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Review

Metabolic evolution suggests an explanation for the weakness of antioxidant defences in beta-cells

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ABSTRACT

The lack of an effective antioxidant system in beta-cells, which renders them susceptible to oxidative stress, is to date without explanation. The particular weakness of beta-cells in females, in both humans and mice, is another unexplained observation. We hypothesise that reactive oxygen species (ROS) in beta-cells, by their negative effect on insulin synthesis/secretion, play a fitness-enhancing role for the whole organism. Under stress conditions, the release of stress hormones produces insulin resistance and, owing to ROS preventing beta-cells from secreting insulin at the level required to maintain homeostasis, diverts glucose to insulin-independent tissues such as the brain and the foetus. We suggest that pancreatic beta-cells lost part of their antioxidant defence in association with brain evolution, and lost even more in females when placental mammals evolved. The unusual antioxidant status of beta-cells may thus be explained as an instance of co-evolution of the brain, cortisol and corticosteroid receptors, and beta-cells in the endocrine pancreas.

1. Beta-cells are surprisingly poorly protected against oxidative stress

Pancreatic beta-cells are slow-turnover cells (Teta et al., 2005) that play a central regulatory role in whole-body glucose homeostasis. Given their importance, it might be supposed that they are highly protected against various insults, including reactive oxygen species (ROS). However, beta-cells have been found actually to have weaker antioxidant defences than other cell types such as liver, kidney, brain, lung, skeletal muscle, heart muscle, adrenal gland and pituitary gland (Grankvist et al., 1981; Lenzen et al., 1996; Malaisse et al., 1982; Tiedge et al., 1997; Zhang et al., 1995). For example, glutathione peroxidase (responsible for the final enzymatic step for ROS degradation) is expressed at very low levels and has almost undetectable activity in both human (Robertson and Harmon, 2007; Tonooka et al., 2007) and rodent beta-cells (Grankvist et al., 1981; Tiedge et al., 1997). Although data on catalase activity in human beta-cells is limited, the available evidence suggests that it is at the same level as, if not even lower than, in rat beta-cells (Sigfrid et al., 2003).

Markers of oxidative stress are significantly higher in the islets of type 2 diabetic patients than normal controls (Chang-Chen et al., 2008). Exposure of beta-cells to prolonged glycaemia impairs their function and turnover mechanisms, ultimately leading to profound glycaemia and diabetes. Increased ROS production and deficient defensive mechanisms are known to mediate a major part of the link between glycaemia and beta-cell functional/turnover impairments (Tanaka et al., 2002). In particular, the sensitivity of beta-cells to ROS has been attributed to their lack of sufficient antioxidants (Kajimoto and Kaneto, 2004; Lenzen, 2008; Robertson et al., 2003).

Another interesting observation is that female mice have lower antioxidant levels of activity in their beta-cells than males (Cornelius et al., 1993), a pattern recently shown also to exist in humans (Tonooka et al., 2007). This gender-specific pattern is particularly surprising since females are generally better protected against oxidative stress (Proteggente et al., 2002), and it suggests that some particular factors might act on beta-cells. Taken together, the evidence prompts the following questions: Is there some advantage in possessing a reduced antioxidant status that outweighs the high price that is paid in terms of cellular vulnerability to ROS? Does the difference between the sexes have its origin in some sex-specific evolutionary factor? We examine here the possibility that an answer to the first question might lie in a regulatory role for ROS in the essential function of beta-cells, i.e. insulin secretion. We also consider the idea that the weaker antioxidant system in females might be related to pregnancy.

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2. ROS down-regulate insulin synthesis/secretion

Glucose metabolism results in a considerable amount of ROS, which in turn pose inhibitory effects on insulin synthesis/secretion via several mechanisms (Wiederkehr and Wollheim, 2006). ROS negatively affect insulin synthesis by inhibiting the transcription factors Pdx-1 (Kaneto et al., 2005; Robertson et al., 2003) and RIPE3b1a/MafA (Harmon et al., 2005; Poitout et al., 1996; Read et al., 1997). Additionally, superoxide activates uncoupling protein-2 (UCP-2)-mediated proton leak, thus lowering ATP levels and impairing glucose-mediated insulin secretion (Krauss et al., 2003).

The literature on the effects of transiently elevated glucose concentrations remains controversial. For instance, glucose was shown to acutely suppress ROS formation in purified rat beta-cells by increasing cellular NADH levels (Martens et al., 2005). However, this effect is limited. ROS production quickly surpasses its rate of elimination, leading to intracellular ROS accumulation (Gurgul et al., 2004; Pi et al., 2007; Tiedge et al., 1997). In any case, controversies regarding the effect of transient glycaemia on ROS production in beta-cells are outside the scope of our current hypothesis, which concerns prolonged stress conditions.

3. Stress, pregnancy, and resource allocation

Stress is associated with a release of stress hormones (e.g. cortisol), which reduce the responsiveness of insulin-dependent tissues to insulin (Qi and Rodrigues, 2007). The ensuing net glycaemia makes possible a reallocation of glucose, preferentially to insulin-independent tissues (Peters et al., 2002). Brain is one of the few insulin-independent tissues in the body. Placenta in mammals is another major insulin-independent tissue which prevents foetal nutrition from being compromised in case of insulin resistance (Watve and Yajnik, 2007).

