PHYSIOLOGICAL REVIEWS Vol. 78 No. 1 January 1998, pp. 247-306


# Functional Significance of Cell Volume Regulatory Mechanisms

FLORIAN LANG, GILLIAN L. BUSCH, MARKUS RITTER, HARALD VÖLKL, SIEGFRIED WALDEGGER, ERICH GULBINS, AND DIETER HÄUSSINGER

With only few exceptions, the membranes of animal cells are highly permeable to water. Animal cell membranes cannot tolerate substantial hydrostatic pressure gradients, and water movement across those membranes is in large part dictated by osmotic pressure gradients. Thus any imbalance of intracellular and extracellular osmolarity is paralleled by respective water movement across cell membranes and subsequent alterations of cell volume.

As outlined below, most mammalian cells are bathed in extracellular fluid with almost constant osmolarity. Nevertheless, considerable alterations of extracellular osmolarity are encountered in a variety of diseases. Excessive alterations of extracellular osmolarity occur in kidney medulla during transition between antidiuresis and diuresis.

Even at constant extracellular osmolarity, cell volume constancy is compromised by alterations of intracellular osmolarity. A wide variety of metabolic pathways leads to cellular formation or dissipation of osmotically active substances. Moreover, transport across the cell membrane modifies cellular osmolarity and thus cell volume.

To avoid excessive alterations of cell volume, cells have developed and utilize a multitude of volume regulatory mechanisms including transport across the cell membrane and metabolism. These mechanisms are triggered by minute alterations of cell volume. They not only serve to readjust cell volume but profoundly modify a wide variety of cellular functions. Thus cell volume is an integral element within the cellular machinery regulating cellular performance.

It is the aim of this review to illustrate the functional significance of cell volume. To this end, a description of the volume regulatory mechanisms and the cellular functions sensitive to cell volume is followed by a discussion of the role of cell volume in several integrated cell functions.

This review does not consider volume regulatory mechanisms in prokaryotic cells or comparative aspects of cell volume regulation, and the reader may refer to the respective pertinent literature .

Instead, the discussion focuses on the significance of cell volume for the performance of mammalian cells. Moreover, the paper stresses recent developments. For a more complete coverage of earlier literature, the reader may refer to previous reviews on cell volume regulation, osmolytes, and the role of cell volume in regulation of cell function.

For various functions, experimental evidence pointing to the involvement of cell volume and cell volume regulatory mechanisms is intriguing but far from conclusive. It is hoped that this review stimulates further experimental effort in this exciting area of research to clarify the many remaining questions.

