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Glucose transporters in gametes and preimplantation embryos.

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Abstract

The oocyte, sperm, and preimplantation embryo have unique metabolic needs that must be met to ensure successful pregnancy. The family of facilitative glucose transporters (GLUTs) plays a major role in providing metabolic substrates to these tissues. The variety of GLUTs expressed in these tissues allows the flexibility to adapt to a changing environment. Alterations in glucose transport and metabolism at the earliest stages of development can impact fetal development. Research into the mechanisms of normal glucose transport into cells is critical to improving outcomes in the increasingly common diabetic maternal environment. Here we review the current understanding in the distribution and role of glucose transporters in gametes and preimplantation embryos under normal and diabetic conditions.

Relevance of glucose transporters in reproduction

Glucose transport is essential for the major components involved in the establishment of pregnancy: oocyte, sperm, and preimplantation embryo. Glucose enters cells by either the active process via sodium coupled glucose transporters (SGLTs) or through facilitative glucose transporters (GLUTs). Although SGLTs are present in oocytes and embryos [1], most evidence supports their minimal role in these tissues [2] and these transporters will not be discussed further. There are fourteen members of the GLUT family, GLUT1–12, the H^+ coupled myo-inositol-transporter (HMIT) and GLUT14 [3, 4]. All GLUTs contain intracellular amino- and carboxy termini, 12 membrane-spanning domains, and a glycosylated extracellular and intracellular loop [5]. The GLUTs exhibit a high degree of sequence homology but differ in their substrate specificity, kinetic characteristics, and tissue and subcellular distribution [3].

The gametes and preimplantation embryo go through major changes in their environment, metabolic needs, and in the latter, cell number and degree of differentiation prior to implanting into the uterus. The variety of GLUTs present in gametes and preimplantation embryos allow them the flexibility to adapt to these changes. However, an abnormal environment can cause dysfunction in nutrient transport leading to decreased fertility, and adverse fetal outcomes [6]. Diabetes is the most common pre-existing medical condition in pregnant mothers and despite advances in care, adverse outcomes in diabetic pregnancies are still 3–9 times more common in non-diabetic pregnancies [6]. Studies in mice show that hyperglycemia in preimplantation embryos causes downregulation of GLUTs, resulting in lower intracellular glucose, abnormal metabolism, and increased apoptosis at the blastocyst stage [7–9]. This hyperglycemia-induced apoptosis of progenitor cells in the embryo may

affect differentiation of the remaining cells, manifesting later as malformations or miscarriages. Besides hyperglycemia, recent research has focused on hyperinsulinemia and insulin resistance on glucose transport in preimplantation embryos, as well as in male and female gametes. This review focuses on glucose transport in gametes and the preimplantation embryo in the normal and diabetic states, with particular attention to the more recently identified GLUTs.

Gametes

Sperm

Sperm metabolism may proceed through either glycolysis, mitochondrial oxidative phosphorylation, or the pentose phosphate pathway; the predominant pathway used depends on species, oxygen content and/or hexose availability [10]. Much of the ATP required by sperm is used for motility [10]. In sperm cells, the mitochondria are localized to the midpiece, the site of oxidative metabolism, while the head and tail are sites of glycolytic activity [10, 11]. Inhibitors of either oxidative metabolism or glycolysis in many species show that either pathway can maintain mobility independently [10]. Early work indicated that GLUTs 1, 2, 3, and 5 appear to be the major GLUTs expressed in sperm cells (Table 1) [12]. GLUT3 localizes to the midpiece in most species, indicating GLUT3 mediated transport may be the predominant method at the site of the mitochondria [12]. Fructose is the most abundant energy source in the male reproductive tract and fructose uptake by human sperm has been shown [13]. Accordingly, the fructose-specific transporter, GLUT5 has been identified uniformly along ejaculated sperm in many species [12, 14, 15].

