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# Osmolarity, ionic flux, and changes in brain excitability

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**Abstract**

The majority of modern epilepsy research has focused on possible abnormalities in synaptic and intrinsic neuronal properties—as likely epileptogenic mechanisms as well as the targets for developing novel antiepileptic treatments. However, many other processes in the central nervous system contribute to neuronal excitability and synchronization. Regulation of ionic balance is one such set of critical processes, involving a complex array of molecules for moving ions into and out of brain cells—both neurons and glia. Alterations in extracellular-to-intracellular ion gradients can have both direct and indirect effects on neuronal discharge. We have found, for example, that when hippocampal slices are exposed to hypo-osmotic bathing medium, the cells not only swell, but there is also a significant increase in the amplitude of a delayed rectifier potassium current in inhibitory interneurons—an effect that may contribute to the increase in tissue excitability associated with hypo-osmolar treatments. In contrast, antagonists of the chloride co-transporter, furosemide or bumetanide, block epileptiform activity in both in vitro and in vivo preparations. This antiepileptic effect is presumably due to the drugs' ability to block chloride co-transport. Indeed, prolonged tissue exposure to low levels of extracellular chloride have a parallel action. These experiments indicate that manipulation of ionic balance may not only facilitate epileptiform activities, but may also provide insight into new therapeutic strategies to block seizures. 

*Keywords:* Ionic regulation; Chloride co-transport; Hypo-osmolarity; Furosemide; Potassium currents

## 1. Introduction

There are, it seems, innumerable factors that modulate and control the excitability of brain tissue, and thus can influence neuronal epileptogenicity. Most current research into these modulatory factors focuses on changes in intrinsic neuronal properties and/or particularly on changes in synaptic (excitatory vs inhibitory) interactions. While these neuronal features are undoubtedly important—indeed, are in some sense an 'end point' for other influential pathways—it is important to identify and characterize other processes that affect cell and synaptic characteris-

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tics. At least within the context of epileptogenesis, much less is understood about such factors as intracellular and extracellular ionic accumulations, changes in osmolarity, glial release and uptake of ions and other neuroactive substances, cell swelling and associated changes in extracellular space, and changes in pH. While it is impossible to adequately review the vast literature on these issues, it is worthwhile examining some of the recent data that indicate an important role for 'non-synaptic' modulation of epileptogenicity. To make this a manageable endeavor, we will organize this discussion around a few interesting observations made recently in our laboratory (Hochman et al., 1995; Baraban et al., 1997; Baraban and Schwartzkroin, 1998).

## 2. Regulation of ionic flux

Ion flux across the neuronal membrane is what depolarizes (or hyperpolarizes) the cell and determines its discharge pattern. As neuroscientists, our view of this flux was initially relatively simplistic, emphasizing the roles of sodium and potassium voltage-sensitive channels underlying action potential generation, and of sodium, potassium, and chloride movement associated with activation of various neurotransmitter receptors. It is quite clear now, however, that the story is much more complex. In addition to a host of voltage- and ligand-gated receptors through which ions flow (or which regulate ionic channels indirectly, in the case of 'metabotropic' receptors), the ionic balance is also determined by activity of a large number of pump, exchanger, and transporter molecules; the net effects of these activities have critical consequences for cell excitability (e.g. Somjen, 1984; Chesler, 1990; Ransom, 1992; Ransom and Sontheimer, 1992). A sampling of the molecules involved in ion movement is shown in Fig. 1. It is important to note that ion flux associated with transporter molecules is electrically neutral, and is 'driven' by gradients established by the pumps (e.g. Na,K-ATPase); with significant changes in ionic gradients, these transporter processes may even operate in the reverse direction. Also of importance is the fact that these pumps and transporters are not confined to neurons, but are also found on glia (Flott and Seifert, 1991; Walz, 1992); indeed, the function of transporters in conjunction with voltage-activated ion channels in astrocyte membrane has been hypothesized to be key in glial 'spatial buffering' of the extracellular environment (Walz, 1989). Finally, it should be clear from Fig. 1 that the activity of any one molecule—transporter, pump, or channel—is likely to have signficant consequences for activity at other molecular sites. The system is one of dynamic equilibrium.

