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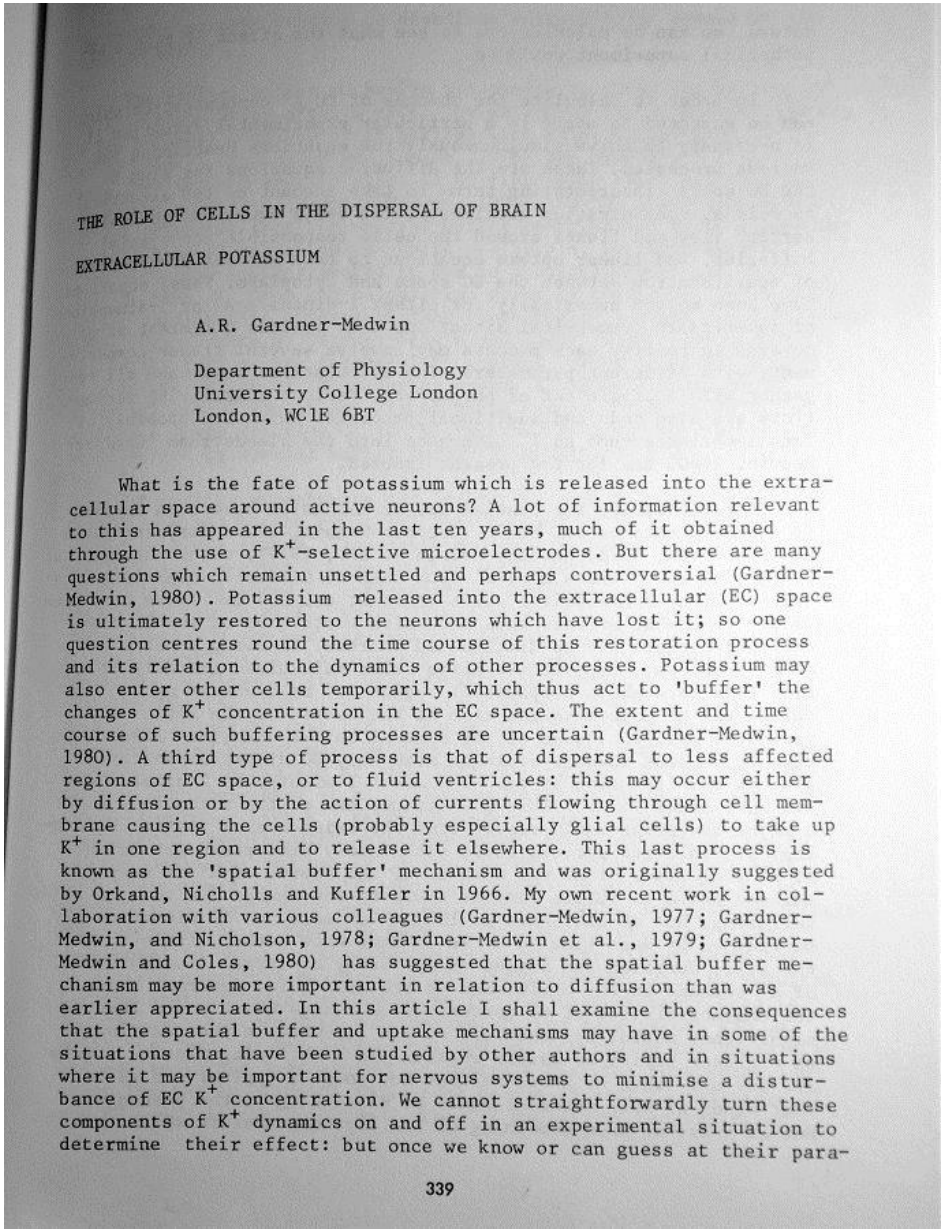

THE ROLE OF CELLS IN THE DISPERSAL OF BRAIN

EXTRACELLULAR POTASSIUM

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What is the fate of potassium which is released into the extracellular space around active neurons? A lot of information relevant to this has appeared in the last ten years, much of it obtained through the use of K^+-selective microelectrodes. But there are many questions which remain unsettled and perhaps controversial (Gardner-Medwin, 1980). Potassium released into the extracellular (EC) space is ultimately restored to the neurons which have lost it; so one question centres round the time course of this restoration process and its relation to the dynamics of other processes. Potassium may also enter other cells temporarily, which thus act to 'buffer' the changes of K^+ concentration in the EC space. The extent and time course of such buffering processes are uncertain (Gardner-Medwin, 1980). A third type of process is that of dispersal to less affected regions of EC space, or to fluid ventricles: this may occur either by diffusion or by the action of currents flowing through cell membrane causing the cells (probably especially glial cells) to take up K^+ in one region and to release it elsewhere. This last process is known as the 'spatial buffer' mechanism and was originally suggested by Orkand, Nicholls and Kuffler in 1966. My own recent work in collaboration with various colleagues (Gardner-Medwin, 1977; Gardner-Medwin, and Nicholson, 1978; Gardner-Medwin et al., 1979; Gardner-Medwin and Coles, 1980) has suggested that the spatial buffer mechanism may be more important in relation to diffusion than was earlier appreciated. In this article I shall examine the consequences that the spatial buffer and uptake mechanisms may have in some of the situations that have been studied by other authors and in situations where it may be important for nervous systems to minimise a disturbance of EC K^+ concentration. We cannot straightforwardly turn these components of K^+ dynamics on and off in an experimental situation to determine their effect: but once we know or can guess at their para-

meters, we can do calculations to see what the effect of such a hypothetical experiment would be.

