Glutamine is the most abundant amino acid in plasma and has numerous roles in the organism. To fulfill these roles glutamine has to be taken into or released from cells by active transporters. Currently, at least 14 amino acid transporters have been identified to transport glutamine. Six of these transporters belong to the SLC38 family: SNAT1, SNAT2, SNAT3, SNAT5, SNAT7 and SNAT8. In this review, after briefly reviewing the SLC38 family members, we focus on the putative physiological function and regulation of SNAT3. SNAT3 is expressed in liver, brain, kidney, pancreas, muscle, adipose tissue, and eye. SNAT3 is able to allow both the import and export of glutamine depending on cellular demand. SNAT3 is involved in energy metabolism, brain physiology, gestation, ammonia detoxification and acid-base balance. Here, we review the evidences for the role of SNTA3 in these processes focusing on most recent advances.

Glutamine is the most abundant free amino acid in the organism with concentrations between 0.2 and 20 mM in intracellular compartments and concentrations on average around 0.7 mM in the extracellular space. Even though the organism is capable to synthesize glutamine, it is a conditionally essential amino acid as it is involved in many biological processes and under specific conditions intake of glutamine is necessary to meet requirements.

Traditionally, glutamine has been seen as the nitrogen carrier between organs and as the nitrogen store in muscle. Glutamine is the preferred fuel of rapidly proliferating cells in the gastrointestinal and immune system. This amino acid is a precursor of peptides, purines, pyrimidines, glucose and other biologically important molecules like the antioxidant glutathione, the excitatory neurotransmitter \( \gamma \)-aminobutyric acid (GABA). Glutamine plays a major role in the glutamate-glutamine cycle in the brain. The glutamate-glutamine cycle in the brain refers to the uptake of glutamate by the astrocytes surrounding the excitatory glutamatergic neurons. In astrocytes glutamate is converted to glutamine and glutamine is transferred back to glutamatergic neurons. In addition, GABAergic neurons take up the released glutamine for the synthesis of GABA. Yet, not all glutamate released is recovered again by neurons but some is also used as energy fuel to allow glutamate and GABA transport into astrocytes and the restoration of the sodium gradient. Therefore, in order to maintain the open glutamate-GABA-glutamine cycle de novo synthesis of glutamine in astrocytes occurs.

Glutamine plays also an important role as a non-toxic nitrogen carrier between organs. Probably, skeletal muscle is the organ contributing most to the de novo synthesis of glutamine. In skeletal muscle, the synthesis of glutamine partly serves to detoxify ammonia produced by amino acid metabolism. A large part of plasma glutamine probably undergoes turnover in intestinal epithelial cells. The ammonium ions produced are excreted to the portal vein and glutamine and ammonium are taken up by periportal hepatocytes. Here, glutamine is broken down to glutamate and ammonia which then enters the urea cycle. This is accomplished by the zonal expression of enzymes in the liver: the enzymes synthesizing urea are present in periportal hepatocytes whereas the glutamine synthetase, the enzyme responsible for de novo synthesis of glutamine, is present in perivenous hepatocytes. The urea synthesized in liver is then excreted by the kidneys into urine.
Glutamine plays also an important role in acid-base balance. In acidosis, glutamine is taken up by the kidney for ammoniagenesis and de novo synthesis of bicarbonate by increased activity of the renal glutaminase enzyme. 70% of the ammonia produced during acidosis is used to carry protons into the urine as ammonium and the remainder is released to the renal vein. On the other hand, during alkalosis less ammonia is produced in the kidney.

