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Review

Mammalian aquaglyceroporin function in metabolism

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ABSTRACT

Aquaglyceroporins are integral membrane proteins that are permeable to glycerol as well as water. The movement of glycerol from a tissue/organ to the plasma and vice versa requires the presence of different aquaglyceroporins that can regulate the entrance or the exit of glycerol across the plasma membrane. Actually, different aquaglyceroporins have been discovered in the adipose tissue, small intestine, liver, kidney, heart, skeletal muscle, endocrine pancreas and capillary endothelium, and their differential expression could be related to obesity and the type 2 diabetes.

Here we describe the expression and function of different aquaglyceroporins in physiological condition and in obesity and type 2 diabetes, suggesting they are potential therapeutic targets for metabolic disorders.

Contents

1. Glycerol metabolism

Glycerol, chemically a polyol, is the backbone of triglycerides (TG) and a precursor of phospholipids; it is an important intermediate in carbohydrate and lipid metabolism, and functions as a shuttle of electrons from cytosol to mitochondria by regenerating NAD + from NADH [1].

The digestion of dietary TG by pancreatic lipase produces mono- and diacylglycerols, which are absorbed by the small intestinal mucosa. A lesser amount of glycerol is also absorbed in the free form (see section 5, "Small Intestine") due to the low concentration of glycero-kinase (GK) within the enterocyte. Monoglycerides and fatty acids undergo TG resynthesis. TG enter the bloodstream as chylomicrons and VLDL. A lipoprotein lipase attached to the capillary endothelial cells of adipose tissue, muscles and the heart hydrolyzes TG to free fatty acids and glycerol. Fatty acids are actively transported into tissues whereas glycerol is mainly converted to glycerol-3-phosphate (glycolysis intermediate) by GK in the liver and the kidney. Glycerol needs to be activated by a phosphorylation reaction before entering the carbohydrate and lipid metabolism.

Glycerol plasma concentration is determined primarily by the amount released by adipose tissue lipolysis, but also by the amount

Abbreviations: TG, triglycerides; GK, glycerol kinase; AQP, aquaporin; GlpF, glycerol facilitator; FDA, Food and Drug Administration; WT, wild type; AMPK, AMP-activated protein kinase; NAFLD, non-alcoholic fatty liver disease; NASH, steatohepatitis; VRAC, volume-regulated anion channels.

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Table 1
Aquaglyceroporins: main organ/tissue expression and localization, and their related functions.

Aquaporin	Localization	Main physiological functions
AQP3	Gastrointestinal tract*	Water and small solutes absorption and secretion
	Kidney*	Contribute to urinary concentration
	Adipose tissue*	Glycerol metabolism
	Skin [139,140]	Skin barrier, hydration and elasticity, cell proliferation and migration (tumorigenesis, wound healing)
	Lymphocytes/Dendritic cells [141,142]	Activation, proliferation, migration
	Erythrocytes [143,144]	Glycerol transport in human erythrocytes and ROS cleaning system by primitive erythroid cells
	Female reproductive system [145]	Vaginal lubrication, cervical water balance in pregnancy and parturition, water and non-charged solutes in placenta
	Male reproductive system [145]	Maintenance of normal fertility
	Eye [146]	Corneal wound healing, involvement in the postnatal retina development
	Heart/skeletal muscle*	Glycerol transport to be used for energy production
	Respiratory tract [147]	Water homeostasis in the epithelia of the upper and lower respiratory tract
	Mammary gland [148,149]	Production of the aqueous component of the milk
	Articular cartilage [150]	Chondrocyte volume regulation and extracellular matrix
	Inner Ear [151,152,153]	Water homeostasis of perilymph and endolymph
AQP7	Gastrointestinal tract*	Water and small solutes absorption and secretion
	Kidney*	Involvement in glycerol reabsorption
	Adipose tissue*	Glycerol metabolism
	Heart/skeletal muscle*	Transport of glycerol to be used for energy production
	Endocrine pancreas*	Could be involved in insulin production/secretion and in the reduction of β-cell mass
	Female reproductive system [145,154]	Endometrial decidualization; fluid transport into antral follicles
	Male reproductive system [145]	Sperm maturation, storage and motility; seminiferous tubule fluid production.
	Eye [155]	May participate in water transport into the vitreous body
	Inner Ear [151,152,153]	Water homeostasis of perilymph and endolymph
AQP9	Gastrointestinal tract [156]	Involvement in the synthesis/secretion of a certain type of mucus
	Liver*	Glycerol uptake for gluconeogenesis
	Adipose tissue*	Glycerol metabolism
	Inner ear [151,152,153]	Water homeostasis of perilymph and endolymph, may be involved in the vestibular sensory transduction system
	Female reproductive system [145,157]	Endometrial decidualization, epithelial water transport in the oviduct and the movement of the embryo from the oviduct to the uterus, fluid transport into antral follicles, transport of water and/or non-charged solutes across the placenta
	Male reproductive system [145]	Water and small solutes transport in Leydig cells; epididymal and seminiferous tubules fluid formation
	Eye [146,155]	may serve to transport lactate, glycerol and metabolites in the retina
	Bone [158,159,160]	Osteoclast differentiation and cell fusion process (in stressed condition?)
	Erythrocytes [161]	AQP9 is the major pathway for glycerol and other small uncharged solutes transport in mouse erythrocytes
	Neutrophil leukocyte [162,163,164]	Cell motility
	Brain [165]	Possible involvement in glucose energy metabolism in astrocyte and in some catecholaminergic neurons
	Skin [80]	Involved in maintaining skin hydration.
AQP10	Gastrointestinal tract*	Water and small solutes absorption and secretion
	Adipose tissue*	Glycerol metabolism
	Male reproductive system [166]	Water balance maintenance
	Skin [140]	Involved in skin barrier