Because the system is so dynamic, it is helpful to identify some change as the 'initiating' event when we analyze the ionic changes as they relate to neuronal excitability. In the epileptic brain, as in the normal CNS, a convenient starting point is cellular discharge. Action potential discharge results in potassium ion flux into the extracellular space, and sodium flow into neurons. Under normal circumstances, the degree of ion exchange is minor, and the balance is rapidly restored—by

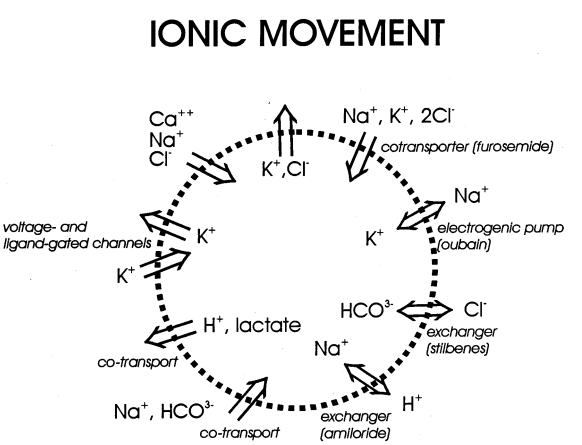


Fig. 1. Diagrammatic sampling of mechanisms for moving ions into, or out of, cells (neurons or glia). The term 'pump' refers to molecular processes that require energy; the term 'exchanger' refers to processes that involve reciprocal movement of ions of the same charge, driven by their ion gradients; and the term 'co-transporter' refers to electro-neutral movement of ions of different charge, again driven by the ion gradients of the participating ion species. Listed also (in parentheses) are drugs that have been identified as specific antagonists of some of these ion movement molecules. Furosemide and bumetanide antagonize both the Na,K,2Cl and K,Cl co-transporters.

diffusion (see Nicholson, 1993) as well as via voltage-gated ion channels (Bevan et al., 1985; Sontheimer, 1994). With larger ionic flux—e.g. when large numbers of neurons discharge simultaneously, as in epileptiform activity—there is a need for an active mechanism to restore ionic balance (Syková, 1991). Of course, the Na,K-ATPase is activated when intracellular sodium climbs too high, or when extracellular potassium increases. Another major contributor to this homeostasis is the Na,K,2Cl transporter, which drives sodium, potassium and chloride into the cell when the extracellular-to-intracellular potassium gradient is high (Walz and Hertz, 1984; Geck and Heinz, 1986). With net chloride Cl flux into the cell, the Cl-bicarbonate exchange is turned on to eliminate chloride from the intracellular space (Walz, 1995). This exchange, in turn, affects intracellular (and extracellular) pH, so a H-Na exchanger is needed to adjust pH (Pappas and Ransom, 1994). The fine-tuning of ionic balance involves a complex set of interacting mechanisms, the results of which directly affect cell excitability—not only the cell's membrane potential, but also the efficacy of its voltage-gated ion channels depend on these ionic gradients. These changes in ionic distribution can also affect synaptic potentials, since excitatory and inhibitory synaptic events are driven by ionic gradients. Finally, ionic flux associated with high levels of activity is accompanied by movement of water across cell membranes (Walz and Hinks, 1985)—and consequently changes in osmolarity, and in cellular and extracellular space volume (Dietzel et al., 1982; Traynelis and Dingledine, 1989; Dudek et al., 1990; Syková and Chvátal, 1993). The identification of exchanger, transporter, and pump molecules participating in this dynamic process is critical to our understanding of excitability controls, as is the localization of these molecules. Just as the functional consequences of ion flux through channels and receptors depend on their location (e.g. neuron versus glia, soma versus dendrite versus axon), so too is the net function of transporters, pumps, and exchangers dependent on the precise membrane in which they are embedded. Glia, in particular, have been implicated in ionic homeostasis in the CNS. Precisely how they accomplish this task remains to be determined.

