Extracellular space ionic composition, volume and geometry during neuronal activity and pathological states

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Introduction

Experiments employing ion-selective microelectrodes revealed that transmembrane ionic fluxes during neuronal activity and pathological states result in transient changes in CNS extracellular space (ECS) ionic composition and volume. This led to the concept of the ECS as a communication and modulation channel (Nicholson 1980; Syková 1983; Syková 1992a; Bach-y-Rita 1993), whose ionic and chemical composition, size and geometry depend on neuronal activity and glial cell function. ECS size and geometry affect the movement (diffusion) of various neuroactive substances in the CNS. It is now accepted that although synaptic transmission is the major means of communication between nerve cells, it is not the only one. Substances can be released non-synaptically, diffuse through ECS and bind to extrasynaptic, high-affinity receptors. This type of non-synaptic transmission was recently termed "volume transmission" (Fuxe and Agnati 1991). The neuroactive substances may diffuse through the ECS to target neurons, glia or capillaries without requiring synapses. This mode of communication can function between neurons as well as between neurons and glial cells, and may be a basis for mechanisms of information processing in functions involving large masses of cells such as vigilance, sleep, chronic pain, hunger, depression, plastic changes etc. On the other hand, impairment of the ionic homeostasis and glial swelling during pathological states lead to impairment of CNS function and neuronal damage.

Methods

Measurements of dynamic changes in the extracellular concentration of biologically important ions *in vivo* as well as *in vitro* become possible with the introduction of ion-selective microelectrodes (ISMs) (for review see Syková 1983, 1992b). An ISM that consists of a liquid membrane (liquid ion-exchanges, ion-carrier) placed in the tip of a glass microelectrode is a miniaturized potentiometric sensor. When introduced into tissue or solution where the activity of the respective ion is to be measured, a Nernst potential develops across the ion-exchanger membrane, i.e. one measures a potential that changes logarithmically with the activity of the ion for which the ion-

exchanger is selective. To eliminate all types of electrical activity including membrane, synaptic and action potentials, double-barrelled microelectrodes are used, which have an ion-exchanger in one channel, while the other channel serves as the reference electrode. Since the reference electrode also records electrical activity in the tissue, the signal from it is used to cancel out the undesired component (Fig.1). ISMs, e.g. tetraethyl- or tetramethylammonium-selective ones (TEA^+-ISM or TMA^+-ISM), are also used to follow the diffusion of an extracellular marker in the ECS. Dynamic changes in the size of ECS and the apparent diffusion coefficient in the tissue can be studied by the iontophoretic application of TEA^+, TMA^+ or other ions to which cell membranes are relatively impermeable and which therefore stay in the ECS. This so-called real-time iontophoretic method, which follows the diffusion of extracellular markers applied by iontophoresis (Nicholson and Phillips 1981), was utilized in our studies to measure diffusion characteristics of the ECS. Fig. 4 shows examples of the diffusion curves of TMA^+ in CNS. The diffusion in ECS is constrained by two geometrical factors: extracellular space volume fraction (α) and tortuosity (λ) (for description see Fig. 3). In addition, the diffusion between two points can be affected by either specific or non-specific uptake (k'), a factor describing loss of material across cell membranes. The α, λ and k' values can be determined by computation procedure developed by Nicholson and Phillips (1981). Their study showed that if we incorporate factors α, λ and k' into Fick's law, diffusion in CNS is described fairly satisfactorily. The three diffusion parameters can be extracted by non-linear curve-fitting simplex algorithm operating on the diffusion curve (see Nicholson and Phillips 1981; Lehmenkühler et al. 1993; Syková et al. 1994b).