Some of the more recently identified GLUTs have been found in sperm. GLUT8 was initially identified in the testes, as well as other tissues [16, 17]. Others have found GLUT8 in mature sperm cells 18–20. Localization of GLUT8 is primarily on the acrosome [18–20]. GLUT8 has an endosomal and lysosomal targeting motif [21], and thus far only translocates to the plasma membrane in response to insulin in blastocysts [22] and therefore may only transport hexoses across endosomes and lysosomes intracellularly. Similar to the lysosome, the acrosome of sperm cells contains lysosomal proteins at a low pH. Possibly GLUT8 has a role in the acrosome reaction upon sperm binding to the oocyte. Sperm from GLUT8$^{-/-}$ mice have decreased ATP concentration and reduced motility compared to wild type; however are able to fertilize oocytes. Because it does not reside on the cell surface, it is proposed GLUT8 could be required for normal mitochondrial function intracellularly [23]. Also recently identified, GLUT9 has a high degree of homology to GLUT5 that transports fructose as well as glucose [24]. Two isoforms; a long form containing 12-transmembrane domains (GLUT9a) and a shorter form lacking 2 transmembrane domains (GLUT9b) are present in sperm cells. GLUT9a and GLUT9b are both expressed in the midpiece, and GLUT9b is also found on the head and tail [18]. Both isoforms are also high capacity urate transporters [25]. Uric acid has been shown to inhibit peroxynitrite (ONOO-) production in sperm and can interact with other reactive oxygen species (ROS) such as hydroxyl radical [26]. Since ROS generated by sperm cells are involved in capacitation [26], it is possible that in addition to providing energy substrates, GLUT9 may regulate redox state and capacitation.

Abnormal glucose homeostasis has adverse outcomes for reproductive function in the male gametes [27]. Testicular function and spermatogenesis are affected in diabetic men [27, 28]. Sperm cells from men with Type I diabetes have structural defects, reduced motility, and decreased zona pellucida binding [27, 28]. Oocytes fertilized with sperm from diabetic mice exhibit decreased fertilization rates and development to the blastocyst stage [15]. Studies in Type I diabetic mice showed that GLUT8 and GLUT9b were decreased in testes and GLUT9a was undetectable [15]. In sperm cells, there was no change in GLUT8 localization or concentration, but in a genetic model of Type I diabetes, GLUT9a was not detected and GLUT9b was decreased. Sperm concentration, motility, and fertility are all decreased in Type I diabetic mice and 7 days of insulin treatment improves sperm motility and concentration [15]. Two studies have reported no change in GLUT3 concentrations in testes or sperm cells of diabetic rats [29] or mice [15]. Interestingly, recent studies have suggested that sperm cells produce and secrete insulin [30] opening the possibility of autocrine regulation of glucose uptake in these cells. Despite knowledge of the presence of GLUTs in sperm cells, further studies are necessary to shed light on their role in the etiology of the reproductive phenotypes observed in diabetic men.

Oocytes

Glucose consumption in oocytes is low and pyruvate is the major energy source [31, 32]. The cumulus cells surrounding the oocyte produce pyruvate that accumulates in follicular fluid and the oviduct [31, 33]. Although pyruvate is the preferred substrate, the machinery for glycolytic metabolism is present and both pyruvate and glucose carrier-mediated uptake have been demonstrated in human and mouse oocytes [31, 34]. This preferential uptake of pyruvate occurs in both oocytes and early embryos, and brief discussion of its uptake is warranted. Pyruvate and lactate are transported by the proton-linked monocarboxylate carrier family (MCT). There are fourteen MCT sequences identified in mammals; however, only MCTs 1–4 are involved in proton-linked lactate and pyruvate transport [35, 36]. Matching the metabolic needs of oocytes, both MCTs and GLUTs have been detected in oocytes (Table 1). The importance of pyruvate for the oocyte is evident; however, little work has been conducted into the transport mechanisms in oocytes. Studies investigating abnormal glucose transport and metabolism due to hyperglycemia or hyperinsulinemia indicate normal glucose transport is essential for oocyte function. In mouse models of Type I diabetes, oocytes are smaller and exhibit delays in maturation; while insulin treatment can reverse these effects [37]. Fertilized oocytes from Type I diabetic mice transferred into non-diabetic recipient mice result in growth-retarded fetuses that display higher rates of growth retardation and malformations such as neural tube closure problems, and abdominal wall and limb deformities [38]. Similar outcomes are seen in babies born to diabetic mothers. This indicates that hyperglycemia in the first 24 h after fertilization can have adverse effects on fetal development [38].

Most studies on diabetes in mice have been conduced on cumulus-enclosed oocytes and many of the adverse effects are likely mediated through the cumulus cells. Without adequate glycolytic production of pyruvate in these cells, the oocyte suffers the metabolic consequences. The cumulus cells surrounding Type I diabetic oocytes display increased tumor necrosis factor-related apoptosis-inducing ligant (TRAIL) and KILLER, a receptor in

the extrinsic apoptotic pathway [39]. It is possible that cumulus cells may exhibit the same down-regulation of GLUTs that leads to decreased intracellular glucose and induction of apoptosis as occurs in embryos [7–9]. Besides nutritional support, bidirectional communication between the oocyte and the surrounding cumulus cells is required for normal maturation and development [40]. Gap junction channels made of connexons allow exchange of nutrients, ions, and regulatory molecules41. In granulosa cells of Type I diabetic mice connexin 37 and 43 transcripts are decreased and gap junction communication between granulosa cells and the oocyte is reduced [41, 42].

