Pharmacology & Toxicology 1992, 71, 250–253.

MiniReview

β-Adrenergic Responsiveness of the Gastrointestinal Tract in Diabetic Rats

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(Received December 30, 1991; Accepted June 28, 1992)

Abstract: Recently, decreased gastrointestinal β-adrenergic responses in experimental diabetes have been demonstrated. Gastrointestinal responses to β-adrenoceptor agonists are impaired in both insulin-dependent and non-insulin-dependent diabetic rat. Insulin treatment improves the impaired gastrointestinal β-adrenergic responsiveness of diabetic rats. The improvement seen with insulin treatment on β-adrenergic responsiveness is closely related to protein biosynthesis. The decreased β-adrenergic responses in diabetic rat gastrointestinal tract seem to result from a decrease in the number of β-adrenoceptors. It is most likely that the decreased gastrointestinal β-adrenergic responsiveness is related to an impairment in the turnover of β-adrenoceptors as a consequence of diabetes and that insulin has a beneficial effect on the impaired receptor turnover.

Diabetes mellitus is a metabolic disease caused by deficiency in β-cells of endocrine pancreas and/or by subsensitivity to insulin in target cells. Certain long-term complications are frequently encountered in conjunction with this metabolic disease, e.g. peripheral vascular disease (Colwell *et al.* 1979), atherosclerosis (Beach & Strandness 1980), cardiomyopathy (Cruickshanks *et al.* 1985), retinopathy (Bhopal & Hedley 1985), nephropathy (Deckert & Poulsen 1981) neuropathy (Thomas & Ward 1973) and certain gastrointestinal manifestations (Ogbonmaya & Arem 1990). The exact mechanisms of these complications are still uncertain. Some of these complication are curable by proper insulin replacement therapy. However, certain diabetic complications such as proliferative retinopathy (Kohner & Dollery 1973) can not be treated by insulin. Atherosclerotic changes in the cardiovascular system due to diabetes seem to be resistant to insulin therapy as well (Stocks & Martin 1969). The effective clinical management of diabetic complications can only be achieved with a thorough understanding of their underlying causes. This review, therefore, will focus on the gastroenteropathy in terms of β-adrenergic responsiveness of this tract.

Clinical picture of diabetic gastroenteropathy.

Disturbances of the gastrointestinal tract were among the first of the autonomic syndromes related to diabetes to achieve prominence, and of these "Diabetic diarrhoea" has attracted the most attention (Niakan *et al.* 1986; Ogbonmaya & Arem 1990). The condition is most troublesome at night or following meals. Nocturnal faecal incontinence may be a distressing feature. The diarrhoea is often intermittent, sometimes alternating with periods of constipation. The results of clinical studies often disagree over the nature of changes that occur in the gastrointestinal tract with diabetes mellitus. The major point of contention is the relative importance of diarrhoea and constipation (Malins & French 1957; Katz & Spiro 1966; Hosking *et al.* 1978). While increased peristaltic activity, rapid transit and reduced intestinal tone have been observed in diabetic diarrhoea (Malins & French 1957; McNally *et al.* 1969), another study has shown delayed transit through the ileum (Scarpello *et al.* 1976), still other studies have reported no change in intestinal tone in this condition (Whalen *et al.* 1969; Keshvarzian & Iber 1986). Furthermore, degenerative changes have not been consistently observed in intestinal Auerbach and Meissner plexuses of diabetic patients; these changes are not specific and have been observed in diabetics both with and without diarrhoea (Whalen *et al.* 1969; Hensley & Spiro 1971; Goyal & Spiro 1971). The lack of the gastro-colonic spike response to feeding has been indicated in diabetic patients suffering from constipation (Battle *et al.* 1980). Another diabetic complication related to the alimentary tract is the atonic dilatation of stomach which appears with or without pernicious anaemia and either achlorhydria or hypochlorhydria (Kassander 1958; Ogbonmaya & Arem 1990).

Gastroenteropathy in experimental models of diabetes.

Studies with experimentally-induced diabetic animals revealed pathological changes in the gastrointestinal tract. Megacolon (Nelson *et al.* 1976) and disturbed spontaneous motor activity of gastrointestinal tract (Karakida *et al.* 1989) have been reported in streptozotocin-diabetic rats. Changes in adrenergic, cholinergic, serotonergic and peptidergic innervation of the gastrointestial tract have also been demonstrated (Schmidt *et al.* 1981; Lincoln *et al.* 1984; Belai *et al.* 1985). Increased contractile responses to acetylcholine and substance P have also been observed (Liu *et al.* 1988). In streptozotocin-diabetic rats, contractile responses of isolated jejunum to bradykinin and neurotensin were decreased, while neurokinin A and B-induced contractions were enhanced (Mathison & Davison 1988). Also, decreased contractile responses to calcium have been observed in K^+-depolarized duodenum from alloxan-diabetic rats (Öztürk

et al. 1987). α-Adrenergic, but neither cholinergic nor purinergic responses, are decreased in the caecum of streptozotocin-diabetic rats as well (Hoyle *et al.* 1988). 5-Hydroxytryptamine receptor affinity seemed to be decreased in the stomach fundus strips from both alloxan- and streptozotocin-diabetic rats (Altan *et al.* 1987). The impaired responses of diabetic rat fundus to 5-hydroxytryptamine were improved following *in vivo* insulin treatment (Yıldızoğlu-Arı *et al.* 1988). Another diabetic complication observed in alloxan-diabetic rats was the reduced gastric acid secretion induced by intravenous histamine infusion *in situ* (Öztürk *et al.* 1990a).

