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CELL RECEPTORS MEDIATING COMMUNICATION BETWEEN PREIMPLANTATION EMBRYO AND SURROUNDING ENVIRONMENT: CLUES FROM MOUSE AND RABBIT MODELS: A REVIEW

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ABSTRACT

Preimplantation period of embryo development is one of the most sensitive phases in the mammalian ontogeny, and disturbances at this developmental stage can result in poor pregnancy outcomes (in both embryos resulting from natural conception or from biotechnology procedures). Results of experimental studies have shown that maternal physiological conditions and external environmental factors can significantly influence preimplantation embryo development, indicating a communication between the early embryo and its environment. The study of communication between the early embryo and surrounding environment has been focused mainly on protein signaling molecules, such as growth factors and cytokines. However, small-molecule ligands, such as biogenic monoamines, have been shown to influence preimplantation embryo development as well, and results obtained on mouse and rabbit models indicate that biogenic monoamine receptors are expressed in preimplantation embryos. Several adrenergic, dopamine, serotonin and histamine receptors were detected in mouse and rabbit ovulated oocytes and preimplantation embryos, and in mouse embryonic stem cells. Although the physiological role of biogenic monoamine receptors in early embryonic cells is not fully understood, experimental data indicate their involvement in the regulation of cell proliferation, differentiation and survival under physiological as well as unfavorable or pathological conditions (e.g. during maternal stress).

Key words: preimplantation embryo; cell receptors; embryo-maternal communication

INTRODUCTION

An important part of animal biotechnology is focused on animal reproduction, and number of approaches, such as artificial insemination, multiple ovulations, *in vitro* fertilization, embryo culture, embryo transfer, cryopreservation of gametes and embryos, nuclear transfer or cloning, transgenesis and embryonic stem cell production, are used in this field. Fertilized oocyte (zygote), which can result from natural conception or artificial insemination, develops several days in the oviduct, and finally it implants into the uterine wall at the blastocyst stage. In some assisted reproductive technologies, the preimplantation development takes place *in vitro* and the blastocyst is then transferred into the uterus. Alternatively, the inner cell mass of blastocysts can serve as a source of embryonic stem cells, which are potentially usable in regenerative medicine.

Although the preimplantation period of development lasts only for a relatively short time, it represents one of the most sensitive phases in mammalian ontogeny (up to 50 % of embryo loss occurs during this period), and disturbances at this developmental stage can result in poor

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pregnancy outcomes in both humans and animals (Nepomnaschy *et al*., 2006; Humblot, 2001; Diskin *et al*., 2008). The preimplantation embryo can develop relatively autonomously in very simple culture media, utilizing transcripts and proteins provided by the oocyte and gene products synthesized by an embryo itself (after activation of the embryonic genome). However, there are data indicating that *in vitro* culture of preimplantation embryos can alter gene expression and epigenetic reprogramming, and can lead to abnormal fetal and perinatal growth as well as to physiological and behavioral alterations in adulthood (for review see Khosla *et al*., 2001; Fleming *et al*., 2004; Ventura-Junca *et al*., 2015). Moreover, results of animal studies and observations in humans have shown that maternal physiological condition (nutritional status, body condition, metabolic and other disorders, stress) as well as external environmental factors, e.g. various xenobiotics that can contaminate food, can significantly influence preimplantation embryo development (Kwong *et al*., 2000; von Borell *et al*., 2007; Fabian *et al*., 2010; Kubandová *et al*., 2014; Burkuš *et al*., 2013; 2015; Janštová *et al*., 2017; Babeľová *et al*., 2017). These data indicate that communication between the embryo and its environment takes place already in very early developmental stages.

The study of communication between the early embryo and surrounding environment has been mainly focused on protein signaling molecules, such as growth factors and cytokines, and relatively many receptors for protein ligands have been identified in preimplantation embryos (for review see Hardy and Spanos, 2002; Thouas *et al*., 2015). However, we and others have demonstrated that small-molecule ligands, such as biogenic monoamines, can significantly influence preimplantation embryo development as well. This minireview focuses on the expression of receptors for biogenic monoamines and their potential role in early embryo development.