In order to fulfill its numerous roles in the organism, glutamine has to be taken in and out of cells. The influx and efflux processes occur by the action of active transporters as glutamine is hydrophilic and zwitterionic at physiological pH and often the flux is against a concentration gradient. Several amino acid transporters allow the uptake and release of glutamine from cells (recently reviewed in ) Moreover, the peptide transporter PEPT1 and PEPT2 allow the uptake of glutamine as di- and tripeptides in intestinal epithelial cells and renal epithelial cells, respectively. Currently, at least 14 amino acid transporters have been identified to carry glutamine. These transporters carry not only glutamine but also other neutral amino acids and in some cases cationic and anionic amino acids. They belong to 4 different families: ASCT2 (SLC1 family); ATB0, and B0AT1 (SLC6 family); LAT1, γ-LAT1, γ-LAT2, LAT2 and b0, AT (SLC7 family); and SNAT1, SNAT2, SNAT3, SNAT5, SNAT7 and SNAT8 (SLC38 family). Some as b0, AT are exchangers, others like ATB0 allow the influx of glutamine into the cells, and others like SNAT3 are capable to take up and release glutamine into or out of cells, respectively. The localization of these transporters in the body is widespread enabling glutamine metabolism and actions.

The members of the SLC38 family transport neutral amino acids and are considered the major glutamine transporters in mammalian cells. The SLC38 family members are not only present in the apical membrane of intestinal and renal epithelial cells, but in membranes that face blood vessels or intercellular space like in astrocytes in the brain.

Here, we briefly review the SLC38 family members focusing in recent work, and focus in more detail on recent advances in the understanding of the physiological functions and regulation of one of these family members, namely SNAT3 (SLC38A3). SNAT3 is the only member of this family which biological relevance has been investigated not only heterologous systems but also in an in vivo model. The mechanism of action of these transporters is not the scope of this review as it has been recently reviewed in detail (see ref. 9).

The SLC38 family

An important feature of the SLC38 family members is that they carry out net transport of amino acids and not only exchange of amino acids, and therefore can modulate intracellular amino acid pools. The solute carrier family 38 comprises 11 mammalian members (reviewed in detail in ). Five of the SLC38 members have been extensively characterized functionally, mainly in heterologous expression systems and cell culture models, and have been divided in 2 major subgroups: system A and system N type transporters. System A is characterized by a transport activity preferring small neutral amino acids such as alanine and which is inhibited by the substrate analog N-methyl-aminoisobutyric acid (MeAIB) and is stimulated by amino acid depletion. It comprises the transporters with similar functional characteristics to SLC38A2 (aliases: SNAT2, SAT2, ATA2, SA1). SLC38A1 (aliases: SNAT1, GlnT, SAT1, ATA1, SA2, NAT2) and SLC38A4 (aliases: SNAT4, SAT3, ATA3, NAT3, PAAT) belong to the system A type transporters. A recent study has also included SLC38A8 (SNAT8) as a system A transporter type after performing expression and functional analyses. System N describes a transport activity specific for glutamine, asparagine and histidine, amino acids with an extra nitrogen in the side chain. This transport activity comprises the transporters with similar functional characteristics to SLC38A3 (aliases: SNAT3, SN1, NAT). SLC38A5 (aliases: SNAT5, SN5) belong also to the system N type transporters. Additionally, SLC38A7 (aliases: SNAT7) has been recently proposed to belong to this subfamily.

System A transporters

SNAT1 was first cloned from rat cerebellar primary cultures. Shortly after, 3 different groups cloned SNAT2 from various rat and human tissues. Both transporters are expressed ubiquitously and are able to transport alanine, serine, cysteine, asparagine, glutamine, histidine and methionine. The transport is electrogenic as 1 Na+ ion is co-transported with 1 substrate molecule. The transport activity is inhibited
by N-methyl-aminoisobutyric acid (MeAIB) and regulated by amino acid levels. In the brain, SNAT1 and SNAT2 are expressed in neurons where they are part of the glutamate-GABA-glutamine cycle. After glutamine release from the astrocytes in the intercellular space, the glutamine is taken up in the glutamatergic and GABAergic neurons by the action of SNAT1 and SNAT2.\(^4\) In L6 muscle cells and probably also other cells where SNAT2 is expressed, one proposed role is that SNAT2 allows taking up neutral amino acids and creates an (electro)chemical gradient which allows the uptake of essential amino acids, like leucine by exchange transporters located in the plasma membrane.\(^9,29\) This mechanism is essential to provide leucine to the mTOR signaling pathway.