In order to calculate the changes of EC K^+ concentration which can be expected to occur in a particular experimental situation it is necessary to solve simultaneously the equations describing the various processes. These are the diffusion equations for flux in the EC space (incorporating terms to take account of the electrical as well as concentration gradients), the cable equations governing current flow and fluxes around the cells responsible for spatial buffering, and linear uptake equations to take account of processes of equilibration between the EC space and cytoplasm. These equations have been solved numerically for either 1-dimensional or 3-dimensional spherically symmetrical situations with various different parameters. In reality each process may involve several tissue compartments with different parameters. The calculations lump them all together with a single set of parameters. Various simplifying assumptions are also made and additional processes which are probably of less importance such as K^+ clearance into the bloodstream (Gardner-Medwin, 1980) are for the present ignored.

Parameters for the spatial buffer mechanism have been derived from experiments on rat brain (Gardner-Medwin, 1977; Gardner-Medwin and Nicholson, 1978; Gardner-Medwin et al., 1979), which suggest that it carries ca. 5 times more K^+ flux than EC diffusion over large distances, with an electrical space constant ca. 0.2 mm. These have been used to see what effects this mechanism would have on the K^+ concentration rises due to distributed sources. Assuming a net release of K^+ from, say, hyperactive nerve cells maintained steadily from time zero throughout a spherical region 0.8 mm diameter we can calculate the K^+ concentration rise at the centre of the region at various times. Inclusion of the spatial buffer equations leads this rise to be less than it would be with only EC dispersal and cytoplasmic equilibration by ca. 40 % after 1 minute, 60 % after 5 min and 70 % after 15 min. This illustrates one of the situations where a major advantage could result from the existence of spatial buffering: if prolonged periods occur with fairly widespread net release of K^+ from zones of neural tissue. If the source of K^+ is very localised there is little benefit close to the source due to spatial buffering. But at distances of 100 μm or more the K^+ elevation may be reduced by more than 50 %. We in fact know rather little about the size, duration and degree of synchrony of normal fluctuations of K^+ release in the brain. And we are also quite ignorant about the characteristics of EC concentration change which could lead to significant neural dysfunction. We are somewhat in the position of an engineer trying to assess whether the stabilising fins on a ship are any use, when he knows neither how rough a typical sea is or what kinds of ship movement would be disturbing to the passengers. But at least we know something of the circumstances in which this

particular process tending to stabilise extracellular potassium may have an effect.

The spatial buffer mechanism also helps to speed the decline of EC K^+ concentration after a rise. The extremely rapid declines (taking a few seconds) observed after periods with brief stimulation (Vern et al., 1977; Cordingley and Somjen, 1978) are probably attributable more, however, to equilibration of EC fluid with cytoplasm than to dispersal processes (Gardner-Medwin, 1980). Somjen and Trachtenberg (1979) suggested that the spatial buffer contribution to K^+ clearance in this kind of situation was quite negligible, but unfortunately they seriously underestimated it due to a calculation error of 10^3 (p. 28, line 2). Once the calculation error is corrected, the spatial buffer contribution appears in fact to be possibly significant (Somjen, 1980). Experiments by Gardner-Medwin and Coles (1980) have investigated the role of the dispersal by spatial buffering of K^+ through glia in the retina of the honeybee drone. A calculation somewhat similar to that of Somjen and Trachtenberg suggests that in this preparation a large fraction of the K^+ released from photoreceptors may be dispersed by spatial buffer currents through the glia.

Two earlier experiments had led to the suggestion that EC diffusion might be the principal factor involved in K^+ movement in mammalian brain tissue. These both employed K^+-selective microelectrodes to measure changes during artificial disturbances. Lux and Neher (1973) measured K^+ concentration changes close to an iontophoretic point source of K^+, while Fisher et al., (1976) measured the changes beneath the cortical surface during superfusion with altered K^+ concentrations. It has already been pointed out elsewhere that there may be flaws in the interpretation of these experiments (Gardner-Medwin, 1978, 1980; Nicholson et al., 1979). The data differ from what should be expected if the added K^+ remained wholly in EC space. Related experiments using EC markers have been performed using iontophoresis (Nicholson et al., 1979) and superfusion of radioactive markers (Fenstermacher et al., 1974) and have produced different results from those with K^+. Attempts have now been made to fit the published K^+ results with solutions of the equations for diffusion, spatial buffering and uptake. A satisfactory fit can be made with both these types of data if suitable parameters are chosen. It is necessary to invoke both cytoplasmic equilibration and spatial buffering (carrying ca. 5 times as much K^+ flux as diffusion over large distances) to obtain a satisfactory fit. But the situation is not completely straightforward since the space constant that is required for the spatial buffer mechanism to fit the iontophoretic data is ca. 120 μm, that required for the superfusion data is ca. 450 μm, while that for my own data is ca. 200 μm. The reason for these discrepancies is not apparent. It is possible that the long space constant for the superfusion data might be due in part to shrinkage of the EC space in the relatively high (12 mmol/l) K^+ concentration

employed. It is also possible that the factors involved in both these experiments are more complex than has been envisaged. Even if this is so, however, the data can no longer reasonably be regarded as supporting the idea that K^+ moves through brain tissue principally by EC diffusion, or as evidence against a contribution of the spatial buffer mechanism.

CONCLUSION

One of the contributions of ion-selective microelectrodes to brain physiology has been to provide data on the dynamics of extracellular potassium. The data indicate that potassium dispersal through glia and equilibration between cytoplasm and EC space are both likely to be important factors in the fate of K^+ released from nerve cells. The situation is not simply or principally one of release, extracellular diffusion and active reuptake as has been suggested. The involvement of glia so as to reduce the perturbations of EC potassium concentration suggests that such perturbations might be a cause of neural dysfunction. We still need further work to find out whether this is so or not.

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