## 3. Cell swelling and changes in extracellular space

That altering extracellular osmolarity would affect cell volume, and thus extracellular space, not only seem logical, but can be easily visualized in in vitro preparations with infrared/differential interference contrast optics (e.g. Baraban et al., 1997). When hypo-osmotic bathing medium is applied to cells/tissue in vitro, water moves into the intracellular compartment in order to establish a new ionic equilibrium condition, thus increasing cell volume. Presumably to prevent such pathological changes, at least some cells—i.e. glia—have developed very effective volume regulatory mechanisms, such that influx of ions and water initiates transporter (and pump) activities to move unwanted ions—and water—out of the cell (Ballanyi and Grafe, 1988; Hoffman, 1992; Sánchez-Olea et al., 1993; Olson and Kimelberg, 1995; Holthoff and Witte, 1996). Whether such a homeostatic response is sufficiently rapid and robust in vivo to compensate for transient and/or large chronic changes in extracellular osmolarity is a matter of current debate (Andrew et al., 1997).

Swelling of glial and/or neuronal elements within the relatively limited volume of the CNS (i.e. within a closed system) obviously means that the extracellular space will shrink when the cells expand. Such activity-dependent changes in extracellular space have been demonstrated by a variety of methods, including tissue resistance measurements (Chebabo et al., 1995) and measures of diffusion of membrane-impermeant molecules (McBain et al., 1990; Nicholson, 1993). The changes in ECS volume may be rather small during normal physiological activities, but the changes may be considerable during synchronized excitatory activity—i.e. during epileptiform burst discharge. There are several possible consequences of such a decrease in ECS. For example: (a) effects of extracellular ion or transmitter accumulation would be magnified due to the reduced volume for dilution; (b) diffusion of neuroactive

elements, away from their targets/receptors, would be diminished due to reduced space and perhaps increased tortuosity; and (c) ephaptic interactions, mediated by current flow through extracellular space, would increase due to the higher resistance of the ECS.

## 4. Effects of hyper- and hypo-osmolarity on excitability

It has long been known that brain excitability is extremely sensitive to acute changes in osmolarity (for review, see Andrew (1991)). A rapid drop in extracellular osmolarity, such as produced with over-hydration, can induce seizure activity (Medani, 1987), whereas dehydration can result in neurological depression and coma (Fay, 1929). Indeed, in the early 1940s, hydration was used clinically as a test for seizure threshold/sensitivity in individuals thought to be epileptic (or seizure-prone) (Garland et al., 1943), much as sleep/wake techniques are used today. At the cellular level, reductions in extracellular osmolarity lead to hyperexcitability and enhanced epileptiform activity (Andrew et al., 1989; Roper et al., 1992). In contrast, epileptiform activity in hippocampal slices (induced with high levels of extracellular potassium or by zero-calcium bathing medium) can be attenuated and/or abolished with hyper-osmolar bathing medium (Traynelis and Dingledine, 1989; Dudek et al., 1990). Further, hypo-osmotic solutions potentiate stimulation-evoked population responses and excitatory postsynaptic currents in the hippocampal slice preparation (Saly and Andrew, 1993; Huang et al., 1997)—conditions associated with hyperexcitability.

The underlying mechanisms by which changes in extracellular osmolarity influence brain excitability were not obvious from previous studies. One plausible explanation is that neuronal ion channel function is modulated during osmolarity changes that give rise to alterations in extracellular space and associated cell swelling. In fact, other investigators have shown that changes in osmolarity, and resultant cell swelling, may modulate the activity of neuronal ion channels (Sackin, 1989; Kim and Fu, 1993; Langton, 1993; Paoletti and Ascher, 1994). These effects have been explained by the presence of membrane-bound ion channels that are sensitive to changes in membrane stretch (Sachs, 1990; Sackin, 1995). However, because these observations were made on cultured neurons, it was not known whether changes in osmolarity could influence ion channel function in a preparation that more closely preserved the 'microenvironment' found in vivo (i.e. with glia, neurons, dendritic and axonal arbors, and a limited extracellular space). Further, it was unclear whether such changes would affect neuronal excitability in a direction that would be consistent with the net hyperexcitability observed during hypo-osmolar conditions. For these reasons, we began to investigate whether the excitability of hippocampal neurons in an acute slice preparation is sensitive to changes in extracellular osmolarity.