Recently, it has been shown that transgenic overexpression of SNAT2 in liver increased the total hepatic free amino acid concentration with the resulting activation of the mTORC1/S6K signaling pathway.\(^80\) This activation leads to the increase of circulating triglyceride in blood due to downregulation of triglycerides hydrolysis mediated by the adipose lipoprotein lipase. Adenoviral overexpression of Rheb in the liver, a known activator of the mTORC1/S6K signaling pathway, leads also to increased triglycerides in plasma. Probably, this liver-adipose tissue interorgan talk is mediated by afferent vagal and efferent sympathetic signals. In the liver, SNAT2 together with SNAT4 are important to provide glutamine and alanine as precursors of glucose for gluconeogenesis, especially in the first hours of fasting. SNAT4 was also cloned in 2000.\(^75\) This system A transporter type is liver specific in humans,\(^38\) where it is expressed in the perivenous hepatocytes.\(^82\)

Moreover, SNAT2 has been proposed to be a “transceptor,” i.e. it modulates signaling pathways in the cells, not only by increasing other amino acid concentrations in the cells, but also SNAT2 itself acts as a substrate sensitive receptor.\(^41\) This implies that after amino acid binding to SNAT2 it activates signals that consequently activate gene expression and signaling. After amino acid depletion, SNAT2 is able to activate gene expression of several amino acid transporters including SNAT2.\(^40\) Yet, the mechanism how SNAT2 “transceptor” modulates gene expression, is to our knowledge, still not fully understood. SNAT2 is also regulated by osmotic stress, hormones, amino acid availability, and growth factors. Therefore, SNAT2 plays an important role in function and state of the cells.

SNAT8 is the least well characterized family member that may belong to the system A transporters.\(^36\) SNAT8 is expressed in neurons in the brain, in GABAergic and glutamatergic neurons. Moreover, it is expressed in pituitary, thymus, stomach and adrenal gland, among other tissues.\(^76\) The function of SNAT8 is still unknown but mutations in the SNAT8 gene have been associated in some patients with foveal hypoplasia 2, a hereditary ocular disease.\(^61,63\)

**System N transporters**

SNAT3 was the first member of the SLC38 family to be cloned.\(^18\) SNAT5 was cloned shortly after.\(^56\) System N transporter types have a narrower substrate specificity than system A transporters. SNAT3 and SNAT5 are able to transport glutamine, asparagine and histidine, and SNAT5 can also transport alanine and serine.\(^9\) Along with 1 substrate molecule, 1 Na\(^+\) ion is cotransported and 1 proton is antiported, resulting in an electroneutral transport process. A unique property of these transporters is that replacement of NaCl by LiCl in flux studies does not abolish transport activity. Moreover, strong activation of transport activity occurs by increasing the pH in the physiological range from 6 to 8 and the transporters are able to function in both directions.

SNAT3 is highly expressed in liver, kidney, and brain, and its expression has also been reported for adipose tissue, pancreas, skeletal muscle, and the eye. In brain, it is mostly localized in astrocytes and endothelial cells of the blood-brain barrier, in the kidney in the proximal tubule, and in the liver in periportal and perivenous hepatocytes.\(^18,34,55,67,72\) SNAT5 is mainly expressed in intestinal tract, kidney, retina, lung and cervix.\(^56,57\)