## TABLE 2. *Factors altering cell volume*

| Factor | Cell Affected |
|---|---|
| ***Factors leading to cell swelling*** | |
| Insulin | Hepatocytes (4, 472, 473, 953, 1287, 1286) and pneumocytes (805) |
| IGF-I | Hepatocytes (1285) |
| Growth hormone | Chondrocytes (557) |
| ADH (AVP) | Glial cells (259, 705) |
| Glucocorticoids | Hepatocytes (660) and Fibroblasts (316) |
| Mineralocorticoids | Leukocytes (1329-1331) |
| Estrogens | Astrocytes (344) and Parathyroid glands (137) |
| Progesterone | Astrocytes (344) and Parathyroid glands (137) |
| Testosterone | Parathyroid glands (137) |
| Gonadotropin | Leydig cells (1346) |
| Somatostatin | Colon cells (277) |
| Adenosine | Erythrocytes (1132) |
| Angiotensin | Vascular smooth muscle cells (296) |
| Interleukin | Lymphocytes (1184) and α-Adrenergic Hepatocytes (1286) and β-Adrenergic Erythrocytes (56, 323, 459, 862) and Salivary glands (172) and Sweat glands (907) |
| Acetylcholine* | Sweat glands (907) and Myogenic L6 cells (1110) |
| Glutamate* | Glial cells (73, 185, 486-488, 594, 1084, 1151) and Neurons (185, 186, 975, 1059) |
| NMDA | Brain (190, 1267) |
| Aspartate | Neurons (1059) |
| Deoxyadenosine | Lymphoblastoid cells (36) |
| cAMP | Sweat glands (907) |
| cGMP | Barnacle muscle (957) |
| Arachidonic acid | Glial cells (1147, 1148) |
| Lithium | Erythrocytes (935, 944) |
| Magnesium | Erythrocytes (332, 943, 944) |
| Amino acid uptake | Hepatocytes (43, 51, 60, 204, 342, 471, 502, 653, 654, 1300, 1341) |
| Glucose uptake | *Necturus* gallbladder (355) and Kidney (67) and Intestine cells (785) and Vascular smooth muscle cells (881) and Mesangial cells (620) |
| Bile acids | Hepatocytes (497, 506) |
| Increase of $K^+$ | Hepatocytes (1261) and Gallbladder epithelium (229, 528, 639) and Proximal renal tubule (261, 631, 689, 1282) and Renal cortical slices (973) and Thick ascending limb (1178) and Neurons (24, 33, 1086) |
| $HCO^-_3$ | Parotid glands (976) |
| Acidosis | Proximal renal tubule (1174, 1175) and Neurons (1149, 1150) |
| (Short chain)fatty acids* | Enterocytes (278, 280, 1032) and Proximal renal tubule (1016) and Erythrocytes (385) and Brain (178) |
| $NH_3$ | Astrocytes (867, 897, 898) |
| Opossum kidney cells | (982) |
| Cytochalasin B | Lymphoblast cells (36) |
| Colchicine | Lymphoblast cells (36) |
| Vinblastine* | Lymphoblast cells (36) |
| Endotoxin | Hepatocytes (127) |
| *N*-methylformamide | HT-29 cells (260) |
| Chlorpromazine* | Erythrocytes (219, 1205) |
| Hydroxyurea | Endothelial cells (2) |
| Ethanol | Hepatocytes (1362) |

Adenohypophysial cells (1063) and Cardiac cells (552) and Proximal tubule cells (600)
Dideoxycytidine Monoblastoid cells (115)
Mercurials MDCK cells (1028)
Shark rectal gland (637)
Dioxin* Hepatocytes (1344)
Veratridine Neurons (190)
Hyperthermia Chondrocytes (335)
Osteoblasts (335)
Hemolysin Erythrocytes (556)
Photofrin Tumor cells (729, 730)
Fertilization Sperm (1212)
Electric field stimulus Outer hair cells (906)

***Factors leading to cell shrinkage***
Glucagon Hepatocytes (379, 473, 1287)
VIP Intestine (276, 901, 1297)
Somatoliberin (hGHRH)
GH-producing cells (307)
ADH MDCK cells (1176)
Hepatocytes (1286)
Atriopeptin (ANF)
glial cells (705)
Cardiac myocytes (198, 199, 201)
NO Heart (200, 201)
ATP Endothelial cells (916)
Hepatocytes (1286)
Bradykinin Enterocytes (1210)
Fibroblasts (1005)
Ehrlich cells (547, 1126)
Endothelial cells (916)
Histamine Enterocytes (1210)
Ehrlich cells (547)
Thrombin Enterocytes (1210)
Ehrlich cells (547, 1126)
Serotonin Leech glial cells (46)
Adenosine Renal collecting duct (1107)
Hepatocytes (1286)
fMLP Granulocytes (955)
Corticostatic peptides Enterocytes (786)
α-Adrenergic Hepatocytes (849)
Salivary glands (797)
Isoprenaline Nonpigmented ciliary epithelium (183)
Acetylcholine* Salivary glands (338, 341, 699, 797, 846, 872, 873, 882, 911, 976, 1363)
Sweat glands (1181, 1189)
Enterocytes (1210, 1297)
$PGE_2$ Erythrocytes (743)
$H_2O_2$ Hepatocytes (470, 1045)
cAMP *Necturus* gallbladder (229, 994)
Hepatocytes (1286)
MDCK cells (828, 829, 833, 1176)
Barnacle muscle (957, 987)