Laboratory mouse is the most widely used model for the study of early mammalian embryo development and most information on mechanisms involved in embryo-maternal communication comes from the mouse model. Recently, the progress in rabbit genome sequencing and advantages of rabbit reproduction (high cell numbers and yield in blastocysts, relatively late implantation at a time when gastrulation is already proceeding, detailed morphologic and molecular knowledge on gastrulation stages and a hemochorial placenta structured similarly to the human placenta) are the reasons for the preferred use of a laboratory rabbit as a model for studying early embryo development (for review see Fischer *et al*., 2012). Results obtained mainly on mouse and rabbit models are presented in this review.

Receptors for biogenic monoamines

Biogenic monoamine receptors are either ion channels or G protein-coupled receptor proteins. Receptor channels (ligand-gated ion channels) are composed of several transmembrane subunits, and binding the ligand induces opening of the channel. G protein-coupled receptors are composed of seven transmembrane domains connected by cytoplasmic and extracellular loops. Binding the ligand results in activation of GTP-binding proteins (G proteins), which then activate various effectors, such as adenylyl cyclases, phospholipase C beta, and other proteins involved in signal transduction (for review see Krauss, 2014).

Most information on the expression of biogenic monoamine receptors during preimplantation development period has been obtained on mouse and rabbit models. Several catecholamine (adrenergic and dopamine) serotonin and histamine receptors were detected in mouse and rabbit ovulated oocytes and preimplantation embryos (see Table 1). Some biogenic monoamine receptors were detected in oocytes and preimplantation embryos of other species as well (Čikoš *et al*., 2014; Amireault and Dubé, 2005).

Embryonic stem cells (ESCs), derived from the inner cell mass of a blastocyst, can serve as an experimental model for studying early development. Although ESCs retain the high developmental potency of the founder embryo cells, several differences in the gene expression between preimplantation embryos and ESCs cells have been identified (Tanaka *et al*., 2002; Tang *et al*., 2010). Expression of catecholamine receptors has been examined in several mouse embryonic stem cell lines, and, in contrast to mouse preimplantation embryos, transcripts of all types of dopamine and adrenergic receptors were detected in mouse ESCs (Lee *et al*., 2006; Kim *et al*., 2008; Layden *et al*., 2010; Čikoš *et al*., 2015).

Differences in the expression of some adrenergic receptors between the spontaneously differentiating ESCs and undifferentiated ESCs indicate a role of these receptors in the process of embryonic stem cell differentiation (Čikoš *et al*., 2015). Interestingly, catecholamine receptor types that couple primarily to G proteins with opposite actions on adenylyl cyclase activity (beta adrenoceptors, DR1 and DR5 stimulate adenylyl cyclase activity, and alpha 2 adrenoceptors, DR2, DR3 and DR4 inhibit adenylyl cyclase activity) are expressed in mouse and rabbit preimplantation embryos and in the mouse embryonic stem cells, indicating a cross-talk between signaling pathways activated by these receptors.

The role of biogenic monoamines in early embryo development

Experimental data indicate that biogenic monoamines can (besides their well-known neurotransmitter function) play an important role in basic developmental processes, such as embryogenesis and morphogenesis (for review see Pendleton *et al*., 1998; Herlenius and Lagercrantz, 2001), and several biogenic monoamines have been identified in reproductive fluids of various mammalian species. For instance, adrenaline and noradrenaline have been detected in rabbit and bovine oviductal fluid and their concentrations varied with the region of the oviduct and the stage of the estrous cycle (Khatchadourian *et al*., 1987; Way *et al*., 2001).

Although the physiological role of biogenic monoamine receptors in early („pre-neural“) embryogenesis is mostly unknown, experimental data indicate that these receptors are functional and can be activated by agonists. Studies in mouse embryonic stem cells demonstrated that activation of dopamine and adrenergic receptors can trigger various signaling pathways influencing DNA synthesis and proliferation (Lee *et al*., 2006;

Table 1. Receptors of biogenic monoamines detected in mouse and rabbit ovulated oocytes and preimplantation embryos