The details on recent advances in SNAT3 function are discussed below, but in general for the system N transporter the following functions are assumed. In the brain SNAT3 and SNAT5 are part of the glutamate-GABA-glutamine cycle being responsible for the glutamine release from the astrocytes in the intercellular space.\(^7,53\) In periportal hepatocytes, SNAT3 and SNAT5 are likely to be involved in the uptake of glutamine and in the perivenous hepatocytes SNAT3 is probably involved in the release of glutamine from the hepatocytes to the circulation.\(^6,34\) SNAT5 and SNAT3 are also expressed in kidney where they are probably involved in ammoniagenesis especially during metabolic acidosis.\(^6,15,55,72\)
SNAT7 is the least well characterized family member that may belong to the system N transporters. Yet, SNAT7 does not tolerate replacement of NaCl by LiCl in flux studies like the other system N transporters and it transports glutamine in addition to histidine and asparagine also arginine, glutamate and aspartate. Further studies, especially regarding its pH dependency are necessary to group SNAT7 to the system N transporters. SNAT7 is highly expressed in liver and also in brain, skeletal muscle, uterus and pituitary. The function of SNAT7 in the organism is still unknown.

The SLC38 orphan family members

An unpublished human gene sequence with 44–48% identity to SNAT1-5 was named SNAT6 (reviewed in ref. 49). SNAT6 is expressed ubiquitously. In the brain, SNAT6 is expressed in glutamatergic neurons. SNAT10 and SNAT11 are also ubiquitously expressed, but SNAT10 shows highest expression by real-time PCR in the lung, pituitary, eye and hippocampus and SNAT11 shows highest expression in the gastrointestinal tract, liver and testis. The subcellular localization, function, and substrate specificity of these putative transporters are still unknown.

SLC38A9, a “transceptor”

Due to 2 recent publications, SNAT9 cannot be included within the orphan SLC38 family members but can also not be assigned to the System A or System N transporters. SNAT9 is ubiquitously expressed. Yet, SNAT9 is not expressed at the plasma membrane but in lysosomes, where it is part of the amino acid sensing machinery that controls the mTORC1 pathway. It has a low affinity for arginine and is also able to transport glutamine. The authors suggest that SNAT9 main function is to be a “transceptor” rather than a transporter. As part of the Rag-Ragulator-mTORC1 complex, SNAT9 is involved in sensing arginine and glutamine availability in the cell. Moreover, the direct sensor of arginine has been recently published, CASTOR1, which interacts via GATOR2 with the SNAT9-Rag-Ragulator-mTORC1 complex. This sensor acts similarly and probably in accordance with the recently discovered leucine sensors Sestrin1 and 2. The direct sensor of other amino acids like glutamine, if existing, remains yet to be identified.

SNAT3 function and regulation and in energy metabolism

Glutamine has a major role in energy metabolism, as a precursor of α-ketoglutarate that enters the tricarboxylic (TCA) cycle for oxidation to generate the substrates for gluconeogenesis producing glucose, the major fuel of most cells in the organism. Glutamine primarily serves as fuel in intestinal cells and the immune system, where SNAT3 is not expressed. In order to maintain glucose plasma levels during fasting, the organism first uses the glycogen stores in the liver and after approximately 4 hours fasting glucose is synthesized via enhanced gluconeogenesis. Major gluconeogenesis substrates are pyruvate, glycerol, lactate and the amino acids alanine and glutamine. These amino acids are mainly derived from protein catabolism in muscle. The liver is the major site of gluconeogenesis but this pathway takes also place to a lesser extent in kidney and small intestine. Probably, the major amino acid used for gluconeogenesis in the liver is alanine where as in the kidney the major amino acid used is glutamine.