Given the experimental results cited above, treatment of hippocampal slices with hypo-osmolar solutions should lead to a hyperexcitable condition. In our recent studies (Baraban et al., 1997; Baraban and Schwartzkroin, 1998), we have shown that hypo-osmolar extracellular solutions alter the function of delayed-rectifier potassium channels in a manner specific to particular neuron types. A 10% decrease in osmolarity (with appropriate control for extracellular sodium concentration) resulted in enhanced voltage-activated potassium currents—but only in hippocampal interneurons (e.g. interneurons in str. lacunosum/moleculare, oriens/alveus, and the hilus), not principal cell types (e.g. CA1 and subicular pyramidal cells, and mossy cells) (Fig. 2). An increase in delayed rectifier potassium currents should be associated with decreased action potential discharge frequency—a result confirmed in our experiments. By reducing the firing activity of inhibitory cells, without altering the activity of excitatory elements, the reduction in extracellular osmolarity would increase hippocampal excitability by decreasing inhibition in the neuronal network. That this effect is mediated by changes in extracelluar osmolarity (and not by mechanical stretch of the membrane) was suggested by its resistance to blockade by gadolinium (a mechanosensitive channel blocker) (Morris, 1990;

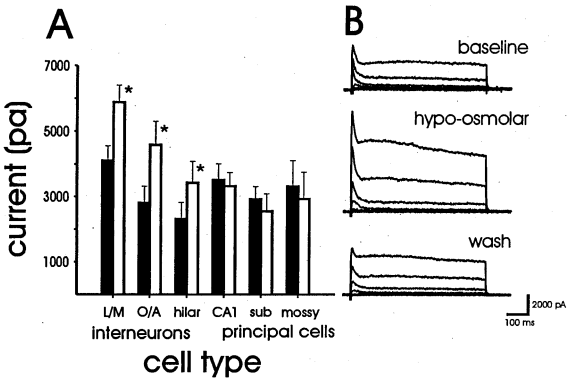


Fig. 2. Modulation of voltage-activated potassium currents by hypo-osmolar solutions in hippocampal neurons. (A) Plot of the amplitude of the delayed rectifier potassium current for six different hippocampal cell types: CA1 str. lacunosum-molecular interneurons (L/M); CA1 str. oriens/alveus interneurons (O/A); dentate hilar interneurons (hilar); CA1 pyramidal cells (CA1); subicular pyramidal cells (sub); and hilar mossy cells (mossy). Measurements were made at the 450-ms time-point of a 500-ms depolarizing voltage step to $+40$ mV. Normo-osmolar bathing medium was 297 Osm (dark bars); hypo-osmolar solution was 267 Osm (open bars). Data represent the mean $\pm$ S.E.M. (significance as $P < 0.05$, Student's $t$-test). Note that only the interneurons, not the principal cells, showed a significant enhancement of the potassium current in hypo-osmolar bathing medium. (B) Representative whole-cell voltage-clamp recordings from an O/A interneuron in normo-osmolar bathing medium (baseline), in hypo-osmolar medium (hypo-osmolar), and in return to normo-osmolar medium (wash). Data adapted from Baraban and Schwartzkroin (1998).

Baraban and Schwartzkroin, 1998), and by the robustness of the effect even in outside-out patch recordings (where a 10% decrease in osmolarity would not be expected to produce any significant mechanical stretch) (Baraban et al., 1997).