Meiotic maturation of oocytes involves negative regulation by cyclic adenosine monophosphate (cAMP) and phosphorylation of downstream targets by AMP-activated protein kinase (AMPK) [43]. AMPK is activated by an increased AMP:ATP ratio and turns on ATP-generating processes and turns off ATP-requiring pathways [44]. Both denuded and cumulus-enclosed Type I diabetic oocytes have decreased ATP concentrations compared to controls, indicative of decreased glucose and pyruvate metabolism. The increased AMP:ATP ratio in these ooctyes should activate AMPK [45, 46]. However, diabetic oocytes exhibit decreased phosphorylated AMPK as well as decreased activities of downstream enzymes activated by AMPK. Addition of the AMPK activator 5-aminoimidazole-4-carboxamide-1-ß-D-ribofuranoside (AICAR) improves delays in oocyte maturation [46]. Other activators of AMPK such as metformin are used to treat anovulation in women with polycystic ovarian syndrome (PCOS). Women with PCOS are often insulin-resistant, and microarray data suggests genes involved in meiosis and mitosis are altered in oocytes from these women [47]. Investigation into alterations in AMPK in insulin-resistant Type II diabetic oocytes may relevant. It has been shown that the IGF-1 receptor is present in granulosa cells and in human and mouse oocytes [48] and that insulin and IGF-1 act through this receptor to affect GLUT expression and translocation in embryos [49]. Oocytes from IGF-$1^{-/-}$ mice exhibit reduced GLUT1 expression that can be restored with exogenous IGF-1 [50]. As an interesting aside, estradiol treatment increases GLUT1 mRNA in wild type and $IGF1^{-/-}$ oocytes, indicating possible steroid regulation of this GLUT in oocytes [50]. A recent study of murine endometrial stromal cells also showed steroid-mediated regulation of GLUT1 and GLUT12 [51]. Research into steroid-mediated transcription and translocation of GLUTs may be especially interesting in reproductive tissues.

Embryos

Similar to oocytes, the preimplantation embryo prior to compaction utilizes pyruvate and lactate as the primary energy sources [32, 52]. The rate of pyruvate uptake decreases at the 8-cell to morula stages, coinciding with an increase in glucose uptake [32, 53]. Pyruvate and lactate are taken up by mouse and human embryos through MCTs [32, 54]. The presence of MCT 1, 2, 3, and 4 has been shown throughout preimplantation development, although little is known about their role (Table 3). Glucose exposure prior to compaction appears to be required for normal MCT1 and MCT4 expression in morula and blastocysts [55, 56]. Besides monocarboxylate uptake, it was shown that MCT1 is involved in maintaining pH in mouse embryos from 2-cell to blastocyst stage [57, 58]. During compaction glycolytic metabolism of glucose begins, while oxidation of lactate and pyruvate continues to occur [32, 59, 60]. Although not an absolute requirement until post-compaction, glucose uptake is

present at all stages of development. Prior to compaction glucose exposure improves development, prevents apoptosis, is used in biosynthetic roles, and may be necessary for transcription of certain genes [55, 60–63].

Preimplantation embryos express a variety of GLUTs (Table 3). GLUT1 is present throughout development and after compaction is localized on the apical, and predominantly basolateral plasma membrane of the trophoblast and the plasma membrane of the inner cell mass (ICM) [64, 65]. Its likely role is to transport glucose into the blastoceole cavity and into the ICM [66]. While not present until the 8-cell stage, GLUT2 is present on both the plasma membrane and intracellularly in inner blastomeres, but in the trophoblast, is localized on the basolateral surface, indicating GLUT2 may have a similar role as GLUT1 [65, 66]. GLUT3 is a high capacity glucose transporter first expressed during compaction [66]. In morula and blastocysts, GLUT3 is localized to the apical plasma membranes and likely transports glucose into the embryo from the maternal environment [66]. Ablation of GLUT3 reduces blastocyst formation and glucose uptake at the morula stage [66]. The presence of GLUT4 is controversial, and has not been shown to translocate in response to insulin or IGF-1 in embryos [49]. Similarly, GLUT5 has not been found in mouse or human embryos, but has been detected in other species [67].