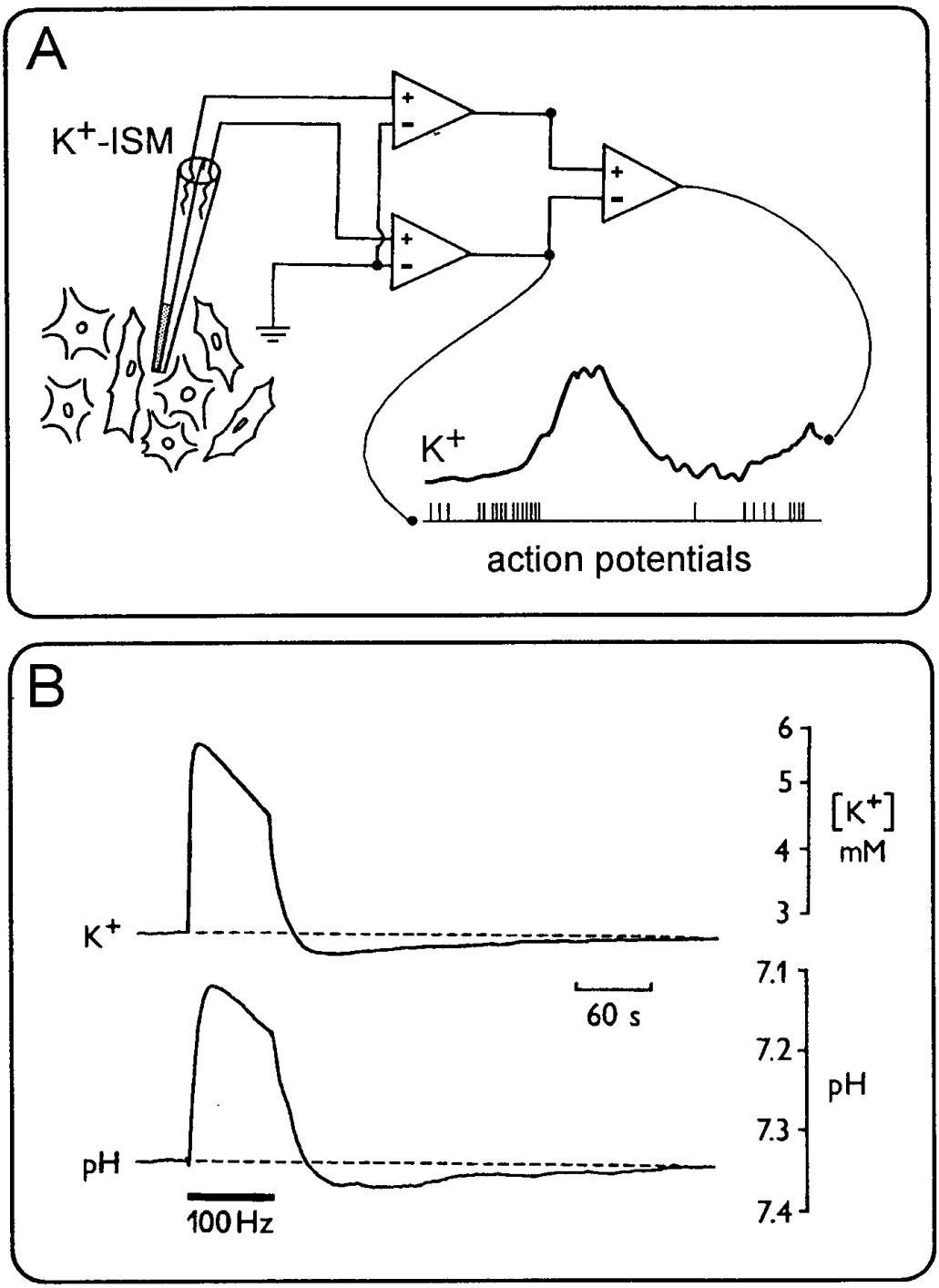


Fig. 1. Dynamic $[K^+]_e$ and pH_e changes measured with ion-selective microelectrodes. **A:** Increase in $[K^+]_e$ in close vicinity to the spontaneously active neuron is associated with bursts of action potentials (AP). Recordings in mesencephalic reticular formation. **B:** $[K^+]_e$ and pH_e changes in dorsal horn of segment L4 of rat spinal cord evoked by repetitive bipolar electrical stimulation with acupuncture needles (100 Hz, 60 s) in plantar muscles of the ipsilateral hind paw. Horizontal bar indicates stimulus duration. Two K^+- and pH-sensitive microelectrodes were inserted separately from dorsal spinal surface.

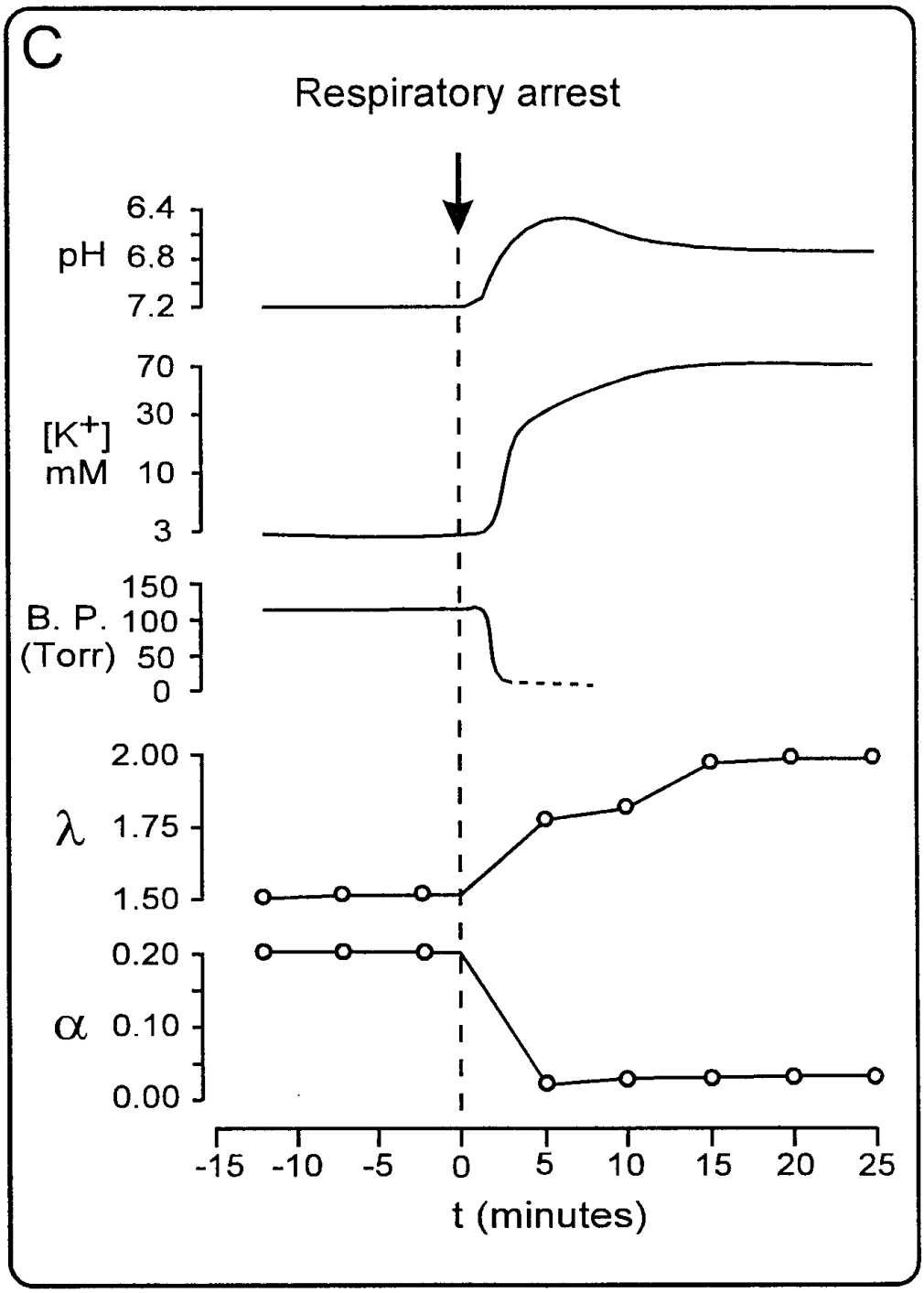


Fig. 1.C: Dynamic $[K^+]_e$ and pH_e changes measured with ion-selective microelectrodes. Increase in extracellular $[K^+]_e$, and decrease in pH_e in L4 spinal segment as recorded after respiratory arrest. BP, concomitantly recorded changes in blood pressure. α, extracellular space volume fraction; λ, extracellular space tortuozity.