Given that interneurons play a critical role in modulating hippocampal excitability, and that potentiation of voltage-activated potassium channels directly affects cell firing, it is not unreasonable to propose osmolarity change as a powerful mechanism in the modulation of brain function. According to such a hypothesis, neurons swell during intense electrical activity—e.g. a seizure—altering the ion concentration, osmolarity of the extracellular space, and consequently cell volume. If these changes lead to reduced inhibitory control of excitation (mediated by hippocampal interneurons), then the osmo-sensitivity of potassium channels may facilitate the seizure-related excitability of the affected brain region. Conversely, agents which play a critical role in regulating cell volume changes (e.g. furosemide) (Kimelberg and Frangakis, 1985; Walz, 1992) may reduce excitability by preventing osmolarity-induced potentiation of potassium channel function in inhibitory interneurons.

## 5. Blockade of chloride co-transport and its consequences for tissue excitability and epileptogenicity

Osmolarity-dependent changes in neuronal and glial properties is based on the complex set of ionic fluxes that are initiated when the ionic balance is perturbed. There are many examples of how excitability can be affected when the ionic composition of the extracellular space is manipulated (and thus ionic balance is altered) or when the ability of the system to respond to these alterations—i.e. via compensatory ionic flux—is blocked. To recapitulate a few familiar scenarios: (a) increasing extracellular potassium, or decreasing extracellular chloride, gives rise to epileptiform burst discharge (Yamamoto, 1972; Traynelis and Dingledine, 1988; Avoli et al., 1990); (b) blockade of neuronal voltage-dependent delayed rectifier potassium channels, with 4-aminopyridine, gives rise to hyperexcitability, consisting of synchronized burst discharge and ictal-like events (Perreault and Avoli, 1991); (c) blockade of inward rectifier potassium channels in glia results in extracellular potassium accumulation and tissue hyperexcitability (Janigro et al., 1997); and (d) blockade of GABA-modulated chloride channels in neurons, e.g. with picrotoxin, results in epileptiform burst discharge (Hablitz, 1984). While these familiar cases all deal with ion flux through channels that are voltage- or ligand-gated, control of ionic equilibrium is maintained critically also by ion exchangers, pumps and transporters. Investigators have shown, for example, that blockade of the Na,K-ATPase (e.g. with ouabain) leads, slowly but inevitably, to neuronal depolarization and a tendency toward long-lasting 'spreading depression'-like events (Haglund and Schwartzkroin, 1990).