* See related section for references.

absorbed in the gastrointestinal tract, and by the variable amount reabsorbed in the kidney tubules [2,3,4,5,6].

In the interprandial state, in starvation and in exercise, the glycerol from lipolysis represents an important substrate for gluconeogenesis together with lactate, pyruvate and the amino acids alanine and glutamine [7,8,9]. In prolonged starvation, the amount of glycerol metabolized to glucose reached 76% in obese subjects [7]. Adipocyte lipolysis is a highly regulated process: it is activated by β-adrenergic agonists, melanocortins, thyroid-stimulating hormone and atrial natriuretic peptide, leptin, glucocorticoids (both directly and through permissive action) and growth hormone and it is inhibited by insulin, neuropeptide Y and peptide YY [10].

However, all the metabolic reactions described above can only occur intracellularly, after the glycerol has crossed the plasma membrane barrier. Glycerol transport across cell membranes requires specific proteins called aquaglyceroporins, a subfamily of the water channel proteins aquaporins (AQPs), [11]. For these reasons AQP expression and functioning play a key role be implicated in the control of fat accumulation and in the associated metabolic alterations.

2. Aquaporins

Aquaporins are integral membrane proteins that were initially thought to function only as bidirectional water-selective channels, but they have successively been found to play a role in important cellular functions, such as cell proliferation, cell differentiation, cell migration and cell adhesion [12,13,14]. Thirteen water channel proteins have been identified in mammals and they have been divided into three groups based on their structural and functional characteristics: (i) aquaporins (AQP1, 2, 4, 6 and 8) selectively permeable to water; (ii) aquaglyceroporins (AQP3, 7, 9 and 10) permeable to glycerol, urea and other small solutes in addition to water (see Table 1 for tissue localization and main physiological functions); (iii) S-aquaporins (AQP11 and 12), with peculiar intracellular localization and functions, currently under study [12,15,16]. AQPs are small proteins (26–34 kDa) assembled as homotetramers in the membrane, with each monomer containing a single aqueous pore. As demonstrated for AQP1, the monomer sequence consists of two repeated segments (tandem repeats), each formed by three α-helical transmembrane domains and five loops (three external and two internal to the membrane), with the amino-and carboxy-termini intracellularly localized. The two tandem repeats contain (in the second and the last loop) two highly conserved domains called NPA boxes (Asn-Pro-Ala) that play a crucial role in pore formation. In the "hourglass model", the six transmembrane helices form the walls of the channel, like two connected bulbs, while the two NPA motifs, folding in the center of the membrane, represent the narrowest part of the pore. This channel conformation allows a trickle of water molecules in single-file from one side of the membrane to the other, which depends exclusively on the presence of an osmotic gradient across the