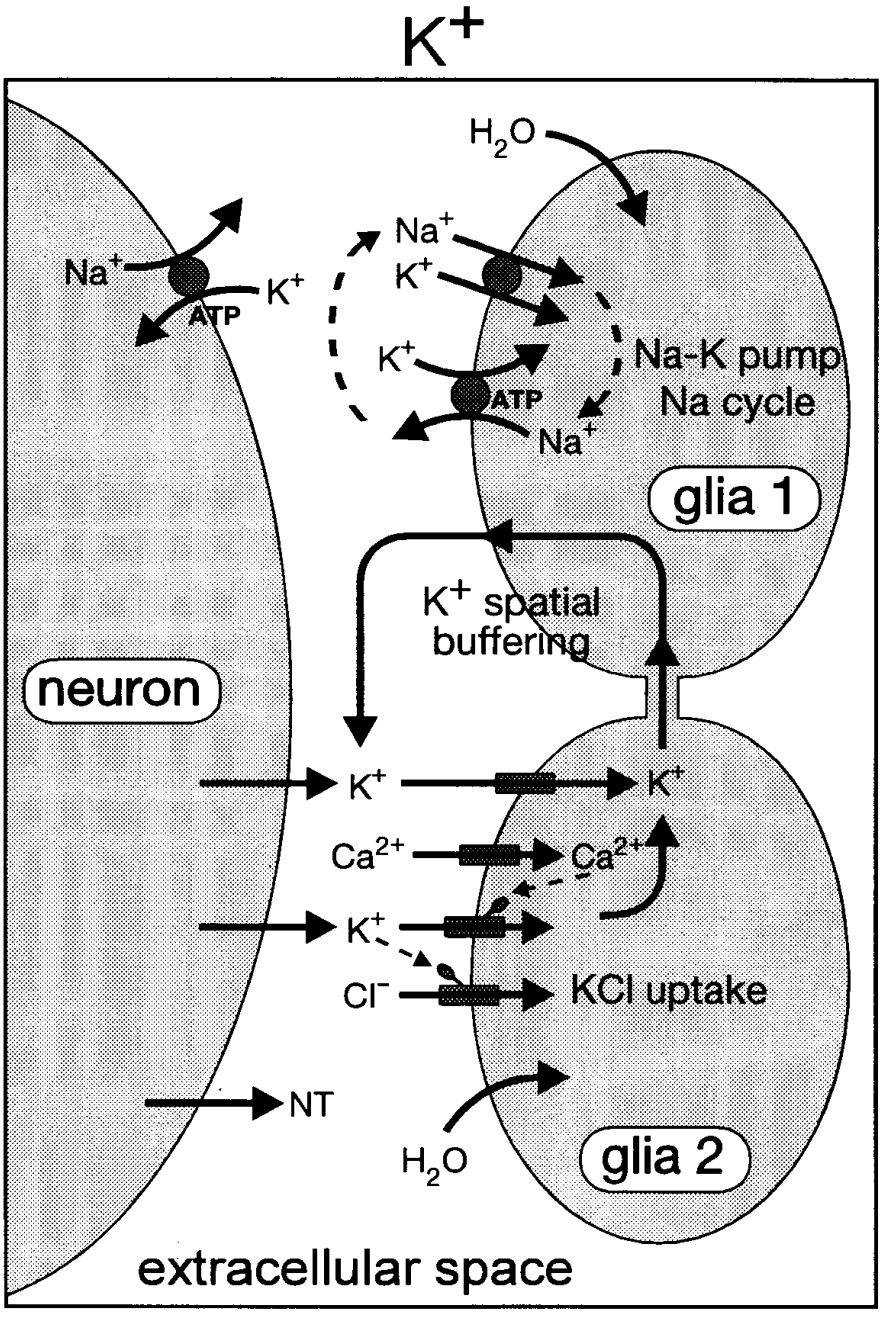


Fig. 2.A. Mechanisms involved in K^+ homeostasis: In neurons homeostasis is ensured by Na^+/K^+ pump which is also present in glia in so-called Na^+ cycle. Glia ensures extracellular K^+ homeostasis by spatial buffering mechanism, by KCl uptake and by K^+ channel opening, which is facilitated by an intracellular rise in Ca^{++}.