Pulmonary epithelium (787)
Pancreatic epithelial cells (1182)
Pancreatic epithelium (643)
Intestine (1251)
Nonpigmented ciliary epithelium (183)
cGMP Heart (199, 201)
A23187[*] Pulmonary epithelium (787)
Enterocytes (786, 1210)
Erythrocytes (134, 310)
Fibroblasts (1358)
Neuroblastoma cells (233)
Thapsigargin Enterocytes (786)
Okadaic acid[*] Hepatocytes (101)
Cytochalasin B MDCK cells (828, 829)
Colchicine Macrophages (821)
Ouabain Neurons (16)
Cardiac myocytes (1131)
Vascular smooth muscle cells (919)
Proximal renal tubules (631)
Decrease in $K^+_o$ Erythrocytes (291)
Leech glial cells (46)
Pigmented ciliary epithelium (301)
Removal of $Na^+_o$ Muscle cells (959)
Pigmented ciliary epithelium (301)
Removal of $Cl^-_o$ Kidney (777)
Pigmented ciliary epithelium (301)
Toad bladder (740)
Amphibian skin (434, 1246)
Erythrocytes (933, 939)
Removal of $Ca^{2+}_o$ Muscle cells (958)
$Mg^{2+}$ depletion Erythrocytes (711)
Starvation Hepatocytes (3, 1140)
Heme oxygenation Erythrocytes (163, 164)
Elastin peptides Tumor cells (946)
Urea Proximal renal tubules (359)
Hepatocytes (474)
Erythrocytes (936)
Mastoparan MDCK cells (1350)
NDS Enterocytes (790)
Furosemide[*] Macula densa cells (964)
MDCK cells (1176)
MAG-3but HL-60 leukemic cells (162)
Ethanol Prolactin-secreting cells (1063, 1068)
Thyrotropin-releasing cells (1063)
Amphotericin B Cornea epithelium (992)
Macrophages (299) Lead Erythrocytes (310)
Cisplatin Renal tubule cells (110)
Noise Auditory hair cells (275)

---

VIP, vasoactive intestinal polypeptide; NDS, neutrophil-derived secretagogue; MAG-3but, monoacetone glucose 3-butyrate; NMDA, *N*-methyl-D-aspartate; IGF-I, insulin-like growth factor I; ADH, antidiuretic hormone; AVP, arginine vasopressin; PKC, protein kinase C; ANF, atrial natriuretic factor; NO, nitric oxide; PG, prostaglandin; fMLP, formyl-methionyl-leucyl-

phenylalanine; hGHRH, human growth hormone-releasing hormone. * Or similarly active drugs. Reference numbers are given in parentheses.

**TABLE 1.** ***Effect of cell volume on gene expression***

| Effect | Gene/Gene Product Affected |
|---|---|
| ***Cell swelling*** | |
| + | c-*jun* in hepatocytes (328) |
| + | c-*fos* in cardiac myocytes (1044) |
| + | ERK-1,2 in cardiac myocytes (1044) |
| + | Ornithine decarboxylase in LLC-$PK_1$ cells (75, 769), leukemia cells (977), CHO cells (761), and hepatocytes (1215) |
| − | TNF-α in macrophages (1392) |
| + | β-Actin (1202) |
| + | Tubulin (511) |
| ***Cell shrinkage*** | |
| + | Aldose reductase in MDCK cells and kidney medulla (373, 1130) |
| + | $Na^+$-inositol cotransporter SMIT (141, 670, 1318) |
| + | $Na^+$-betaine cotransporter BGLT1 (319, 878, 1319, 1372, 1393) |
| + | $Na^+$-taurine cotransporter (1238, 1239, 1320, 1322) |
| + | Amino acid transport system A (182, 380, 1135, 1373) |
| + | $\alpha_1$-Subunit $Na^+$-$K^+$-ATPase (322) |
| + | P-glycoprotein (1333) |
| + | ClC-K1 in kidney (1241) |
| + | Serine/threonine kinase h-sgk (1295) |
| + | Egr-1 in MDCK cells (205, 206, 208) and cardiomyocytes (1361) |
| + | $\alpha_1$-Chimerin in neurons (286) |
| + | c-*fos* in MDCK cells (208), hypothalamic cells (396), and cardiomyocytes (1361) |
| + | Heat shock proteins (11, 208, 1116, 1192) |
| + | Cyclooxygenase-2 (1391) |
| − | Tyrosine hydroxylase in PC12 cells (621) |
| − | Dopamine β-hydroxylase in PC12 cells (621) |
| + | Tyrosine aminotransferase (1317) |
| + | Vasopressin (866) |
| + | CD9 antigen in MDCK and PAP-HT25 cells (1115) |