As already mentioned, SNAT3 is expressed both in liver and kidney. It has been also reported to be expressed in muscle. Both, SNAT3 and SNAT5 are expressed in fast-twitch and slow-twitch fibers. In muscle, SNAT3 could contribute to the uptake of glutamine for metabolism or storage and for the release of glutamine from skeletal muscle when it is required as glucose precursor in the liver and kidney. However, this hypothesis needs further investigation as it has been recently shown in pigs that insulin perfusion did not affect SNAT3 expression in muscle, although the authors discussed that this lack of response could be due to too short perfusion time. A previous study showed that indeed insulin regulates SNAT3 expression, at least in hepatocytes. Expression of SNAT3 is upregulated in calorie restricted mice. Additionally, a chronic insulin treatment resulted in SNAT3 downregulation via the mTOR pathway whereas an acute treatment with insulin resulted in stimulated migration and surface expression of SNAT3. Yet, although the mechanism is not known, a clear sign of the involvement of SNAT3 function in glucose homeostasis is the hypoglycemia observed recently in mice after ablation of SNAT3 function. Ablation of SNAT3 function by N-ethyl-N-nitrosourea (ENU) mutagenesis in the whole organism led to several phenotypes that end in
the death of the animals at approximately 21 d of age. One of the clinical signs was hypoglycemia. Interestingly, insulin levels were also decreased probably in order to compensate the hypoglycemic state. Glutamine and alanine in the liver were also decreased, thus reducing the availability of these substrates for gluconeogenesis. As alanine is not a SNAT3 substrate, its reduction could be due to SNAT4 action or an increased utilization instead of glutamine as phosphoenolpyruvate carboxykinase (PEPCK) protein levels were increased and glutaminase 2 (GLS2) protein levels were decreased. PEPCK is a key enzyme in gluconeogenesis and GLS2 is the enzyme responsible for the breakdown of glutamine to glutamate which enters the TCA cycle as α-ketoglutarate to provide substrates for gluconeogenesis. Ablation of SNAT3 function led also to a substantial reduction in the activated forms of mTOR and S6K levels in liver. The mTORC1/S6K signaling pathway is involved in energy metabolism, cellular proliferation, protein synthesis and body growth. SNAT3 ablation led to a reduction of glutamine, phenylalanine, tryptophan, glucose, insulin and IGF1 availability and these together could account for the decrease in mTORC1/S6K signaling activity. Probably, the role of SNAT3 in the mTORC1/S6K pathway in the liver is as a transporter providing glutamine which is used by other amino acid transporters as exchanger substrate for leucine and other amino acids which activate the mTORC1/S6K signaling pathway. This role is similar to the one described for SNAT2 in muscle and recently in liver, and differs from the proposed role of SNAT9 as a “transceptor” in mTORC1/S6K signaling.

A further proposed role of SNAT3 in energy metabolism is as a “transceptor” in the pancreas for glutamine-induced insulin secretion. Glutamine has been reported to trigger insulin secretion by the β-cells in pancreas, and SNAT3 is apparently responsible for glutamine uptake in these cells. It has been proposed that glutamine uptake by SNAT3 in the endocrine pancreas due to elevated glutamine serum levels may stimulate insulin secretion. The glutamine transport may act as a signal itself or the conversion of glutamine to glutamate may be the trigger as glutamate acts as an intracellular signaling molecule stimulating insulin release in β-cells. On the contrary, if the glutamine levels in serum are decreased between meals, glutamine might be released from β-cells in pancreas via SNAT3. Moreover, SNAT3 is not only expressed in the endocrine pancreas, but also in the exocrine pancreas. SNAT3 together with SNAT5, LAT1 (SLC7A5) and LAT2 (SLC7A8) are the amino acid transporters showing the highest expression in acinar cells and only SNAT3 and SNAT5 are downregulated during pancreatitis. The role of SNAT3 in pancreas needs further investigation.