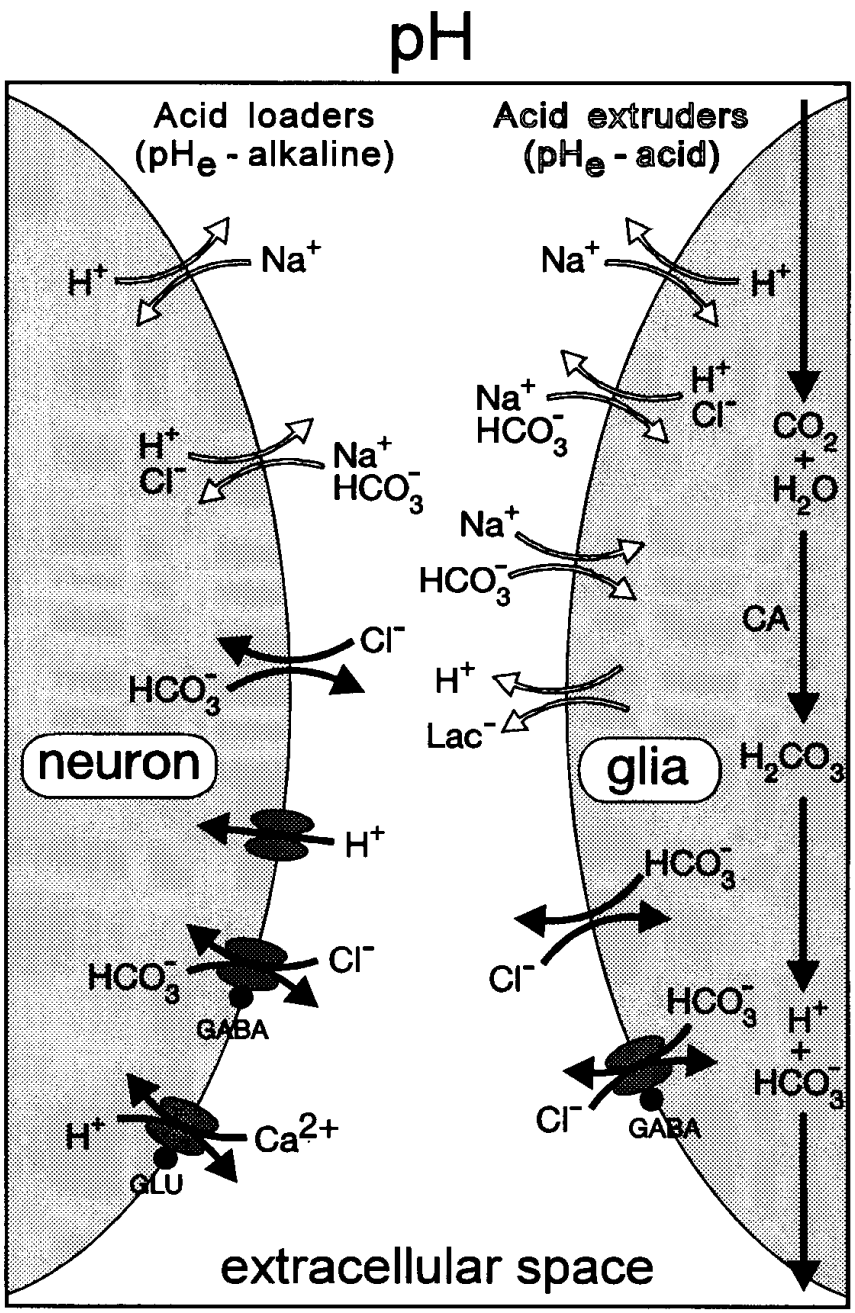
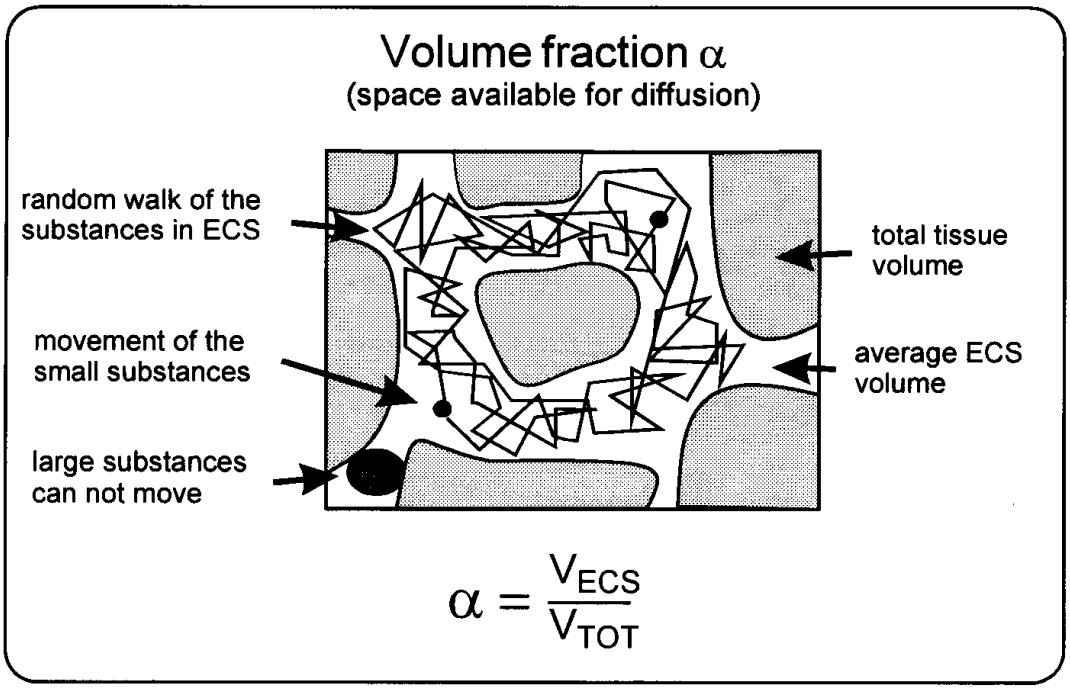


Fig. 2.B: Mechanisms involved in pH homeostasis: Some of the membrane transport processes regulating intra- and extracellular pH, such as Na^+/H^+ exchange and $Na^+/H^+/Cl^-/ HCO_3^-$ cotransport, are present in both neurons and glia; others are specific for neurons (H^+ channels, H^+ or HCO_3^- permeability of the ionic channels opened by GABA or glutamate) or for glia as the voltage-dependent Na^+ - HCO_3^- cotransport and lactate extrusion. Glial cell membrane is also easily permeable for CO_2, which react with H_2O to form bicarbonic acid, which in turn is quickly dissociated to water and protons. This reaction is catalyzed and sped up by the enzyme carbonic anhydraze (CA), which is present in glia. Some of the membrane transport mechanisms result in alkaline shifts in pH_e (acid loaders, black arrows) while others results in acid shifts in pH_e (acid extruders, white arrows). It is evident that acid loaders are dominant in neurons, while acid extruders are dominant in glia (for details see Chesler 1990, Syková 1992).



