6.2: Regulation of Cell Volume

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As most cell membranes are freely permeable to water and do not possess water pumps in their membranes, cells will shrink or swell in response to changes in ECF tonicity. This is generally undesirable for most cells which need a constant cell volume to maintain optimum function.

Among the few exceptions to this rule are the epithelium of the urinary bladder and certain special cells and segments in the renal tubule.

How do cells respond to these extracellular osmotic stresses and maintain a constant volume?

Cells contain a significant concentration of large molecular weight anionic colloids (mostly proteins and organic phosphates) which cannot cross the cell membrane. In contrast, interstitial fluid generally has a low protein concentration. The high intracellular concentration of non-diffusible anions leads to a Gibbs-Donnan equilibrium across the cell membrane. At equilibrium (if it occurred), electroneutrality would be preserved on both sides of the membrane but there would be more particles (higher osmolality) intracellularly. Water would enter the cell down its concentration gradient and the cell would tend to swell. This would upset the Gibbs-Donnan equilibrium and more solute particles would enter the cell which would swell even more ... ... and so on. This is an unstable situation which, if unopposed, would lead to cell rupture.
How can this be as we know that cell volume tends to be very stable? The above argument is valid and applicable to all cells. What is the mechanism which prevents cell swelling and rupture? The answer is the sodium pump (Na\(^+\)-K\(^+\) ATPase) in the cell membrane. The pump together with the membrane's low permeability to sodium, effectively prevents sodium from entering the cell. The sodium becomes an extracellular cation to which the membrane is effectively impermeable. This sets up another Gibbs-Donnan equilibrium now with Na\(^+\) as the impermeable charged species.

Overall, the equilibrium situation is that the Gibbs-Donnan effect due to the impermeant extracellular sodium balances the Gibbs-Donnan effect due to the impermeant intracellular colloids. This double-Donnan effect stabilises cell volume.

If the sodium pump was blocked (eg by drugs), sodium would enter the cell and water would follow until the cell ruptured. The sodium pump is important in stabilising cell volume in addition to its critical role in the generation of the resting membrane potential.

In summary so far

- Intracellular colloid (mostly proteins and organic phosphates) cannot cross the cell membrane. These anions affect the distribution of the diffusible ions according to the Gibbs-Donnan effect
- The sodium pump renders the membrane effectively impermeable to sodium: this sets up another Gibbs-Donnan equilibrium which has effects opposite to the first
- The balance between these two effects allows the cell to maintain a normal cell volume

What happens to cell volume when cells are stressed by a change in ECF tonicity?

Water crosses membranes freely, so this change in tonicity will have rapid (several minutes) effects on cell volume. A hypertonic ECF will cause cells to shrink; a hypotonic ECF will cause cells to swell. This is undesirable for normal cell function and this is especially disadvantageous in the brain.

On acute exposure to a hypotonic ECF, cells do swell within a couple of minutes but then their volume starts to decrease towards normal. This decrease is termed volume regulatory decrease and is due to loss of intracellular solute particularly potassium.

In hypertonic ECF, cells decrease in size but are able to partially recover: this is termed volume regulatory increase and acutely is due to a net leak of solute (mostly Na\(^+\) and Cl\(^-\)) into the cell.

If the ECF tonicity is only slowly changed, then the response of the cell is different. The cells are able to adapt as the tonicity is changed. They are able to minimise any change in cell volume over a wide range of osmolality. This happens because the cell is able to lose or gain solute at a rate which almost matches the effect of the change in tonicity.

If a cell which has partially recovered towards its normal cell volume is suddenly returned to a situation of normal ECF tonicity, then the reverse effect occurs eg a swollen cell which has lost solute and decreased its cell volume will shrink markedly if suddenly returned to normal ECF tonicity. This is the predictable outcome based on the lowered intracellular tonicity responsible for the return of volume towards normal.
An example of this is the difference in symptomatology of acute hyponatraemia versus chronic hyponatraemia. For the same absolute plasma [Na⁺], chronic hyponatraemia is much better tolerated than acute hyponatraemia. The brain cells in chronic hyponatraemia have reduced their cell volume and significantly restored their normal functioning. The converse holds for rapid correction of the hyponatraemia. Rapid normalisation of ECF tonicity in chronic hyponatraemia can result in marked symptoms due to rapid decrease in cell size; but rapid correction of acute hyponatraemia may be much better tolerated.

### Idiogenic Osmoles

For many types of cells an additional very important mechanism is operative. Consider the brain which has been subjected to a hypertonic ECF. The brain cells may gain solute (principally Na⁺ and Cl⁻) from the extracellular environment and return their volume towards normal. However, the brain cells are capable of increasing their tonicity by gaining solute using another mechanism. They can produce more particles from cellular metabolism. These substances are known as idiogenic osmoles (or osmolytes) and include taurine, glycine, glutamine, sorbitol and inositol. An increase in these idiogenic osmoles have been detected in brain cells as early as 4 hours after an acute hypertonic challenge.

The production of extra osmoles within the cell is very important. The problem with taking in inorganic ions like Na⁺ and Cl⁻ from the ECF is that higher than normal concentrations of these ions have adverse effects on intracellular enzyme systems. Coping with intracellular dehydration is a problem common to many animals. The evolutionary response has been to allow cells to generate extra osmoles inside the cell by producing certain compounds which do not disrupt enzyme function. These idiogenic osmoles have also been termed compatible osmoles because of their relatively benign effect on intracellular proteins.

### Points to Note

- The kidney is the major regulator of ECF tonicity (in response to sensitive osmoreceptor monitoring and ADH activity)
- Normally ECF tonicity is relatively constant and this maintains the volume of all cells in the body (and thus determines total intracellular volume and the distribution of total body water between ICF and ECF).
- All cells have their own local mechanisms which attempt to maintain a constant cell volume. (The sodium pump is critically important in rendering the cell effectively impermeable to sodium and counteracting the Gibbs-Donnan effect of the intracellular colloids. This maintains a normal cell volume under isotonic conditions).
- In situations of osmotic stress, cells attempt to return their cell volume to normal by either gaining or losing intracellular solute.
- Extra intracellular solute may come from ECF solute (more disruptive to cell function) or from metabolic generation of extra idiogenic solute (more compatible with cell function)
- These volume regulatory processes operate at the level of the individual cell and protect the cells from the volume changes that would occur due to changes in ECF [Na⁺] (tonicity).

These cellular events have great significance if rapid correction of a chronic osmolar disturbance is attempted. Rapid normalisation of chronic hyponatraemia can cause severe neurological symptoms.
Remember also that plasma [Na\(^+\)] is an index of water balance rather than of sodium balance and is regulated by the processes which control water balance (ie the thirst-ADH mechanism).

**Brief Overview**

- Kidneys regulate ECF [Na\(^+\)]
- ECF [Na\(^+\)] controls the distribution of water between ECF and ICF at any instant
- Cells can also regulate their own cellular volume by changing intracellular solute content to minimise the adverse functional effects of changes in ECF tonicity