**Model of swelling-activated myo-inositol transport**

As evident from Fig. 1, *equiosmotic* replacement of sucrose by inositol at tonicities below 200 mOsm not only abolished RVD but also induced a considerable secondary cell swelling. Unlike the initial hypotonic swelling caused by an osmotic shift (e.g. 300 → 100 mOsm), the secondary swelling occurred under isosmoticconditions, i.e. *no* osmotic pressure gradient existed across the cell membrane. In our experiments, the isosmotic cell swelling implies a diffusion-driven influx of the major extracellular solute myo-inositol into cells. In contrast, the isosmotic cell shrinkage by RVD involves the release of intracellular electrolytes.

The following set of equations based on the two-parameter formalism [Kleinhans, 1998, Shirakashi et al., 2004] can be used for modeling isosmotic changes in cell volume:

  (A1),

  (A2),

  (A3),

where *C’s* are molar solute concentrations [mol/m3]; *V*0 and ν=V/V0 are the isotonic and normalized cell volumes, respectively; ε is the osmotically inactive volume fraction under isotonic conditions; *S* is the cell membrane area [m2] (assumed invariable); *P*’s are the membrane permeability coefficients [m/s]. The *subscripts* “*el”* and “*ino*” denote, respectively, *electrolyte* and *inositol*. The superscripts “*o*” and “*i*” stand for extra- and intracellular concentrations, respectively.

Equation A1 describes an osmotic equilibrium between the cytosol and external solution. Equation A1 implies that only two solutes, i.e. myo-inositol and electrolyte, maintain the osmotic equilibrium and that the membrane permeability to water is much higher than its permeability to either solute. Equation A2 relates the flux of myo-inositol across the cell membrane to the difference of its concentrations $\left(C\_{ino}^{o}-C\_{ino}^{i}\right)$ on the two sites of the membrane. Equation A3 is the corresponding relation for electrolytes. Combination of Eqs. A1-A3 leads to the following expression:

  (A4)

Given that  (Eq. A1), as well as *C*oel and *C*oino are constant, Eq. A4 can be transformed to:

 . (A5).

Combination of Eqs. A5 and A2 leads to the following expression:

  (A6),

which in turn simplifies to

  (A7)

Finally, the substitution of (*Coino* - *Ciino*) with (*Coel* - *Ciel*) (Eq. A1) transforms Eq. A7 to:

  (A8),

In case of the membrane-impermeable sucrose, *C*oino, *C*iino and *P*ino can be replaced, respectively, by *C*osuc, *C*isuc=0 and *P*suc=0 in Eqs. A1 and A7, thus leading to:

  (A9)

  (A10).

For spherical cells, the surface-to-volume ratio *S*/*V*0 = 3/*R*0, where *R*0 is the cell radius and Eq. A10 can be rewritten as:

  (A11).

Equation A11 (or Eq. 1 in the main text) was used to calculate the *P*el during RVD. For these calculations we used the cell radius *R*0 = 7.9 µm;  and , according to experimental conditions. The rate of RVD Δν/Δ*t*RVD was determined from the slope of volumetric curves, as illustrated in Fig. 1 (*blue lines*).

If during RVD, sucrose is replaced by an equiosmotic amount of myo-inositol, Eq. A10 is no longer valid. Instead, cell volume changes in the presence of membrane-permeable myo-inositol can be described by Eqs. A1, A7 and A8. The initial condition (for the time point just after the solution exchange) simplifies Eq. A8 to:

  (A12).

Equation A12 can be rewritten as follows:

  (A13).

Eq. A12 and Eq. A13 (or Eq. 2 in the main text) are valid only for a short time after the replacement of sucrose by myo-inositol, where the initial condition is fulfilled.

In Eq. A13 (or Eq. 2 in the main text), the HEK293 cell radius *R*0 = 7.9 µm;  and , according to our experimental conditions. The rate of myo-inositol-mediated secondary swelling (Δν/Δ*t*ino) was determined from the volumetric data, as illustrated in Fig. 1 (*red lines*). The corresponding electrolyte permeability *P*el was determined from the RVD rate (Eq. A11) at the time point of solute exchange (*blue fitted lines* in Fig. 1).