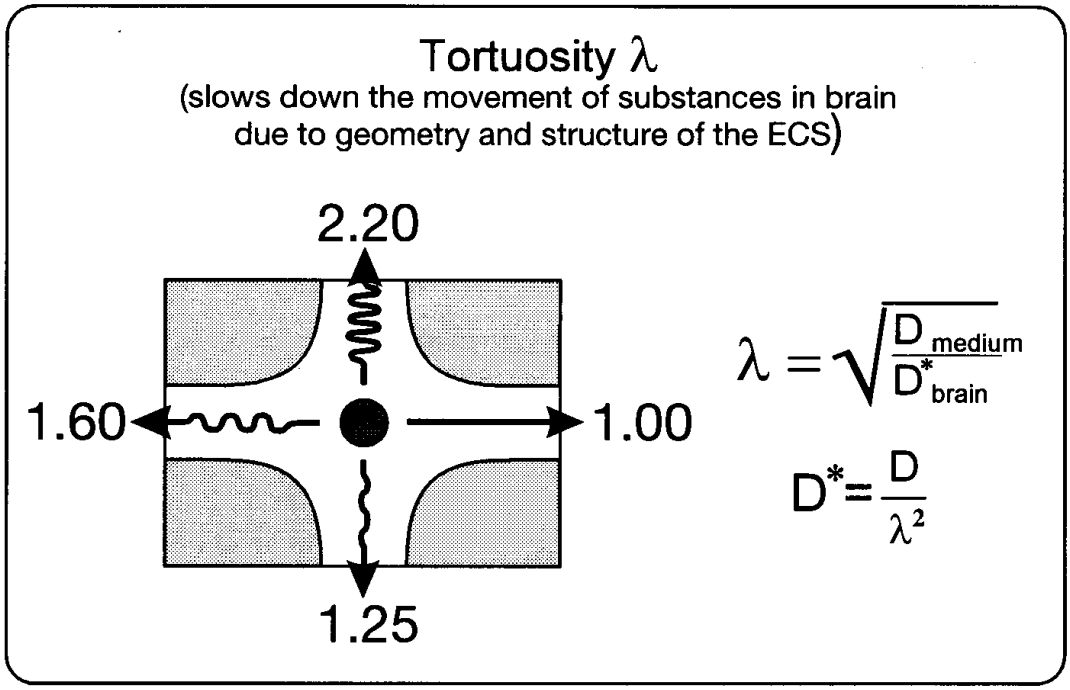


Fig. 3. Concept of extracellular space volume fraction (α) and tortuosity (λ). VECS is volume of the ECS, VTOT is the total brain (spinal cord) volume. D is free TMA+ diffusion coefficient, D* is TMA+ apparent diffusion coefficient (ADCTMA) in nervous tissue. Values of λ correspond to: 1.00 - free solution, 1.60 - adult rat cortex, 1.25 - severe edema, 2.20 - severe anoxia/ischemia.