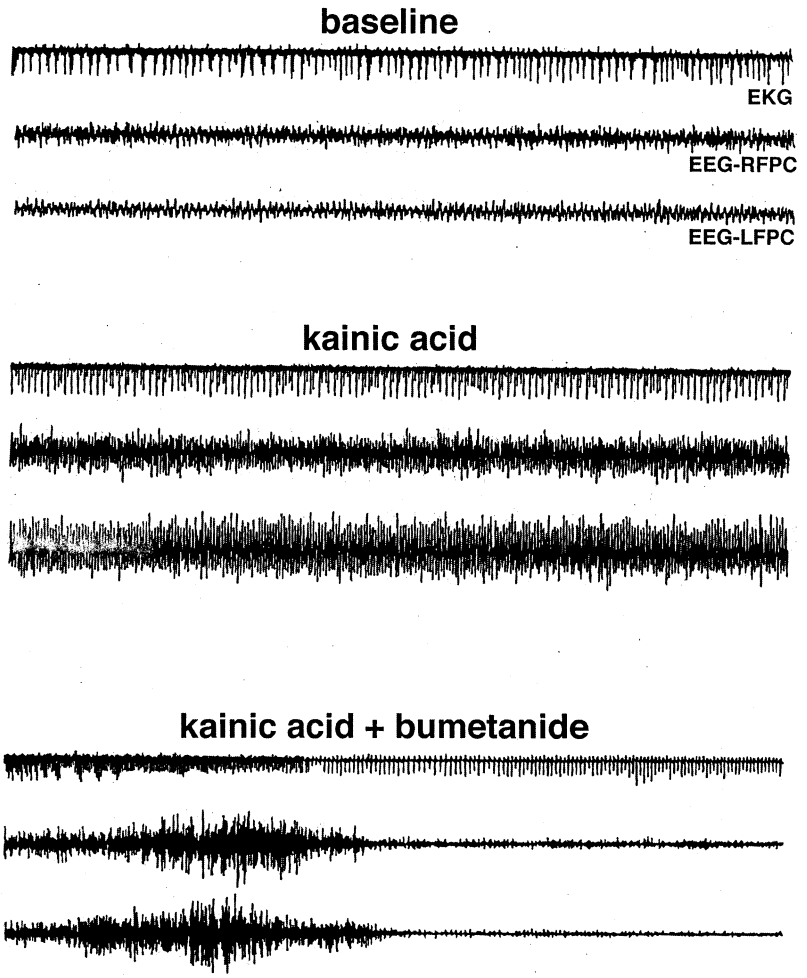


Fig. 3. Effect of bumetanide on kainate-induced electrographic status epilepticus in intact rat. Heart rate (EKG) and surface cortical electroencephalographic activity (EEG) were recorded from urethane-anesthetized rats (RFPC, right fronto/parietal cortex; LFPC, left fronto/parietal cortex) before (top traces) and after the animal was injected (10 mg/kg, i.v.) with kainic acid. Kainate (KA) induced a long-lasting (approximately 4 h), generalized electrographic discharge, consisting initially of isolated epileptiform 'spikes' (middle traces) and then involving periods of ictal-like activity (left part of bottom traces). The ictal activity was usually associated with a significant increase in heart rate. When KA-induced EEG 'status' had stabilized, the rat was injected with bumetanide (two boluses of 5 mg/kg, i.v. each, at 80 and 115 min after KA); within 20–30 min, epileptiform activity was abolished and heart rate returned to a near-normal level (bottom traces).

Our laboratory recently became interested in the effects of blocking chloride transport (and of altering extracellular chloride concentration). This interest was triggered by experiments which showed that furosemide, a blocker of the Na,K,2Cl and K,Cl transporters (Geck and Pfeiffer, 1985; Alvarez-Leefmans, 1990), blocks spontaneous epileptiform activities in a variety of models and preparations. Both in vitro (in hippocampal slices bathed with high potassium, bicuculline, 4-aminopyridine, low magnesium, or zero calcium) and in vivo (in anesthetized rat in which status epilepticus was produced with i.v. injections of kainic acid), furosemide blocked epileptiform activities. So, too, did bumetanide (Fig. 3), a drug that is more specific for the chloride co-transporters than furosemide (Haas, 1994) (and a considerably more potent antago-

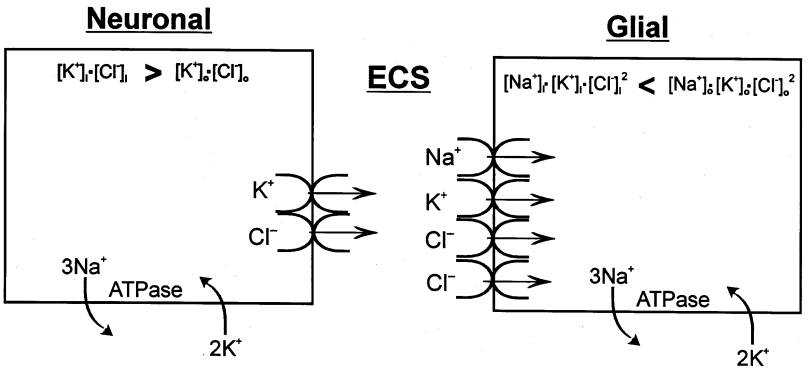


Fig. 4. Diagram showing the proposed function of K,Cl and Na, K, 2Cl co-transporters in neurons and glia. In neurons, the Na-independent co-transporter normally moves chloride out of the cell, driven by the high intracellular potassium concentration (established by the Na,K-ATPase). This efflux of chloride maintains a gradient that produces an inhibitory (hyperpolarizing) potential when GABA-mediated chloride channels are opened. In glia, the sodium-dependent chloride transporter drives chloride and potassium into the cell, providing a means for clearing high levels of extracellular potassium (along with voltage-dependent, inwardly rectifying potassium channels).

nist). Our result was surprising, since earlier studies had shown that by blocking the Cl transporter (presumably on neuronal membrane), furosemide led to hyperexcitable responses to afferent stimulation in hippocampal slices (Misgeld et al., 1986; Thompson et al., 1988; Thompson and Gähwiler, 1989). This latter effect was explained by the ability of furosemide to block chloride extrusion from neurons, with a consequent degradation in the normal chloride gradient such that GABA-A mediated inhibition becomes less effective. The 'antiepileptic' furosemide effect had a longer time course than the hyperexcitable effect, and was seen after a brief period of hyperexcitability.