As previously mentioned, hyperglycemia causes reduced GLUT expression and decreased glucose uptake that in turn leads to apoptosis [7–9]. Specifically, when preimplantation embryos are exposed to elevated glucose concentrations GLUT1, 2, and 3 are down-regulated [8, 9]. Embryo transfer experiments show that either in vivo, or in vitro exposure to hyperglycemic conditions during the preimplantation period results in growth retardation and malformations in fetuses, and increased rates of resorption or miscarriage [38]. Transgenic mice that have reduced or deleted GLUT1 or GLUT3 recapitulate the outcomes seen in hyperglycemic conditions. For example, mice that are heterozygous for antisense GLUT1 expression display stunted growth, microophthalimia, and micrognathia, as well as caudal regression syndrome, all of which are seen in fetuses from diabetic mothers [68]. $GLUT3^{-/-}$ mice display embryonic lethality in homozygotes at the neurulation phase and a reduction in heterozygous pups [69]. $GLUT3^{+/-}$ blastocysts from these mice demonstrate atypical GLUT3 and atypical GLUT1 staining, with a moderate increase in apoptosis. $GLUT3^{-/-}$ blastocysts exhibit greatly increased apoptosis and atypical GLUT1staining [69]. A separate GLUT3 knockout mouse also reported atypical localization in $GLUT3^{+/-}$ blastocysts and embryo loss by d 12.5 [70].

The preimplantation embryo expresses the insulin and IGF-1 receptors when the embryo begins glycolytic metabolism [71]. The IGF-1 receptor is present on the surface of the trophectoderm and increased glucose uptake in response to insulin or IGF-1 acts through this receptor [72]. GLUT8 is insulin sensitive in the murine blastocyst and traffics from an intracellular compartment to the plasma membrane of the trophectoderm following insulin treatment [22]. This results in increased glucose uptake that can be inhibited by GLUT8 antisense probes while addition of GLUT1 and GLUT3 antisense has no effect [22]. Exposure to antisense IGF-1R probes blocks this translocation and culture with either GLUT8 antisense or IGF-1R antisense probes causes increased apoptosis in blastocysts [73]. Recently two GLUT8 knockout mice have been developed and both show significant

reduction in the number of GLUT8$^{-/-}$ offspring following heterozygous mating, indicating possible embryonic demise of GLUT8$^{-/-}$ mice [23, 74].

Anti-apoptotic signals such as those activated by the insulin or IGF-1 receptor have a role in normal embryo metabolism; however, high concentrations of insulin or IGF-1 result in downregulation of the IGF-1 receptor. This can reduce insulin-stimulated glucose uptake and lead to apoptosis in blastocysts [75]. Embryo transfer experiments show that high IGF-1 during the preimplantation period results in increased resorptions. [76]. Insulin and IGF-1 signal through the phosphatidylinositol 3-kinase (PI3K) pathway. The serine-threonine kinase Akt is the primary mediator of the anti-apoptotic signal in this pathway and PI3K/Akt signaling regulates processes such as cellular proliferation, growth, and glucose metabolism [49]. Components of the PI3K/Akt signaling pathway are present in murine and human embryos from the 1-cell to blastocyst stage and are involved in glucose uptake and metabolism [77–79]. Inhibition of the PI3K/Akt pathway results in decreased insulin stimulated glucose uptake and hexokinase activity, along with increased apoptosis in blastocysts and trophoblast cell lines [77, 79]. In other tissues, activators of AMPK such as metformin also signal through the PI3K/Akt pathway to improve glucose uptake in insulin-resistant tissues [80]. As discussed, AMPK activation by metformin is used for treatment of women with PCOS. Recently, it was shown that high IGF-1 concentrations caused decreased AMPK activation and decreased insulin stimulated glucose uptake, as well as increased apoptosis and smaller litters. Activation of AMPK through metformin or AICAR improved these outcomes [44]. Further studies showed that disrupted insulin signaling in trophoblast stem cells reduced AMPK activation, and that AMPK activators not only improved insulin stimulated glucose uptake, but also resulted in phosphorylated mTOR and p70S6K, two components downstream of the PI3K pathway [81]. Studies into this crosstalk between the AMPK and insulin signaling may be useful for further studies of insulin resistance in embryos.