**SNAT3 function in the brain**

Probably a major role of SNAT3 in the brain is the contribution to an optimal neurotransmission, via the GABA-glutamate-glutamine cycle. Glutamine is the precursor of the excitatory amino acid glutamate and the inhibitory neurotransmitter GABA. In the brain the glutamate released into the synapse is taken up by the surrounding astrocytes through the glutamate transporters EAAT2 (SLC1A2) and EAAT1 (SLC1A3). Glutamate is then converted to glutamine and released via SNAT3 and SNAT5 to the extracellular fluid where is taken up again by neurons probably via SNAT1 and SNAT2. In neurons, glutamine is then converted to glutamate restoring the neurotransmitter pool. A similar process happens for the inhibitory neurotransmitter GABA. In this case astrocytes surrounding GABA releasing neurons take up GABA by the GAT3 transporter (SLC6A12). SNAT3 and SNAT5 are probably the major mediators of glutamine release from astrocytes. These transporters have a different spatial distribution in the brain: SNAT3 is more abundant in neocortex, cerebellum, olfactory bulb and brain stem, whereas SNAT5 is more abundant in striatum, spinal cord and neocortex. Probably due to the abundance in the cerebellum, ablation of SNAT3 function in the organism leads to ataxia in these mice which corroborates the importance of SNAT3 in allowing an optimal neurotransmission. Additionally, recent work shows that ablation of SNAT3 and SNAT5 function by small interfering RNA (siRNA) in cultured neocortical astrocytes impaired the released of glutamine from astrocytes. SNAT3/SNAT5- astrocytes when compared to wildtype astrocytes showed 3.5-fold increased levels of glutamine and a 2-fold increase of glutamine related metabolites as glutathione, aspartate, alanine and glutamate. Interestingly, SNAT3 in astrocytes has been proposed to act as a sensor of neuron-derived glutamate. Incubation of cultured astrocytes with physiological concentrations of glutamate caused a
2-fold increase of SNAT3 mediated transport activity. Martinez-Lozada et al. using the cerebellar Bergmann glial cells model showed that D-aspartate (a substrate of EAAT1), enhanced the coimmunoprecipitation of EAAT1 and SNAT3 whereas glutamine tended to reduce this association. This observation could explain the functional coupling of glutamate uptake and glutamine release in brain.52

In brain, SNAT3 is also expressed in the endothelial cells forming the blood-brain barrier (BBB). Confocal microscopy and in vivo biotinylation data revealed SNAT3 expression in mice at both luminal and abluminal plasma membranes of larger microvessels and BBB capillaries.67 Therefore, SNAT3 was suggested to be the system N transporter responsible for the low but significant uptake of glutamine from blood to brain.5,28,67 Yet, ablation of SNAT3 function led to increased glutamine levels in the whole brain. Therefore, SNAT3 may be involved in the export rather than the import of glutamine into the brain, or the transport direction is determined by glutamine availability in the cerebrospinal fluid. Clearly, the function of SNAT3 at the BBB needs further investigation.

**SNAT3 function in ammonia detoxification**

The hepatic metabolism of urea, the waste product of amino acid and protein catabolism, is zonated. Urea is predominantly synthesized in the periportal hepatocytes from glutamine and ammonia that enter the urea cycle. Ammonia escaping detoxification in the urea cycle is trapped downstream in the perivenous hepatocytes. Here, glutamine is synthesized by the enzyme glutamine synthetase from glutamate and ammonia.34,81 SNAT3 could therefore be responsible for the uptake of glutamine into the periportal hepatocytes and for the release of the synthetized glutamine from the perivenous hepatocytes. Surprisingly, ablation of SNAT3 function in mice led to increased urea levels and non-altered ammonia levels in plasma.15 SNAT5 mRNA levels were increased in these mice which could account for the increased glutamine uptake in periportal hepatocytes (unpublished data from the authors). Moreover, 2 enzymes involved in the urea cycle, arginase 1 (Arg1) and argininosuccinate lyase (Asl) mRNA levels were also increased, whereas carbamoylphosphate synthetase and ornithine transcarbamoylase mRNA levels were not altered.15 Conditional ablation of SNAT3 in liver is necessary to further explore the cell-type specific function of SNAT3 in ammonia detoxification.

**SNAT3 function in acid-base balance**

The kidney controls together with other organs (lungs, liver, bone, skeletal muscle or intestine) systemic acid-base homeostasis. The kidney senses the levels of protons and bicarbonate continuously and adapts to these levels by generating bicarbonate from glutamine in the proximal tubule or synthesising bicarbonate in the collecting duct to keep the pH in a narrow range.84 Metabolic acidosis can occur during starvation and uncontrolled diabetes as a result of excessive lactate, hydroxybutyrate and acetoacetate production.30 It is compensated by respiratory and metabolic changes resulting in the extrusion and buffering of protons. In the kidney, mostly in the proximal tubule, glutamine is extracted from blood and converted to α-ketoglutarate by the action of phosphate-dependent glutaminase (PDG) and glutamate dehydrogenase (GDH) thereby releasing ammonia (Fig. 1). α-ketoglutarate serves as substrate for renal gluconeogenesis and
ammonia binds to protons to form ammonium ions which are released into urine.