Receptor	Species	Stage (mRNA)	Stage (protein)	Reference
H2R	mouse	Blast	Blast	Zhao *et al.*, 2000
5-HT_{1D}	mouse	Ooc, Zyg, 2-cell, 8-16-cell, Blast	not tested	Veselá *et al*., 2003 Iľková *et al*., 2004
5-HT_7	mouse	Ooc, Zyg, 2-cell, 4-cell	Ooc, 4-cell	Amireault & Dubé 2005
α1B-AR	rabbit	Ooc	not tested	Čikoš *et al*., 2014
α2A-AR	rabbit	Ooc, Morul, Blast	not tested	Čikoš *et al*., 2014
α2C-AR	mouse	Ooc, 8-16-cell, Blast	Ooc, 8-16-cell, Blast	Čikoš *et al*., 2007
	rabbit	Ooc, Morul, Blast	not tested	Čikoš *et al*., 2014
β1-AR	rabbit	Ooc, Morul, Blast	not tested	Čikoš *et al*., 2014
β2-AR	mouse	Ooc, 4-cell, 8-16-cell, Blast	Ooc, 4-cell, 8-16-cell, Bl	Čikoš *et al*.,2014 Chen *et al*., 2011
	rabbit	Ooc, Morul, Blast	not tested	Čikoš *et al*., 2014
β3-AR	mouse	Ooc, 4-cell, 8-16-cell, Blast	not tested	Čikoš *et al*., 2005
DR1	mouse	Blast	not tested	Čikoš *et al*., 2015
DR2	mouse	Ooc, 8-16-cell, Blast	not tested	Čikoš *et al*., 2015
DR3	mouse	Ooc, 4-cell, 8-16-cell, Blast	not tested	Čikoš *et al*., 2015
DR4	mouse	4-cell, 8-16-cell, Blast	not tested	Čikoš *et al*., 2015
DR5	mouse	Ooc, 4-cell, Blast	not tested	Čikoš *et al*., 2015

Receptors: H2R, histamine receptor subtype 2; 5-HT_{1D}, serotonin receptor subtype 1D; 5-HT_7, serotonin receptor subtype 7; 5-HT_{2A}, serotonin receptor subtype 2A; α1B-AR, adrenergic receptor subtype alpha 1B; α2A-AR, adrenergic receptor subtype alpha 2A; α2C-AR, adrenergic receptor subtype alpha 2C; β1-AR adrenergic receptor subtype beta 1; β2-AR, adrenergic receptor subtype beta 2; β3-AR adrenergic receptor subtype beta 3; DR1-5, dopamine receptor subtypes 1-5.
Developmental stages: Ooc, unfertilized oocytes (metaphase II stage); Zyg, fertilized oocytes (zygotes); 2-cell, two-cell embryos 4-cell, four-cell embryos; 8-16-cell, eight- to sixteen- cell embryos; Morul, morulas; Blast, blastocysts.

Kim *et al*., 2008; Sun *et al*., 2015). Most catecholamine receptors can regulate the intracellular cyclic adenosine monophosphate (cAMP) level, and it has been demonstrated that the cAMP signaling pathway can contribute to the regulation of mouse embryonic stem cell selfrenewal and differentiation (Faherty *et al*., 2007; Layden *et al*., 2010). Results of *in vitro* and *in vivo* experiments showed that catecholamine and serotonin receptors can activate signaling pathways regulating cell proliferation and survival in mouse preimplantation embryos (Markova *et al*., 1990; Čikoš *et al*., 2005; 2007; Veselá *et al*., 2003; Iľková *et al*., 2004). Moreover, there are data suggesting that catecholamine receptors (embryonic or uterine) can participate in the process of blastocyst implantation (Henriquez *et al*., 2006; Chen *et al*., 2011). The involvement of histamine receptor subtype 2 (regulating cAMP level) in the process of embryo implantation has been documented in the mouse model as well (Zhao *et al*., 2000). Results of *in vivo* experiments obtained on the mouse model indicate that catecholamine receptors together with glucocorticoid receptors could mediate effects of maternal stress on early embryo (Burkuš *et al*., 2013; 2015; Janštová *et al*., 2017; Zheng *et al*., 2016; Tan *et al*., 2017), and that expression of catecholamine receptors in early embryos can be influenced by maternal physiological status (Seeling *et al*., 2017).

CONCLUSION

Mammalian preimplantation embryo is equipped with a variety of cell receptors indicating active communication between the early embryo and its environment. Results obtained in mouse and rabbit models indicate that except of receptors binding protein ligands, the receptors that bind small-molecule ligands, such as biogenic monoamines, are expressed in preimplantation embryos and in the embryonic stem cells derived from mouse blastocysts. Catecholamine receptors of all types can be expressed in mammalian preimplantation embryos, with some species-specific differences, and activation of these receptors can significantly influence preimplantation embryo development. Although the physiological role of biogenic monoamine receptors in early embryonic cells is not fully understood, experimental data indicate their involvement in the regulation of cell proliferation, differentiation and survival under physiological as well as unfavorable or pathological conditions (e.g. during maternal stress).

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