+, Stimulation; −, inhibition; CHO, Chinese hamster ovary; TNF-α, tumor necrosis factor-α; MDCK, Madin-Darby canine kidney; PEPCK, phospho*enol*pyruvate carboxykinase. For review, see Reference 144. Reference numbers are given in parentheses.

## TABLE 3. *Influence of cell volume on metabolism*

Cell volume changes modify a wide variety of metabolic functions. Most importantly, cell swelling favors the synthesis and inhibits the degradation of proteins, glycogen, and to a lesser extent lipids. Cell shrinkage has the opposite effect. Thus cell swelling can be considered as an anabolic signal, whereas cell shrinkage favors cell catabolism.

| Effect | Process Affected |
|---|---|
| + | Glycogen synthesis in hepatocytes (4, 12) and muscle (762) |
| − | Glycogenolysis (406, 696) |
| − | Glucose-6-phosphatase activity (409) |
| + | Glucokinase activity in hepatocytes (1261) |
| − | Glycolysis in muscle and fibroblasts (196, 918) |
| + | Glycolysis in hepatocytes (953) |
| | Macrophages and lymphocytes (1366) |
| + | Lactate uptake in hepatocytes (696) |
| + | Pentose phosphate shunt in hepatocytes (496, 1046) |
| − | Release of glutamine and alanine from muscle (945) |
| + | Protein synthesis in hepatocytes (1007, 1159) and mammary cells (825) |
| − | Proteolysis in hepatocytes (471, 472, 498, 499, 767, 1284, 1285, 1287) |
| + | Amino acid uptake (100, 500, 502) |
| + | Glutamine breakdown in liver (502), lymphocytes, and macrophages (1366) |
| − | Glutamine synthesis (502) |
| + | Glycine and alanine oxidation (496, 510, 676) |
| + | Urea synthesis from amino acids (505) |
| − | Urea synthesis from $NH^+_4$ (500, 502) |
| + | Glutathione (GSH) efflux (503) |
| + | Ornithine decarboxylase activity and expression (769, 1215) |
| + | RNA and DNA synthesis in HeLa cells (1008) |
| + | Ketoisocaproate oxidation (510) |
| + | Acetyl CoA carboxylase (49, 51, 53, 555) |
| + | Lipogenesis (51) |
| − | Carnitine palmitoyltransferase I activity (457, 841, 1389) |
| + | Taurocholate excretion into bile (469, 497, 508) |
| + | Respiration in glial cells (609) and sperm (231) |
| − | Cellular ATP concentration in hepatocytes (820) |
| − | Phosphocreatine concentrations in glioma cells (747) |
| + | Formation of active oxygen species in neutrophils (658, 659) |
| + | Bile secretion (497) |

+, Stimulation upon cell swelling and/or inhibition by cell shrinkage; −, inhibition upon cell swelling and/or stimulation by cell shrinkage. For effects on gene expression, see Table 1. For effects on intracellular signaling, see text. Reference numbers are given in parentheses.