We have postulated that the antiepileptic effect of furosemide (and bumetanide) is a function of blockade of the inward, sodium-dependent movement of chloride mediated by the Na,K,2Cl transporter thought to be localized to glial membrane (Fig. 4) (see below). If such were the case, then lowering extracellular chloride should have the same effect as applying furosemide, since a 'rate-limiting' component of this transporter is the chloride driving force. Preliminary experiments in our laboratory (Hochman and Schwartzkroin, 1997) have confirmed that low extracellular chloride and furosemide do indeed have similar effects, producing a similar sequence of changes in excitability: first, a brief (20–30 min) period of hyperexcitability, with spontaneous epileptiform bursting activity and large stimulus-evoked potentials; second, a longer period (60–90 min) characterized by loss of spontaneously-occurring epileptiform events, but during which stimulation continues to evoke burst discharges; and third, a period in which the stimulus threshold for evoking epileptiform bursts rises and even stimulus-evoked cellular activity becomes desynchronized.

These results highlight an important concept—that hyperexcitability per se cannot be equated with epileptiform activity; spontaneous, synchronized discharge was blocked by furosemide, while facilitating stimulus-evoked burst discharges. The experiments also suggest that an agent that blocks chloride co-transport—and thus hyper-activity-dependent cell swelling—can antagonize spontaneous epileptiform activity. This interpretation of our data is consistent with other observations (from our laboratory as well as other investigators) showing that furosemide blocks activity-dependent alterations in extracellular space (monitored with optical imaging techniques) (MacVicar and Hochman, 1991). It is important to note, however, that blockade of the chloride co-transporter results in many changes beyond that of cell swelling—and particularly in complex ionic re-distributions. The relative contributions of these ionic shifts to the antiepileptic effects of furosemide remain unclear.

## 6. Neuronal versus glial actions in maintaining homeostasis of the extracellular milieu

Both neurons and glia have ion channels, pumps, and transporters that are critical for maintenance of normal activities. As mentioned above, blockade of the Na,K-ATPase gradually leads to abnormal electrophysiological activity. However, it has long been postulated that one of the major functions of astrocytes in the CNS is to maintain the ionic balance, thus providing an ionic milieu that optimizes neuronal function. These glia have been thought to take up excess potassium (produced by neuronal activity)—i.e. potassium 'buffering' (Somjen, 1984; Walz and Hinks, 1985)—and move it to areas of lower concentration—i.e. potassium 'siphoning' (Newman, 1993; Cooper, 1995). That at least some astrocytes perform this function is suggested by recent experiments in which inwardly rectifying potassium channels on glia were blocked with cesium; under such conditions, slow stimulation of the tissue—which normally has no pathophysiological effects—led to gradual epileptiform activity (Janigro et al., 1997).