Besides the GLUTs mentioned above, three other GLUTs have been recently identified in preimplantation embryos, though their precise roles are undefined. In mice, GLUT9a was found at the blastocyst stage and localized intracellularly in trophectoderm cells. Downregulation of GLUT9a did not alter glucose transport or apoptosis; however, transfer of these embryos into recipient mice resulted in increased resorptions, indicating GLUT9a may be important in embryo development [82]. GLUT12 mRNA transcripts were identified in murine unfertilized oocytes, zygotes, 2-cell embryos, absent at the morula stage, and again expressed in blastocysts [83]. GLUT12 has high sequence homology to GLUT8 and is expressed in insulin sensitive tissues and could represent a second insulin-responsive GLUT [84]. GLUT14 was first identified in the human testes and is highly similar to GLUT3 [4]. In a cross-species microarray using human cDNA probes, GLUT14 was identified in bovine blastocysts; no other studies have investigated its role in the embryo [85].

Conclusions and future directions

This review has highlighted current research into the role of GLUTs in gametes and embryos under normal and diabetic conditions. Although many GLUTs are expressed, a few seem to play key roles in these tissues, while the function of some GLUTs are yet to be defined.

Cumulatively, the data suggests that GLUT1, 3, and 8 are the most critical to the preimplantation embryo. These GLUTs must work in concert for optimal development, as either targeted degradation or knockout of each one separately has caused adverse outcomes. In light of the increased incidence of Type II diabetes continued research into the effects of insulin resistance may be especially important. A major impact of diabetes on embryos is downregulation of GLUTs and decreased glucose transport. Also activated by lack of nutrients is the lysosome-dependent mechanism of intracellular organelle degradation, autophagy [86, 87]. Autophagy plays a critical role in preimplantation embryo development, and may participate in the elimination of oocytes during fetal development [88–91]. The interaction of both apoptosis and autophagy in response to glucose transport dysfunction during diabetes may be another interesting avenue of future research.

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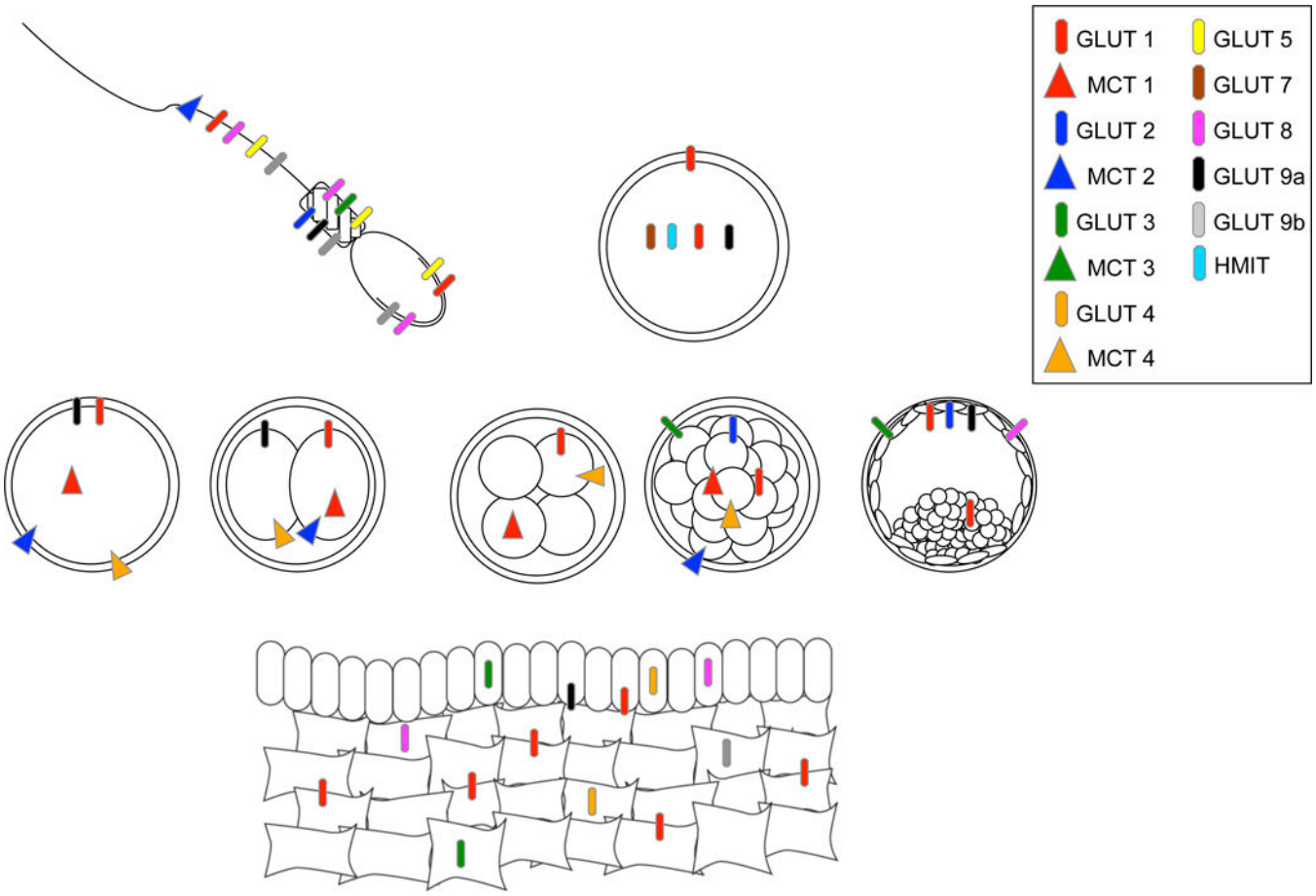