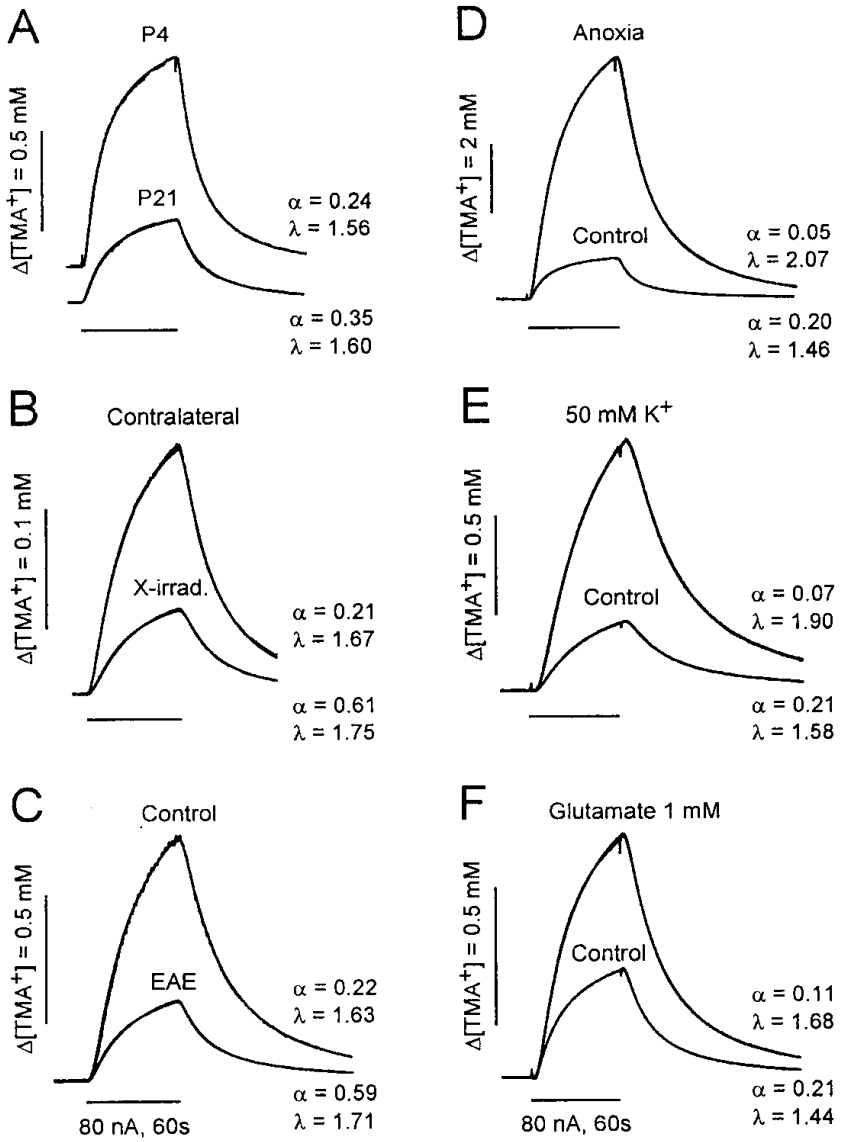


Fig. 4. Tetramethylammonium ion (TMA^+) diffusion curves and ECS diffusion parameters in brain and spinal cord of the rat during physiological and pathological conditions. Volume fraction (α) and tortuosity (λ) and non-specific uptake (k', not shown) were determined from extracellular concentration-time profiles of TMA^+ by real-time iontophoretic method using TMA^+-ISMs (see Nicholson and Phillips, 1981). In principle, TMA^+ diffusion profiles were first analyzed in control medium (0.3 % agar) where, by definition, $\alpha=\lambda=1$ and $k'=0$, and parameters, such as electrode transport number (n) and TMA^+ diffusion coefficient (D) were extracted by curve fitting (not shown). Knowing n and D, the parameters α, λ and k' can be obtained when the experiment is repeated in the nervous tissue. Representative records of the TMA^+ diffusion curves, with α and λ shown with each curve: A - diffusion curve layer VI in rat cortex of 4-day-old rat (P4); B - diffusion curve in cortex X-irradiated at P1; the curve was recorded in layer V at P18, contralateral - diffusion curve recorded in non-irradiated contralateral hemisphere of the same rat; C - diffusion curves from spinal dorsal horn of the control rat at P90 and in the rat with experimental autoimmune encephalomyelitis and with clinical signs of paralysis (EAE); D - diffusion curves in normal cortex, lamina V (control) and in the same place after cardiac arrest (anoxia) in adult rat; E and F - diffusion curves in isolated rat spinal cords at P10 and curves from the same spinal cords after 20 min of application of 50 mM K or 1 mM glutamate in isoosmotic superfusing solution.

Results

Activity-related transient changes in extracellular K^+, pH and Ca^{++}

Dynamic changes in $[K^+]_e$ were recorded in the immediate vicinity of individual neurons in the mesencephalic reticular formation (MRF) of the rat. MRF is recognized as a structure with high spontaneous activity level. During a burst of spontaneous action potentials, $[K^+]_e$ steadily increases by as much as 0.2 mM (Syková et al. 1974). The neurons start to fire again at the same time the K^+ elevation returns to the "resting" K^+ baseline (Fig. 1), suggesting that accumulation of K^+ in the ECS blocks spontaneous activity.

An activity-related increase in extracellular K^+ concentration ($[K^+]_e$), alkaline and acid shifts in extracellular pH (pH_e) and a decrease in extracellular Ca^{++} concentration ($[Ca^{++}]_e$) have been found to accompany neuronal activity in a variety of animals and brain regions, in vivo as well as in vitro (for review see Syková 1983; Chesler 1990; Syková 1992a). It has been recognized that their origin and mechanisms are similar, but the amplitude and sequence vary with brain region. Most frequently, neuronal activity results in an increase in $[K^+]_e$, a decrease in $[Ca^{++}]_e$ and a fast extracellular alkaline shift, followed by a slower but longer-lasting acid shift (Fig. 1, Syková et al. 1974, Jendelová and Syková 1991, Syková and Svoboda 1990). After sustained adequate stimulation of the afferent input or after repetitive electrical stimulation, the ionic transients reach a certain steady state, the so-called "ceiling" level, which in the mammalian cortex is about 7 mM K^+ (Heinemann and Lux 1977) and in the mammalian spinal cord 6-8 mM K^+ (Kriz et al. 1975; Syková and Svoboda 1990). The alkaline shifts in mammalian cortex, cerebellum or spinal cord do not exceed 0.02 pH units, while the acid shifts are about 0.2 pH units. For example, after the tetanic stimulation of the sciatic nerve (30-100 Hz) the $[K^+]_e$ "ceiling" level in the adult rat or cat spinal cord is attained in 5-8 s, while the "ceiling" level of the acid shift is reached in 10-20 s. When stimulation is continued beyond this, a gradual decrease of both transients, $[K^+]_e$ and pH_e, occur after the ceiling levels are reached (Fig. 1) due to homeostatic mechanisms in neurons and glia (Fig. 2).

Adequate stimulation, such as innocuous stimuli, acute nociceptive stimuli, or peripheral tissue injury of a hind paw, result in activity-related transient K^+ and pH_e changes in the spinal dorsal horn (Svoboda et al. 1988; Syková and Svoboda 1990). In the visual cortex of the cat (Singer and Lux 1975) and in the ectostriatum of chicks (Syková et al. 1990), a rise in $[K^+]_e$ and pH shifts accompany neuronal activity during stimulation of the receptive field with visual stimuli. Stimulation with pure-tone acoustic stimuli over a frequency range of 500 Hz - 25 kHz produced changes of about 1 mM K^+ in the organ of Corti, with the maximal change between supporting cell and inner hair cell (Johnston et al. 1989). The K^+ and pH changes evoked by adequate stimulation are generally of smaller amplitude than those evoked by electrical stimulation, with an increase in $[K^+]_e$ of about 1-3 mM and an acid shift of up to about 0.05-0.1 pH units, but they can last longer. For example, after peripheral injury the $[K^+]_e$ increase and pH_e decrease in the spinal dorsal horn begin 2-10 min after injury, reach their maximum in 15-40 min and then persist for more than 2 h.

Ionic changes during postnatal development

Stimulation-evoked transient changes in $[K^+]_e$ and pH_e in the rat spinal cord are different during early postnatal development, presumably because of incomplete glial cell function. Glial cells play an important role in buffering changes in the concentration of ions and small molecules in the tortuous extracellular space (Fig. 2). The extensive area of glial cell membranes across which ions and small molecules can move provides an efficient transport system to minimize the drastic changes in the extracellular space which impair neuronal function. Besides their role in K^+ and amino acid homeostasis, glial cells play an important role in buffering changes in extracellular pH.

