Available online at www.sciencedirect.com
ScienceDirect
Theriogenology 68S (2007) S40–S48
Theriogenology
www.theriojournal.com

To be or not to be—Determinants of embryonic survival following heat shock

P.J. Hansen *

Department of Animal Sciences, University of Florida, PO Box 110910, Gainesville, FL 32611-0910, USA

Abstract

Elevated temperature can reduce developmental competence of the preimplantation embryo. Whether an embryo survives elevated temperature depends on its genotype, stage of development, exposure to regulatory molecules and redox status. Following fertilization, the embryo is very sensitive to heat shock. By Days 4–5 after insemination, however, the embryo has acquired increased resistance to elevated temperature. One system that may potentiate embryonic survival at later stages of embryonic development is the apoptosis response—inhibition of apoptosis responses at Day 4 exacerbated effects of heat shock on development. Embryo responses to heat shock at Days 4–5 also depend upon genotype because *Bos indicus* embryos are more resistant than embryos from non-adapted *B. taurus*. Some experiments (although not all) indicate that survival following heat shock can be increased by reducing oxygen tension, suggesting involvement of reactive oxygen species or hypoxia-induced factors. Embryonic responses to heat shock are also affected by regulatory molecules that act to modify cellular physiology and improve cell survival. The best characterized of these is insulin-like growth factor-1 (IGF-1). Actions of IGF-1 to allow development following heat shock are independent of its anti-apoptotic actions because inhibition of the phosphatidylinositol-3 kinase pathway through which IGF-1 blocks apoptosis does not prevent thermoprotective effects of IGF-1 on development. Identification of specific determinants of embryonic survival creates the opportunity for new strategies to improve pregnancy rates in animals exposed to heat stress. Many environmental perturbations activate similar cellular responses. Therefore, molecular and cellular systems that improve embryonic survival to heat shock may confer protection from other embryotoxic conditions.

Keywords: Embryo; Heat shock; Apoptosis; Insulin-like growth factor-1; Bovine

1. Introduction

A key determinant of embryonic development is the microenvironment formed by the oviduct and uterus. Perturbations in that environment can lead to altered cellular function and errors in development. Adverse environmental conditions do not necessarily lead to embryonic death because mechanisms exist within the embryo to preserve key components of cellular function in the face of stress. Whether or not an embryo survives a stressful environment depends upon its genetic and non-genetic inheritance, its internal state (including stage of development and presence or absence of biochemical pathways promoting survival), and the presence of cytoprotective molecules in the microenvironment that alter cellular function to provide protection from adverse stimuli. Thus, the embryo exposed to stress may either adjust successfully to the adverse environment and continue development or fail to adjust and die as a result of extensive necrosis or apoptosis.

One of the most well-characterized stresses affecting embryonic development is exposure to elevated

* Tel.: +1 352 392 5590; fax: +1 352 392 5595.
E-mail address: Hansen@animal.ufl.edu.

0093-691X/$ – see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.theriogenology.2007.03.013

temperature (i.e., heat shock). Interest in this phenomenon has been driven in large part by the large reduction in female fertility in hot environments. In lactating dairy cattle, where the metabolic demands of lactation exacerbate the decline in fertility caused by hot environments [1], heat stress arrests embryonic development in vivo [2,3]. There are probably a multitude of causes for reduced embryonic survival during heat stress including alterations in hormone secretion and uterine blood flow [4]. Importantly, elevated temperature can act directly on the embryo to compromise development [5–7]. The importance of disruption of the embryo as compared to the uterine environment in which the embryo resides was highlighted by an experiment using reciprocal embryo transfer in sheep [8]. Three days of heat stress compromised the embryo itself and, only to a lesser extent, the capacity of the uterus to support embryonic development. In contrast, recent studies in mice suggest that maternal heat stress compromises embryonic survival primarily because of effects on the oviduct rather than on the embryo directly [9].

The main purpose of this review is to describe factors intrinsic and extrinsic to the embryo that determine whether it survives heat shock. A second purpose is to delineate what is known about the mechanisms through which these factors control thermotolerance. Primary focus will be on domestic cattle because they have been studied most extensively but reference will be made to other species when pertinent.

2. Determinants of embryonic resistance to heat shock

2.1. Stage of development

Preimplantation bovine embryos become more resistant to elevated temperature as they advance in development. Data illustrating this concept are presented in Fig. 1. Heat-shock conditions that caused a large reduction in the proportion of two-cell embryos becoming blastocysts had intermediate effects when applied to four to eight-cell embryos and little or no effect on development of morulae [5,10,11]. Similarly, heat shock on Days 0 and 2 relative to fertilization was more detrimental to subsequent development to the blastocyst stage than heat shock on Day 4 or 6 [7] and heat shock was more detrimental when applied at Day 3 after insemination than at Day 4 [12]. Developmental acquisition of thermotolerance is also apparent in vivo. Exposure of cows to heat stress reduced development and viability of embryos on Day 8 after estrus if

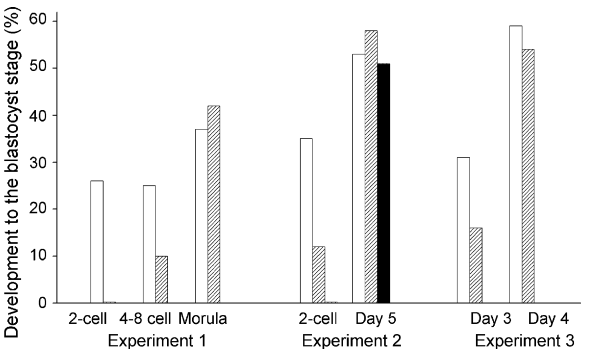

Fig. 1. Developmental changes in resistance of preimplantation bovine embryos to heat shock. Embryos at various stages of development or days after insemination were cultured at a temperature similar to homeothermic temperature of the cow (38.5–39 °C, open bars) or to a period of heat shock (hatched and black bars). Heat-shock conditions were 41 °C for 12 h (Experiment 1; Ref. [5]), 41 °C for 6 h (hatched bar) or 9 h (black bar) (Experiment 2; Ref. [10]) or 43 °C for 1 h (Experiment 3; Ref. [12]).

superovulated cows were exposed to heat stress at Day 1 after estrus but not if heat stress was imposed on Day 3, 5 or 7 [3]. Heat stress is also more likely to cause embryonic mortality when applied sooner after estrus in sheep [13] and pigs [14]. In the mouse, in contrast, there was little difference in resistance to heat shock between embryos at the two-cell, four-cell and morula stage of development [15].

The cellular consequences of heat shock have been best described for the bovine two-cell embryo. At that stage, exposure to 41 °C causes disruption of the microfilament and microtubule network which in turn results in a redistribution of organelles into the interior of the cell [16,17]. There is also an increase in the proportion of mitochondria which have a swollen phenotype indicative of depolarization [16,17] and, consistent with the idea of reduced oxidative phosphorylation, a tendency for reduced oxygen consumption [18]. Despite these apparently serious changes in cellular function, the 2-cell embryo exposed to 41 °C is capable of development until the 8–16-cell stage, when development becomes blocked [18]. Given that this is also the stage when the embryo first becomes capable of transcription on a major scale [19], it may be that heat shock reduces ability of the embryo to become transcriptionally competent.

2.2. Genotype

There is evidence that cattle which have evolved in hot climates have acquired genes that protect embryos from elevated temperature (Fig. 2). When heat shock was applied at Day 4 or 5 after fertilization, the