Figure 1.

Localization of glucose and monocarboxylate transporters in gametes, preimplantation embryos, and endometrium during decidualization. Symbols represent detection of protein for an individual GLUT or MCT. For references and details, see Tables 1, 2, and 3.

Table 1.

Glucose and monocarboxylate transporters in gametes

MCTs in the sperm cells			
MCT	**Location**	**Notes**	**Ref**
1	head	only in testis and proximal epidymus	35
2	tail		35, 36
GLUTs in sperm cells			
GLUT	**Location**	**Notes**	**Ref**
1	faint in head, tail	not detected in mouse sperm in two studies	25, 39, 43
2	midpiece		39
3	midpiece in most species, head and tail also in human		25, 39, 43
5	head, midpiece, tail	transports fructose	39, 42, 43
8	head, midpiece, tail	decreased ATP and motility in GLUT8$^{-/-}$ sperm	43, 45, 53, 54
9a	midpiece	transports uric acid and fructose as well, not detected in Akita mouse sperm	43, 45
9b	midpiece and tail	transports uric acid and fructose	43, 45
MCTs in the oocyte			
MCT	**Location**	**Notes**	**Ref**
1	n/a	mRNA detection	23
2	n/a	mRNA detection	23
4	n/a	mRNA detection only in mice, not in human	23
GLUTs in the oocyte			
GLUT	**Location**	**Notes**	**Ref**
1 through 12 and HMIT	n/a	mRNA detection	17
1	throughout	increased with estradiol treatment, reduced in IGF$^{-/-}$ mice	15, 16, 17
7	throughout		17
9	throughout		17
HMIT	throughout		17

Table 2.

Glucose and monocarboxylate transporters in preimplantation embryos

MCTs in preimplantation embryos

MCT	Location	Stage	Notes	Ref
1	diffuse in cytoplasm	all stages	becomes more abundant in trophoblast	23, 61, 62, 63
2	apical membrane of blastomeres and in cytoplasm	all stages		23, 62
3	n/a	all stages		61
4	plasma membrane until morula	all stages	detected in mouse, not human	23, 62

GLUTs in preimplantation embryos

GLUT	Location	Stage	Notes	Ref
1	cytoplasm, basolateral plasma membrane	all stages		74, 76, 77, 78, 79
2	cytoplasm, basolateral plasma membrane	8-cell and later		74, 76, 77
3	apical PM of trophoblast	morula and blastocyst		74, 77
5	n/a	8–16 cell and later	detected in rabbit and bovine	85, 86
8	trophectoderm trophendoderm	blastocyst	translocates from cytoplasm to plasma membrane in response to insulin	91
9a	cytoplasm of trophoblast	blastocyst	truncated form	95
12	n/a	one and two-cell, then disappears until blastocyst	mRNA	96
14	n/a	blastocyst	bovine mRNA	99

Table 3.

Glucose transporters in endometrium at the time of implantation

GLUTs in endometrium			
GLUT	**Location**	**Notes**	**Ref**
1	stroma and epithelium	upregulated in stroma during decidualization	102, 108, 109, 112
3	CD45 positive immune cells only		102
4	stroma and epithelium	no change in stroma during decidualization	108, 109, 112
8	stroma and epithelium	no change in stroma during decidualization	108, 109
9b	stroma and epithelium	no change in stroma during decidualization	108. 109
12	stroma	decreases during decidualization	108