At physiological pH almost no glutamine is removed from blood by the kidneys, but when metabolic acidosis occurs net extraction can reach 30%. SNAT3 has been suggested as the transporter responsible for the extraction of glutamine from the circulation to the renal cells due to its localization and observed parallelism of SNAT3 induction and increased renal ammoniagenesis. Other enzymes and transporters together with SNAT3 are pH sensitive and are responsible to maintain the acid-base balance. SNAT3 increases expression in the renal cortex and the medullary stripe during chronic acidosis. A recent study suggests that the expression of SNAT3 during acidosis is mediated by a different mechanism than the tissue-specific expression. The authors studied the renal cell line LLC-PK1, a recognized model system to study renal pH and ammoniagenesis regulation. During acute acidosis, increased SNAT3 expression is triggered by Sp1 binding to the SNAT3 promoter, but during chronic acidosis up-regulation is due to stabilization of SNAT3 mRNA. By contrast, tissue-specific expression of SNAT3 is mediated by epigenetic mechanisms like histone modification and promoter methylation.

A further confirmation of the role of SNAT3 in ammoniagenesis is the fact that ablation of SNAT3 function in the whole organism leads to a decrease in the urinary ammonium excretion. Moreover, these mice showed increased renal phosphoenol pyruvate carboxykinase (PEPCK) protein levels. Increased renal PEPCK levels have been suggested to reflect impaired ammoniagenesis rather than increased gluconeogenesis in acidosis as fasting increases PEPCK mRNA levels, and this increase cannot be reverted by glucose or insulin, but by bicarbonate (lynedjian, Ballard et al. 1975). Furthermore, heterozygous Snat3+/− mice, which show haploinsufficiency, require a higher expression of PDG and PEPCK mRNA levels to achieve a similar ammonia excretion rate in urine as wildtype animals when challenged by an acid load (NH4Cl) for 2 d. This further suggests that partial loss of SNAT3 function impacts on ammoniagenesis.

Renal metabolic acidosis is also common in the late stages of chronic kidney disease (CKD). It is associated with several complications and to the mortality rate in both dialysis and non-dialysis CKD patients. Metabolic acidosis per se could be associated with progression of CKD and recent evidence suggest that alkalinization of blood in CKD patients is associated with improved survival and reduction in proteinuria. The mechanism behind is still unknown. Using Han:SPRD, a rat model for CKD, a recent study shows that urinary ammonium excretion was highly reduced in CKD compared to control animals accompanied by a concomitant decrease of the levels of PDG, PEPCK and the bicarbonate transporter NBCe1. Interestingly, SNAT3 protein and mRNA levels were also reduced in CKD rats compared. Another recent study shows that podocyte alkalization protects the podocyte cytoskeleton which probably leads to a reduced proteinuria. In physiological conditions SNAT3 is not expressed in podocytes, but SNAT3 has been reported to be expressed in the mitochondrial membrane of damaged podocytes with a paralleled increased glutamine utilization. Overexpression of SNAT3 in mice led to alkalinized glomeruli and development of less foot processes (FP) effacement and proteinuria in a LPS podocyte injury model. Therefore, through modulation of podocyte glutamine utilization and pH, proteinuria in CKD patients might be diminished. However, the manuscript does neither report the source of antibodies nor provide evidence for the specificity of antibodies used against SNAT3. Thus, the finding that SNAT3 can be expressed in mitochondria remains to be validated.

An acid load challenge in obese and wildtype animals led to a higher SNAT3 induction in the obese than the wildtype mice independently of the insulin resistance state of the animals. This increase was probably an unsuccessful attempt to compensate in the kidneys the impaired ammonium excretion in response to an acid load in obese and insulin resistance animals.

