K^+ concentration. Release of K^+ in the ECS by neuronal activity results in an increase in ECS K^+ concentration. The high K^+ permeability of the glial membranes enables some of the K^+ to enter the glia cells. More importantly, for my model, I postulate that the increase in ECS K^+ concentration increases the chemical gradient favoring entry of NaCl-KCl into the glial cell via the bumetanide-sensitive NaCl-KCl symport. This movement of solute into the glial cell results in: (i) osmotically driven movement of water out of the ECS into glia, thereby accounting for the reduction in the volume of the ECS; (ii) moving Na^+ out of the ECS, thereby lowering the Na^+ concentration in ECS by up to 5–8 nM; (iii) movement of Cl^- out of the ECS; and (iv) because there will be equal quantities of Na^+ and K^+ move via the symport into the glial cell where there is a high intracellular concentration of K^+ and a low intracellular concentration of Na^+ , the intracellular K^+ concentration will decrease slightly and the intracellular Na^+ concentration will increase (the concentration of K^+ and Na^+ in the incoming H_2O will each be about 75 mM — i.e., less

than the resting intragial K^+ concentration but greater than the resting intragial Na^+ concentration). The increase in intragial Na^+ concentration provides more substrate (Na^+) to the glial membrane Na^+K^+ ATPase, thereby increasing the activity of the $3Na^+ + 2K^+$ (electrogenic) pump, which will result in a lowering of the Na^+ concentration in glia toward the resting level. This increase in activity of the electrogenic Na^+K^+ ATPase in turn results in: (i) the observed (Tang *et al.*, 1980) hyperpolarized deviation of the glial membrane potential away from the K^+ equilibrium potential; (ii) increased uptake of K^+ from the ECS via the Na^+K^+ ATPase; (iii) a tendency for restoration of a Na^+ gradient favoring further $KCl-NaCl$ entry; and (iv) increased consumption of ATP. The increased consumption of ATP will increase ADP and P_i availability to mitochondria, producing the observed NADH oxidation, which will persist as long as there is increased ATP consumption — i.e., as long as intragial Na^+ concentration is elevated above the resting level. Moreover, the increase in NADH oxidation will be stoichiometrically related to the amount of ADP generated, the ADP generated will be stoichiometrically related to the quantity of excess sodium that entered the cell, and the quantity of excess sodium that enters the cell is stoichiometrically related to the amount of K^+ that enters the cell via the $NaCl-KCl$ symport. Therefore, as observed by Lewis and Schuette (1975), NADH oxidation will be directly related to the initial K^+ added to the ECS. My model predicts that the sustained increase in the activity of the ATPase also produces the uptake of K^+ from the ECS that results in the observed “undershoot” of K^+ concentration — the undershoot will persist as long as there is increased ATP consumption — i.e., as long as intragial Na^+ concentration is elevated. Therefore, the burst of NADH oxidation in mitochondria and the undershoot in ECS K^+ concentration will have the same time course, as observed (Lewis and Schuette, 1975). Finally, the increased uptake of K^+ that is found if K^+ is applied during the undershoot (Dietzel *et al.*, 1980) can be accounted for by the increased activity of the Na^+K^+ ATPase. Thus, my model accounts for all nine features of the glial K^+ uptake system described above. It should be noted that this model does not eliminate a “spatial buffer” activity by glia in which the accumulated K^+ (and $Na^+ + Cl^- + H_2O$) are returned to the ECS at regions of the glial cell spatially distant from the site of uptake of ions and H_2O . I hope that publication of this model will stimulate investigators to devise new experiments that will more fully elucidate the role of glia in K^+ homeostasis in the central nervous system.

Acknowledgements

Fruitful discussions with Drs. Kevin Beaumont and Chun Sik Park are gratefully acknowledged. Supported by NIH SCOR #PHS HL 25457.

References

Dietzel, I., Heinemann, U., Hofmeier, G., and Lux, H. D. (1980). Transient changes in the size of the extracellular space in the sensorimotor cortex of cats in relation to stimulus-induced changes in potassium concentration. *Exp. Brain Res.* **40**, 432–439.

- Heinemann, U. and Lux, H. D. (1975). Undershoots following stimulus-induced rises of extracellular potassium concentration in cerebral cortex of cat. *Brain Res.* **93**, 63–76.
- Johnson, J. H., Dunn, D. P. and Rosenberg, R. N. (1982). Furosemide-sensitive K^+ channel in glioma cells but not neuroblastoma cells in culture. *Biochem. Biophys. Res. Comm.* **109**, 100–105.
- Lewis, D. V. and Schuette, W. H. (1975). NADH fluorescence and $[K^+]_o$ changes during hippocampal electrical stimulation. *J. Neurophysiol.* **38**, 405–417.
- Saier, M. H., Jr. and Boyden, D. A. (1984). Mechanism, regulation and physiological significance of the loop diuretic-sensitive $NaCl/KCl$ symport system in animal cells. *Mol. Cell. Biochem.* **59**, 11–32.
- Tang, C.-M., Cohen, M. W. and Orkland, R. K. (1980). Electrogenic pumps in axons and neuroglia and extracellular potassium homeostasis. *Brain Res.* **194**, 283–286.
- Walz, W. and Hertz, L. (1983a). Functional interactions between neurons and astrocytes. II. Potassium homeostasis at the cellular level. *Prog. Neurobiol.* **20**, 133–183.
- Walz, W. and Hertz, L. (1983b). Comparison between fluxes and potassium and chloride in astrocytes in primary cultures. *Brain Res.* **277**, 321–328.