Studies on K^+ and pH_e in the spinal cord during maturation underscore the role of glial cells in the maintenance of extracellular ionic homeostasis. Both $[K^+]_e$ and pH_e activity-related changes were studied in spinal cords during early postnatal days, since glial cell proliferation, maturation and myelination occur postnatally, and more slowly than maturation of neurons. In the neonatal rat spinal cord, stimulation-evoked changes in $[K^+]_e$ are much larger than in the adult animal. In

the ECS alkaline shifts dominate, while in adult animals acid shifts dominate (Jendelová and Syková 1991; Syková et al. 1992). For example, at P3-P6, the $[K^+]_e$ changes evoked in the dorsal horn by a single electrical stimulus were as large as 1.5-2.5 mM. Such changes in $[K^+]_e$ can be evoked in the adult rat spinal cord only with stimulation at a frequency about 30 Hz (Svoboda et al. 1988). At P3-P6 single as well as repetitive electrical stimulation evoked a dominant alkaline shift which was followed by a smaller poststimulation acid shift when the stimulation was discontinued. At P10-P14, when gliogenesis in rat spinal cord gray matter peaks, the K^+ ceiling level decreases and the stimulation evokes acid shifts of about 0.1-0.2 pH unit, which are preceded by scarcely discernible alkaline shifts, as is also the case in adult rats.

Activity-related $[K^+]_e$ and pH_e changes in spinal cords were also studied after "early" postnatal X-irradiation (PI) - a procedure which blocks gliogenesis but leaves the neurons intact (Syková et al. 1992). In X-irradiated animals, the stimulation-evoked $[K^+]_e$ increase is larger than in control animals, and stimulation evokes a dominant alkaline shift. These results show that postnatal X-irradiation which blocks gliogenesis impairs the normal development of K^+ and pH_e homeostasis.

Mechanisms of extracellular K^+ and pH_e homeostasis

Fig. 2 shows that K^+ and pH homeostasis in the CNS is ensured by a variety of mechanisms in both neurons and glial cells (for reviews see Syková 1983; Chesler 1990; Syková 1992a). After returning to the prestimulation $[K^+]_e$ values, a transient decrease in $[K^+]_e$ occurs below the original K^+ baseline, so-called poststimulation K^+-undershoot (Fig. 1, Kríz et al. 1975). This K^+-undershoot is blocked by ouabain or during hypoxia. These findings suggest that the recovery of the activity-related $[K^+]_e$ change is dependent at least partly on Na^+/K^+ pump activity in neurons and presumably also in glial cells. Besides the Na^+/K^+ pump, the ECS K^+ homeostasis is maintained by 3 other mechanisms ensured by glia:

(1.) K^+ spatial buffering,
(2.) KCl uptake and
(3.) Ca^{++}-activated K^+ channels (Fig. 2).

Extra- and intracellular pH (pHi) homeostasis is ensured by a variety of mechanisms in neurons and glia, as summarized in Fig. 2. The membrane transport processes which lead to the changes in pHi and pHe are either non-specific (both in neurons and glia) or specific for neurons or glia. We can divide them into acid loaders and acid extruders. From Fig. 2, it is evident that in neurons acid loaders dominate (making the pHe alkaline), while in glia acid extruders dominate (making the pHe acid). This is further evidence for the neuronal origin of the alkaline shifts and the glial origin of the activity-related acid shifts. In addition, stimulation-evoked alkaline shifts are abolished by the blockage of synaptic transmission by Mn^{++}or Mg^{++}, while the acid shifts are unaffected (Jendelová and Syková 1991). Stimulation-evoked alkaline shifts in the isolated rat spinal cord are substantially blocked by the GABA antagonist picrotoxin and by glutamate receptor antagonists and channel blockers such as MK801 (non-competitive NMDA receptor antagonist and channel blocker) and CNQX (competitive AMPA/kainate receptor antagonist) (Syková et al. 1992; Jendelová et al. 1994). Activity-related extracellular acid shifts are a consequence of neuronal acidosis, extracellular K+ increase, glial depolarization and alkaline shift in glial pHi, all leading to stimulation of classic acid extrusion systems in glial cells.

Extracellular ionic changes during pathological states

Pathological states are accompanied by lack of energy, seizure activity, excessive release of transmitters and neuroactive substances, neuronal death, glial cell loss or proliferation, glial swelling, production of metabolites and loss of ionic homeostasis. Dramatic K^+ and pH_e changes in the brain and spinal cord occur during anoxia and/or ischemia. In adult rats, within 2 minutes after respiratory arrest, blood pressure begins to increase and pH_e begging to decrease (by about 0.1 pH unit), while the $[K^+]_e$ has not yet changed (Fig. 1). With the subsequent blood pressure decrease, the pH_e decreases by 0.6-0.8 pH units to an actual pH level of 6.4-6.6. This increase is accompanied by a steep rise in $[K^+]_e$ to about 50-70 mM (Syková and Svoboda 1990; Syková et al.

1994b), and by decreases in $[Na^+]_e$ to 48-59 mM, $[Cl^-]_e$ to 70-75 mM, $[Ca^{++}]_e$ to 0.06-0.08 mM, pH_e to 6.1-6.8 (for review see Erecinska and Silver 1994), and a decrease in ECS volume of 4-7 % (Fig. 1, Syková et al. 1994a, Syková et al. 1994b). During early postnatal development (P5), the anoxia-evoked $[K^+]_e$ increase and pH_e decrease are of about the same magnitude as in adult rats, but these changes develop about 10 times more slowly (Vargová et al. 1994). This may explain the well-known resistance of immature CNS to anoxia.

Dynamic changes in extracellular space volume and geometry.

Diffusion in ECS obeys Ficks's law subject to two important modifications (Nicholson and Phillips 1981). First, diffusion in ECS is constrained by the restricted volume of the tissue available for diffusing particles, i.e. by the extracellular volume fraction (α) (Fig. 3). The concentration of a released substance in the ECS is therefore greater than it would be in a free medium (e.g. 0.3 % agar). Second, the free diffusion coefficient, D, is reduced by the square of the tortuosity (λ) to an apparent diffusion coefficient $D^* = D/\lambda^2$, because a diffusing substance encounters obstructions, i.e. an increase in path length for diffusion between two points, and because the diffusing substance encounters membrane obstructions, glycoproteins, macromolecules of the extracellular matrix, charged molecules and glial cell processes (Fig. 3, for details see Methods).