**SNAT3 function in gestation**

SNAT3 is weakly expressed in uterine bovine endometrium. In rats SNAT3 has been found expressed in the placenta, but in contrast to other amino acid transporters SNAT3 is highly expressed in the early stages of pregnancy and its expression decreases during pregnancy until the last stages. In humans, SNAT3 was detected in isolated cytotrophoblasts but its expression decreased significantly as differentiation of cytotrophoblasts progressed. The authors proposed a role of SNAT3 in the existing active glutamate-glutamine...
cycle (reviewed in [5]) to provide glutamine to the fetus and to excrete glutamate and ammonia from fetal circulation in the early stages of gestation.

### Other features of SNAT3 regulation

In the previous sections we have already mentioned that SNAT3 expression and probably function is regulated by changes in pH, insulin levels, and nutrient availability and in disease stages like CKD. In this section we compile further aspects of SNAT3 regulation that could not be related to any of the putative physiological actions of SNAT3 discussed in the previous sections.

Injury or damage causes higher glutamine requirements of cells that are met by increasing SNAT3 expression (and probably other glutamine transporters), as shown in 3 in vitro models of podocyte damage, a genetic (α3 integrin deletion), an immunological (administration of lipopolysaccharide (LPS)) and a toxic model (exposure to puromycin aminonucleoside (PAN)). In a previous study, also treatment with LPS led to an increased expression of SNAT3 and SNAT5 in a time- and dose-dependent manner, probably due to a higher demand of glutamine.66

Cadmium is a known human lung carcinogen. In a peripheral lung epithelia cell line, HPL-1D, chronic exposure to cadmium provoked signs related to carcinogenesis like hyperproliferation, invasion and colony formation in vitro. In this model SNAT3 expression was downregulated at the protein level.62 However, SNAT3 expression in lung in vivo is very low and whether SNAT3 dysregulation contributes to cancer pathology remains to be further examined. Exposure to manganese, which causes neurotoxicity and is a risk factor for neurodegenerative brain disorders, also leads to decrease SNAT3 protein levels in astrocytes. This decrease is caused by increased SNAT3 protein degradation by the ubiquitin-mediated proteolytic system.71

Last, in transfected cells it could be shown that SNAT3 is regulated by phosphorylation mediated through protein kinase C α (PKC α) and PKC γ. Phosphorylation reduced dramatically the V_{max} but no significant effects were seen on the apparent affinity for glutamine (K_m). Phosphorylation occurs at a single serine residue (S52 in the SNAT3 sequence from rat) and results in sequestration of the protein into intracellular reservoirs.58 Moreover, prolonged activation of PKC results in partial degradation of SNAT3 probably via the ubiquitin-mediated proteolytic system.

### Conclusion

SNAT3/SLC38A3 is widely expressed and has numerous roles in the organism due to its capacity to release or take up glutamine (see Fig. 2). In energy metabolism, SNAT3 provides substrates to the gluconeogenesis pathway, it is involved in insulin metabolism, probably by function in the pancreas, and it is
involved in the mTORC1/SK6 pathway. SNAT3 plays an important role supporting neurotransmission in the brain via its action in the glutamate-glutamine cycle allowing the release of glutamine from astrocytes. In the brain, a role that needs further investigation is the export or import function at the blood-brain barrier. SNAT3 is also involved in ammonia detoxification by modulating glutamine catabolism or anabolism in the periportal and perivenous hepatocytes. A well-studied role of SNAT3 is its contribution to maintain the acid-base balance in the organism by regulating renal ammoniagenesis. Moreover, it could be involved in the protection of damaged podocytes in CKD. A less-studied role is the function of SNAT3 in gestation, probably in the glutamine-glutamate cycle in the placenta. Despite all the insights displayed here, more studies using in vivo models are required to further understand the multiple functionalities of the glutamine transporter SNAT3.

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No potential conflicts of interest were disclosed.

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