5 Dynamic Changes in Extracellular Na\(^+\), Cl\(^-\), and Ca\(^{2+}\) Concentration

In addition to \([K^+]_e\) changes, neuronal activity is accompanied by changes in the concentration of other ions in the microenvironment of the CNS and receptor organs. In the case of Na\(^+\) and Cl\(^-\) it is difficult to measure the changes directly, since the sensitivity of the relevant ISMs is relatively small in the high resting extracellular concentration of these ions. Changes in Na\(^+\) and Cl\(^-\) can therefore only be measured when they exceed several mmol/l; they are thus hard to demonstrate during electrical stimulation and impossible to demonstrate during adequate stimulation. However, the dramatic changes (i.e., the decrease in \([\text{Na}^+]_e\) and in \([\text{Cl}^-]_e\)) which occur during anoxia, epilepsy, and spreading depression can be measured dynamically (see Fig. 45; Nicholson 1980; Nicholson et al. 1981).

The decrease in \([\text{Ca}^{2+}]_e\) due to neuronal activity may be essential for the modulation of transmission in the CNS. The decrease results from the movement of Ca\(^{2+}\) into neurones and presynaptic endings. A decrease in \([\text{Ca}^{2+}]_e\) has been observed during excitation in different parts of the brain and spinal cord, during electrical stimulation of afferent input, and in pathological states.

5.1 Changes Induced in Resting \([\text{Ca}^{2+}]_e\) During Stimulation of Afferent Input

The resting \([\text{Ca}^{2+}]_e\) in the brain and spinal cord of amphibians and mammals varies from 1.2 to 1.6 mmol/l. Repetitive electrical stimulation causes a 0.1–0.5 mmol/l drop in the resting level, i.e., \([\text{Ca}^{2+}]_e\) falls below 1.0 mmol/l (Nicholson 1980; Chvátal et al. 1988). In the cerebral cortex, cerebellum, thalamus, and hippocampus, \([\text{Ca}^{2+}]_e\) falls during repetitive electrical stimulation until it reaches the minimum level, which is about 0.8–0.9 mmol/l (Lux 1974; Heinemann and Lux 1977; Somjen 1979; Morris 1981; Krnjević et al. 1982a,b; Chvátal et al. 1988). When stimulation is discontinued, recovery takes place quickly – as does recovery from an increase in \([K^+]_e\) – and there is an “overshoot” to concentrations higher than the original resting level. The depth profile of stimulation-induced \([\text{Ca}^{2+}]_e\) changes in the cortex, cerebellum, thalamus, and spinal cord is identical to the depth profile of \([K^+]_e\) changes (Heinemann et al. 1977; Nicholson et al. 1976).

Figure 54 illustrates the typical decrease in \([\text{Ca}^{2+}]_e\) in the dorsal horn of the isolated frog spinal cord (Chvátal et al. 1988). During stimulation, the maximum decrease (up to 0.5 mmol/l) was found in the deeper layers. The decrease in \([\text{Ca}^{2+}]_e\) is always proportional to the intensity, frequency, and duration of stimulation. If, however, electrical stimulation of the dorsal spinal root lasted longer than 20–30s, there was no further change in \([\text{Ca}^{2+}]_e\), i.e., the ceiling
value had been reached. The time course of $[\text{Ca}^{2+}]_e$ recovery to the resting level was similar to that observed after $[\text{K}^+]_e$ and pH$_e$ changes (see Fig. 61; Chvátal et al. 1988). As was the case with $[\text{K}^+]_e$ and pH$_e$, $[\text{Ca}^{2+}]_e$ changes in the ventral spinal horns were only slight.

### 5.2 $[\text{Ca}^{2+}]_e$ Changes in Pathological States

Whereas the $[\text{K}^+]_e$ has repeatedly been shown to increase during interictal and ictal discharges (see Sect. 4.3.6.2), the $[\text{Ca}^{2+}]_e$ decreases during such activity (Fig. 55; Heinemann et al. 1977, 1978, 1981; Prince 1978; Heinemann and Louvel 1983). An increase in dendritic permeability for Ca$^{2+}$ may be significant in the development of epileptic activity; changes in epileptic activity are probably reflected in changes in $[\text{Ca}^{2+}]_e$. In cats, it was, in fact, demonstrated that the onset of paroxysmal activity after the administration of pentylenetetrazol, or in an epileptic focus, was preceded by a drop in $[\text{Ca}^{2+}]_e$. Seizure periods are always preceded by a decrease in $[\text{Ca}^{2+}]_e$ (Heinemann et al. 1977). A particularly pronounced decrease in $[\text{Ca}^{2+}]_e$ was found in the cortical layers adjoining a chronic epileptogenic scar. It is possible that dendritic permeability for Ca$^{2+}$ is activated by the increase in $[\text{K}^+]_e$, since a decrease in $[\text{Ca}^{2+}]_e$ always follows close on the heels of such an increase. Pumain et al. (1983) found that individual epileptic action potentials were preceded by an abrupt

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**Fig. 54.** Depth profile of $[\text{Ca}^{2+}]_e$ changes ($\Delta/Ca^{2+}$/f) in the isolated frog spinal cord during repetitive electrical stimulation of dorsal root (30 Hz, 60 s). The maximum decrease in $[\text{Ca}^{2+}]_e$ was found in the deeper layers of the dorsal horns. (From Chvátal et al. 1988)