MODEL FOR POTASSIUM EFFECTS ON ELECTROLYTE AND OXIDATIVE METABOLISM IN GLIA

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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, 1973); (vii) an
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The same amount of K⁺ is added either before or after the undershoot (Dictzel 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 (~2000 nmole.min⁻¹.mg⁻¹) (Walz and Hertz, 1983b), a finding consistent with behavior 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 medium (Johnson et al., 1982), produces swelling of the cells (Johnson et al., 1982; and (v) chloride influx in primary glial cultures (~35 nmole.min⁻¹.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 electroneutral co-transport system, which facilitates the movement of one Na⁺, one K⁺ and two Cl⁻ across cellular membranes (Saier and Boydyn, 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 Boydyn, 1984). Since the carrier is electroneutral, 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 Boydyn, 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 (Dictzel 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 H₂O will each be about 75 mM — i.e., less...
than the resting intraglial K⁺ concentration but greater than the resting intraglial Na⁺ concentration). The increase in intraglial 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 Pi availability to mitochondria, producing the observed NADH oxidation, which will persist as long as there is increased ATP consumption — i.e., as long as intraglial 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 intraglial 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⁻ + H₂O) are returned to the ECS at regions of the glial cell spatially distant from the site of uptake of ions and H₂O. 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.

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References