The results of our furosemide experiments, reported above, suggest that glial-mediated movement of ions—via the Na,K,2Cl-transporter—may also be critical to regulation of excitability. Ion transport into cultured astrocytes has been shown to be dependent upon a furosemide-sensitive co-transporter (Tas et al., 1986, 1987). Investigators have also demonstrated that the chloride co-transporter system is involved in volume regulation in astrocytes in response to changes in osmolarity (Kimelberg and Frangakis, 1985; Walz, 1992). Although these studies have implicated Na,K,2Cl co-transport function in astrocytes, immunohistochemical and molecular biological studies have indicated a primarily neuronal expression pattern for chloride co-transporters in the mammalian brain. In situ hybridization for KCC2 (a gene encoding a loop diuretic-sensitive K,Cl co-transport molecule) indicated a neuron-specific expression in all layers of the cortex, hippocampus, and cerebellum (Payne et al., 1996)—a pattern consistent with our hypothesized localization of the K,Cl co-transporter (see Fig. 4). However, Plotkin et al. (1997) recently demonstrated that mBSC2 (or NKCCl)—a gene encoding a mouse bumetanide-sensitive Na,K,2Cl co-transporter molecule—is widely expressed in neuronal cell bodies and dendrites in the rat brain. Co-localization studies with an antibody to glial fibrillary acidic protein failed to demonstrate the expression of this Na,K,2Cl co-transporter in astrocytes. Further, the authors of this immunohistochemical study suggested that this co-transporter is prominently expressed on dendrites; they interpreted their data to support the concept of heterogeneous distribution of intracellular chloride within a given neuron, and postulated that this intracellular chloride gradient is maintained by a spatially localized (to dendrite) furosemide-sensitive co-transporter (see also Hara et al. (1992, 1993)).

Chloride co-transporter function has long been thought to be directed primarily to move chloride out of cells. Certainly, the sodium-independent transporter (shown to be neuronally localized) moves Cl out of neurons—and blockade of this transporter should lead to hyperexcitability (as had been previously reported)—the short-term response to furosemide. The antiepileptic effect of furosemide, however, is hard to explain in terms of blockade of neuronal chloride efflux (Thompson et al., 1988). So, too, is the antiepileptic action of low extracellular chloride concentration. These results seem more consistent with a transporter that normally moves chloride into the cell (whether located on neuronal dendrite or glia)—driven either by the sodium gradient or by potassium which accumulates in the extracellular space.

The functions of neuronal and glial pumps, transporter, and ion channels are obviously interactive, and there are presently few adequate pharmacological tools to distinguish between them. We would predict, based in part on our own experimental results, that glial-specific isoforms of pumps, transporters, and even channels will eventually be identified. In theory, the differences in localization can be established based on biophysical differences in pharmacological sensitivities to agonists/antagonists. Because these processes are all so inter-dependent, isolating a single mechanism to neuron or glia is an almost impossible

task. Clearly, however, we should include glia, as well as neurons, as targets for newly-developed agents designed to control the ionic dis-equilibria that facilitate seizure activities.

## 7. Practical and clinical applications

Dramatic changes in ionic balance are associated with the high levels of neuronal discharge which occur during seizures. These changes have generally been viewed as consequences of seizure activity, and therefore perhaps not critical to mechanisms underlying seizure genesis—and thus somewhat irrelevant to the development of new antiepileptogenic treatments. It should be clear, however, that the ionic changes associated with seizure activity lead to significant 'positive feedback', such that neuronal excitability and synchronization are enhanced. The effect of positive feedback is seen clearly in the variation in extracellular potassium levels associated with hyperexcitability. If uptake and redistribution of potassium is inadequate, then extracellular potassium levels rise. This change will have consequences for neuronal (and glial) membrane potential, as well as for potassium efflux from neurons (and potassium uptake into glia)—processes that normally helps to maintain neurons at a relatively hyperpolarized level. Breaking this positive feedback loop may provide a window through which one can control/terminate seizure activity. In a sense, our current antiepileptic drugs (AEDs) do just that. But it may be useful to think about control of ionic homeostasis in a more global sense, not just as an adjunct of dysfunction in neurotransmission. Furosemide administration, itself, may be a useful treatment under special conditions—e.g. intractable status epilepticus. And although furosemide may not be practical as a chronically-administered AED, related agents that are targeted to brain (glial?)-specific transporters may be available in the not-too-distant future. Further, it should now be clear that even rather subtle changes in pump, transporter, or ion channel function can, over time, initiate seizure events. The gradual build-up of unwanted ions (or neurotransmitters) may lead to the sudden explosion of seizure activity. We need a more detailed understanding of how ionic balance changes at seizure onset—and whether control of those changes could lead to effective antiepileptogenic treatment.

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