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Arachidonic Acid Fights Palmitate – New insights into fatty acid toxicity to β -cells

Commentary on “Arachidonic acid actions on functional integrity and attenuation of the negative effects of palmitic acid in a clonal pancreatic β -cell line”.

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Abstract

Saturated fatty acids are toxic to pancreatic β -cells. By inducing apoptosis, they contribute to a decrease in β -cell mass, a hallmark of type 2 diabetes. In this issue of Clinical Science, Keane and co-workers show that the polyunsaturated fatty acid arachidonic acid protects the β -cell against the toxic effects of palmitate. As type 2 diabetes is characterised by subclinical inflammation, and arachidonic acid and metabolites thereof are produced during states of inflammation, it is possible that pancreatic β -cells use arachidonic acid as a compound for self-protection.

Main text

Pancreatic β -cells are conspicuously vulnerable to saturated long-chain fatty acids [1]. Most extensively studied is the 16 carbon long palmitic acid. When given acutely, this long-chain fatty acid - like other saturated and unsaturated fatty acids - serves to enhance glucose-stimulated insulin secretion [2]. However, upon prolonged exposure this fatty acid induces endoplasmic reticulum stress and production of oxygen radicals, eventually ending up in apoptotic β -cell death [3]. While saturated fatty acids are potent cytotoxic molecules, monounsaturated fatty acids (*e.g.* oleate) also display some cytotoxicity albeit with lower potency [4]. Interestingly, oleate can prevent the cytotoxic actions of palmitate when the two fatty acids are given together to insulin-producing cells and isolated islets of Langerhans [5]. In this issue of Clinical Science, Keane and co-workers present novel results that show a similar effect of the polyunsaturated fatty acid arachidonic acid. Beyond conferring protection against palmitate-induced cell death and inhibition of insulin secretion, arachidonic acid

reduced the formation of reactive oxygen species that appeared after palmitate exposure. Overall, arachidonic acid relieved the β -cells from oxidative stress induced by palmitate as indicated by an increased GSH/GSSG ratio. This finding can be important because plasma levels of palmitate are elevated in patients with type 2 diabetes [6] and given the deleterious actions of palmitate observed *in-vitro*, it can very well be so that palmitate cytotoxicity contribute to the reduction in β -cell mass observed in patients with type 2 diabetes [7]. Certainly, more research is needed. The study presented by Keane et al. solely use the insulin-secreting cell line BRIN-BD11 for their experiments. Further steps are to verify the results in primary β -cells. Next, the protective effects of arachidonic acid on β -cell function should be investigated in obese models of type 2 diabetes like high-fat diet feed animals and genetically obese animal models. Nevertheless the data presented by Keane and co-workers have interesting implications that are discussed below.

Can the protective effect of arachidonic acid be of physiological importance?

Arachidonic acid is endogenously produced from membrane phospholipids via the action of phospholipases A2 (PLA2), a large family of enzymes that hydrolyse the sn-2 position in phospholipids to generate arachidonic acid. This polyunsaturated fatty acid is the precursor lipid for production of prostaglandins (via the action of cyclooxygenases [COX] 1 and 2), hydroxyeicosatetraenoic acids and leukotrienes (via the action of lipoxygenases [LOX]). The expression of PLA2, COX 1, COX 2, 5-LOX and 12-LOX have all been verified in human islets of Langerhans [8]. Keane and co-workers use COX inhibitors to show that the effects of arachidonic acid on insulin secretion can be attributed to some of its metabolites formed by the action of COX enzymes. It should be noted that the data presented by Keane and co-workers are not absolutely clear. For instance the two COX 1 inhibitors acetaminophen and SC-560 have different effects on nutrient stimulated insulin secretion in the presence of arachidonic acid. Potentially, the use of siRNA-mediated knock-down of COX 1, COX 2, 5-LOX and 12-LOX might have given clearer results. However, while COX 1 is regarded as a house-keeping gene, COX 2 expression is up-regulated during states of inflammation. In recent years, several studies have been published that implicate subclinical chronic inflammation, especially in adipose tissue, as an important pathogenetic factor in the development of insulin resistance and type 2 diabetes [9]. This inflammatory state leads to the release of so-called adipokines from fat cells, of which interleukin (IL)-6 and tumour necrosis factor α (TNF- α) are elevated in patients with type 2 diabetes [10]. Thus, both mediators of an inflammatory response and palmitate are elevated in the circulation in type 2 diabetes. This opens the perspective to view a scenario where these adipokines stimulates metabolism of arachidonic acid via COX enzymes in the β -cells and thus production of a compound capable of providing protection against palmitate-induced cytotoxicity. It could be speculated that these series of events provide a mechanism for β -cell self protection against palmitate.

Another situation when β -cells are exposed to a state of inflammation is of course during the cell mediated immune attack that culminates in type 1 diabetes [11]. In this process, the islets are invaded and infiltrated by macrophages and T-cells in an inflammatory reaction termed insulinitis. These immune cells promote β -cell death both by establishing direct contact with the β -cells and by releasing cytokines like IL-1 β , interferon- γ and TNF- α . Cytokines also induce COX 2 expression and subsequent prostaglandin production in human islets of Langerhans. Inhibition of COX 2 attenuates cytokine-induced prostaglandin production, but do not influence cytokine-induced islet destruction [12]. It would be interesting to investigate

whether arachidonic acid might afford protection against the deleterious effects of cytokines on islets.

Which is the dominant route for arachidonic acid metabolism in β -cells?

The findings reported by Keane and co-workers indicate that, in least in their system, arachidonic acid metabolism via COX signalling dominates over the LOX pathway. Admittedly, the data presented in the paper does not allow for this conclusion to be drawn but some lines of evidence argues that this is the case. It has been noted that increased expression of 12-LOX in β -cells occurs during the prediabetic phase of β -cell dysfunction in the Zucker diabetic fatty rat model [13]. Furthermore, when human islets were treated with stable metabolites derived from LOX these compounds were all able to induce β -cell dysfunction and apoptosis [14]. Taken together these observations indicate that metabolism of arachidonic acid via the LOX pathway generates metabolites that are harmful to the β -cell. Thus, if arachidonic acid metabolism via LOX-catalysed reactions would be dominating over COX-catalysed reactions it is unlikely that a cytoprotective effect of arachidonic acid would be observed as Keane and co-workers do.

Can the effect of arachidonic acid be exploited therapeutically?

Direct treatment of humans with arachidonic acid, or derivatives thereof, has to the best of my knowledge not been performed. On the other hand, the fact that salicylates in doses of about one gram can evoke hypoglycaemia has been known since 1870. Hypoglycaemic effects have been reported both for salicylates and non-steroid anti-inflammatory drugs (NSAIDs), which inhibit the COX enzymes. Certain COX inhibitors are able not only to enhance glucose-induced insulin release in humans, but also to improve glucose tolerance and glucose-induced insulin release in patients with type 2 diabetes [15].

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