The average plasma glucose levels in pregnancy are lower than in non-pregnant women. This is mostly due to increased plasma volume in the first trimester and increased foeto-placental glucose utilisation in late gestation. Also, the glucose set-point is lowered by prolactin, which promotes glucose oxidation in beta-cells by up-regulating the expression of glucose transporters on the cell surface and increasing the activity of glucokinase (glucose sensor) (Weinhaus et al., 1996). This resetting takes place in the first trimester (Butte, 2000; Mills et al., 1998) and ensures that the mother will be able to avoid glycaemia as insulin sensitivity declines during the course of pregnancy (see below).

During the third trimester the average diurnal plasma glucose shows a gradual rise, well within the normal range owing to the above protective mechanisms (Parretti et al., 2001) (Fig. 1). Decreased insulin sensitivity (Yamashita et al., 2000) and increased fasting hepatic glucose production (Catalano et al., 1992), resulting in increased postprandial glucose, are responsible for this change. Insulin resistance of pregnancy results from impaired insulin signalling due to well-known post-receptor defects (Catalano et al., 2002; Kirwan et al., 2004; Saad et al., 1997; Shao et al., 2000), mainly in skeletal muscles and adipose tissues (Gonzalez et al., 2002). In particular, insulin sensitivity is blunted by up to 45–70% during the third trimester (Butte, 2000; Catalano et al., 1991, 1993), which is associated with a compensatory rise of fasting plasma insulin (Assel et al., 1993; Catalano et al., 1993). Tumour necrosis factor-α plays the role of classical stress hormones (see above) in mediating insulin resistance in pregnancy (Kirwan et al., 2004).

The process of beta-cell mass regulation undergoes some alteration during pregnancy resulting from the interplay of several factors, most importantly glucocorticoids and lactogens (Arumugam et al., 2008). Glucocorticoids are an essential component of normal pregnancy with pluripotent effects on decidualisation, implantation, and placental development (Arcuri et al., 1996; Malassine and Cronier, 2002). They have, however, some undesired effects on both the mother and foetus if not counteracted. The placenta protects the foetus from high levels of maternal cortisol through its enzyme 11β-hydroxysteroid dehydrogenase type 2, which converts cortisol to inactive cortisone (Shams et al., 1998). On the maternal side, cortisol concentrations double in late gestation leading to increased beta-cell apoptosis and decreased proliferation (Freemark, 2006; Ranta et al., 2006; Weinhaus et al., 2000). The effects of lactogens on beta-cells are exactly opposite to those of cortisol (Arumugam et al., 2008; Fujinaka et al., 2007), and may therefore function to counteract the detrimental effects of corticosteroids on the glucose homeostatic system. The net result may be enhanced beta-cell mass during gestation.

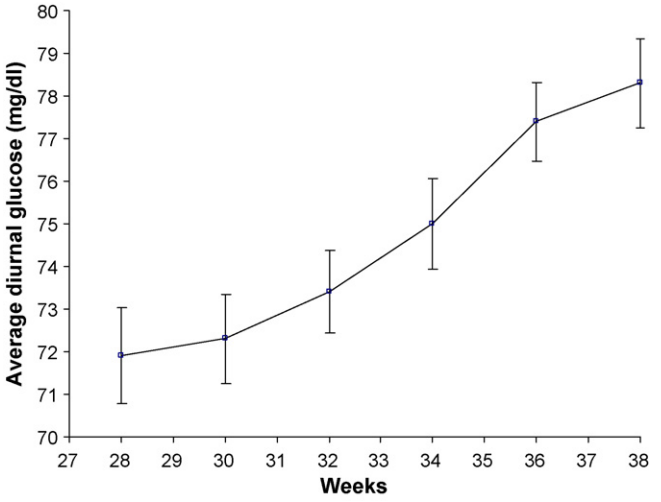

Fig. 1. Mean diurnal glucose concentrations in the third trimester. Data were collected from 51 women with normal glucose tolerance who delivered term live-born infants without evidence of congenital malformations (Adapted from Parretti et al., 2001)

4. Hypothesis: ROS in beta-cells have an adaptive function in stress conditions including pregnancy

Natural selection strongly favours strategies that maximize the production of offspring and is therefore expected to have acted, in female mammals, to tune physiological systems to optimize the chances of a successful pregnancy. Since the placenta is an insulin-independent tissue, maternal insulin resistance can help divert more glucose to the foetus (Watve and Yajnik, 2007). The gradual increase in maternal average plasma glucose following the development of insulin resistance is also explained by the necessity to meet the increasing nutritional requirements of the growing foetus. In support of this, we note that utero-placental glucose consumption, glucose transfer to the foetus and foetal plasma glucose are all directly and strongly related to maternal plasma glucose (Hay, 1995; Hay and Meznarich, 1989).

However, if the above argument is correct, then why is the compensatory hyperinsulinaemia unable to return glucose back to the set-point, thereby maintaining homeostasis at a relatively constant glucose level? There are two possibilities. Either at some point, beta-cells are simply unable to increase the rate of insulin secretion further, perhaps because they are exhausted or because insulin resistance progresses faster than they can compensate for by augmenting insulin secretion. Or, there is some reason, possibly adaptive, why beta-cells do not increase insulin secretion rate further.