Changes in ECS diffusion parameters (ECS volume decrease and tortuosity increase or D* decrease) result from activity-related transmembrane ionic shifts and cell swelling under physiological conditions, e.g. electrical or adequate stimulation (Svoboda and Syková 1991). Indeed, in the spinal cord of the rat or frog repetitive electrical stimulation results in an ECS volume decrease from about 0.24 to about 0.12, i.e. a decrease of as much as 50% (Svoboda and Syková 1991; Syková 1992a). The changes in ECS diffusion parameters outlast the stimulation for many minutes or even hours. The diffusion parameters differ during development (Fig. 4A) and ageing. The ECS volume in cortex and subcortical white matter (corpus callosum) is almost doubled in the newborn rat (α = 0.30-0.40) and diminishes with age, while the variations in tortuosity (λ = 1.5-1.6) are not statistically significant at any age (Lehmenkühler et al. 1993). A reduction in ECS volume fraction correlates well with gliogenesis and myelination. The constancy of the tortuosity shows that diffusion of small molecules is no more hindered in the developing brain than in that of the adult. The large ECS volume fraction of the neonatal brain could significantly dilute ions, metabolites and neuroactive substances released from cells, relative to release in adults, and may be a factor preventing anoxia, seizure and spreading depression in young individuals.The diffusion parameters could also play an important role in the developmental process itself. Recently we observed that the volume fraction is either not changed or increased in aged rats, but the tortuosity is increased, suggesting that diffusion of the ions and neuroactive substances may be hindered (Mazel, Roitbak and Syková, unpublished observations).

During hypoxia and terminal anoxia (Fig. 4 D), the ECS volume in rat cortex or spinal cord decreases from about 0.20 to about 0.04, tortuosity increases from 1.5 to about 2.2 and non-specific uptake significantly decreases (Hansen and Olsen 1980; Syková et al. 1994a; Syková et al. 1994b). The same ultimate changes were found in neonatal and adult rats, in gray and white matter, in cortex, corpus callosum and in spinal cord. However, the time course in neonatal rats was about 10 times slower than in adults (Syková et al, 1994a). In our recent studies using diffusion-weighted 1H MRS/MRI, we measured the apparent diffusion coefficient of water (ADCW). Anoxia evoked similar decreases in ADCTMA (measured by the iontophoretic method and ISMs) and ADCW (measured by the NMR method). Moreover, the time courses of ADCW was the same as the decrease in ECS volume and tortuosity (Toorn et al. 1995).

On the other hand, damage of the blood-brain-barrier, cell damage, inflammation or edema formation, e.g. after X-irradiation (Fig. 4 B, Syková et al. in press) or during EAE (Fig. 4 C, Syková et al. 1994c), resulted in an ECS volume increase and in acute phases, in a tortuosity decrease. However, in chronic lesions such as occur 1-2 weeks after X-irradiation, the volume fraction remains elevated and tortuosity increases, presumably partly due to astrogliosis (Fig. 4B).

Mechanisms of ECS volume decrease.

It is generally accepted that the ECS volume decrease is primarily due to astrocytic swelling, although swelling of neurons, particularly of dendrites and fibres, also occurs. A number of different mechanisms have been proposed as leading to astrocytic swelling, namely: osmotic imbalance, uptake of extracellular K^+, acid-base changes, glutamate uptake and excitatory amino acid-induced swelling, block of Na^+/K^+ pump activity and accumulation of fatty acids and free radicals (for review see Kimelberg et al, 1993). In the isolated rat spinal cord, application of hypotonic solution, application of Ringer's solution with elevated $[K^+]_e$, and application of glutamate or specific glutamate receptor agonists (NMDA, AMPA), all resulted in dramatic cell swelling, a compensatory ECS volume decrease and an ECS tortuosity increase (Vargová et al, 1995). Measurements on the isolated rat spinal cord also revealed that the moderate changes in pH of Ringer's solution lead to changes in ECS volume: namely, an alkaline shift in pH leads to an ECS volume increase and an acid shift leads to an ECS volume decrease.

Discussion

A non-specific feedback suppressing neuronal activity may exist in the CNS:

1. Neuronal activity results in the accumulation in $[K^+]_e$,
2. K^+ depolarize glial cells, and this depolarization induces an alkaline shift in glial pH_i,
3. the glial cells therefore extrude acid,
4. the acid shifts in pH result in a decrease in the neuronal excitability (see Ransom, 1992; Syková 1992a).

The cellular swelling is compensated for by ECS volume shrinkage and is accompanied by increased tortuosity, presumably by the crowding of molecules of the ECS matrix and by the swelling of fine glial processes. These long-term changes in CNS architecture may affect

1. Synaptic transmission (width of synaptic clefts, permeability of ionic channels, concentration of transmitters, dendritic length constant, etc.),
2. non-synaptic transmission by diffusion (diffusion of diffusible factors such as ions, NO, CO, transmitters, neuropeptides, neurohormones, growth factors and metabolites)
3. Neuron-glia communication,
4. ECS homeostasis. The long-term changes in local architecture would therefore affect the efficacy of signal transmission, and may underlay plastic changes and changes in behaviour.

Glial swelling is a consequence of the role of glia in ionic (particularly K^+, pH) and amino acid (glutamate) homeostasis, and it generally accompanies the phenomena of repetitive neuronal activity, seizures, anoxia, injury and many other pathological states in the CNS. Activity-related or CNS damage-related ionic changes and release of amino acids result in pulsating or long-term glial swelling, which leads to a compensatory decrease in the ECS volume and increased tortuosity (i.e. decreases in ADC). In

turn, an ECS volume decrease would result in a greater accumulation of neuroactive substances. This can either increase synaptic or non-synaptic efficacy or induce damage to the nerve cells by reaching toxic concentrations. Chemical and physical properties of the ECS as described by ECS diffusion parameters therefore significantly affect signal transmission in the CNS.

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