β-Adrenergic responses in diabetic rats.

β-Adrenergic responses of the gastrointestinal tract to salbutamol were decreased in both insulin-dependent (Altan *et al.* 1987) and non-insulin-dependent diabetic rats (Öztürk *et al.* 1990b) and with radioligand binding a decreased number of β-adrenoceptors have been demonstrated in the stomach fundus isolated from streptozotocin-diabetic rats (Sakai *et al.* 1990). The decreased gastrointestinal β-adrenergic responses due to experimental diabetes are improved following both *in vivo* and *in vitro* treatments with insulin (Yıldızoğlu-Arı *et al.* 1988). *In vivo* insulin treatment (166.7 μg/kg/day intraperitoneally) for 6 weeks corrected the changes observed in gastrointestinal tract from streptozotocin-diabetic rats. Insulin incubation in the organ bath for 4–5 hr enhanced the decreased gastrointestinal β-adrenergic responses, but not the responses evoked by 5-hydroxytryptamine. The improvement seen in β-adrenergic responses was prevented by anti-insulin antibodies as well (Öztürk *et al.* 1992b). This phenomenon seems to be in accordance with the hypothesis that insulin plays a role in the regulation of inflammatory process (Garcia Leme 1981) and microvascular reactivity to histamine and bradykinin (Fortes *et al.* 1983 & 1984). Although insulin undoubtedly plays a long-term role in the regulation of some gastrointestinal functions, it would appear that defects in the β-adrenoceptor function are improved rapidly with short-term insulin treatments (Altan *et al.* 1989; Yıldızoğlu-Arı *et al.* 1988). These data strongly suggest that the improvement of gastrointestinal β-adrenergic responses seen with insulin treatment is direct in nature and that short-term insulin treatment may enhance the β-adrenoceptor biosynthesis *in vitro*. We have recently established that this is indeed the case, since the improvement in β-adrenoceptor-mediated responses seen with short-term insulin treatments *in vitro* were abolished by the protein synthesis inhibitors, cycloheximide and actinomycin D (Öztürk *et al.* 1992a). Similarly, diminished hypotensive response to isoprenaline and impaired β-adrenergic responses of cerebral circulation have been reported in streptozotocin-diabetic rats (Jobidon *et al.* 1989; Lass *et al.* 1989). Myocardial β-adrenergic responses in rat have been shown to be decreased depending on alloxan- and streptozotocin-induced diabetes (Savarese & Berkowitz 1979; Karasu *et al.* 1990). The decreased β-adrenergic responses in diabetic myocardium have been attributed to a decrease in the number of β-adrenoceptors (Savarese & Berkowitz 1979; Sundaresan *et al.* 1984). *In vivo* insulin treatment improves the decreased β-adrenergic responses of diabetic rat myocardium as well (Nishio *et al.* 1988; Karasu *et al.* 1990). Insulin administration to thyroidectomized diabetic rats does not reverse the diabetes-induced changes in myocardium suggesting that the improving effect of insulin in this tissue occurs via an indirect mechanism (Karasu *et al.* 1990). *In vitro* insulin treatment, however, is ineffective in reversing the diabetes-induced decrease in myocardial β-adrenergic responsiveness (Öztürk *et al.* 1992b).

Conclusion.

The data obtained from both diabetic rat gastrointestinal smooth muscles and atria strongly suggest that the decreased β-adrenergic responses in these two tissues are different in terms of the mode *in vivo* improving effect of insulin. In fact, β_1-adrenoceptors are predominant in myocardial tissue, while β_2-adrenoceptors are the main responsible receptor subtype in the effects of adrenergic agonists in the gastrointestinal tract (Bülbring & Tomita 1987). Since *in vivo* insulin treatment following thyroidectomy (Karasu *et al.* 1990) and *in vitro* insulin treatment (Öztürk *et al.* 1992b) did not improve the decreased β-adrenergic responsiveness of diabetic rat atria, it is most likely that the pathological mechanisms involved in the impaired β-adrenergic responsiveness of gastrointestinal tract and myocardium may also be different.

The decreased gastrointestinal β-adrenergic responses seem to result from a decreased number of β-adrenoceptors. At first sight, this might be attributed to a down-regulation phenomenon due to increased catecholamine levels in the gastrointestinal tract. The increase in gastrointestinal catecholamine levels, however, has not been observed in every segment of the intestine isolated from experimentally-induced diabetic rats. Increased noradrenaline and dopamine levels have been observed in duodenum from alloxan- and streptozotocin-diabetic rats (La Croix *et al.* 1989; Di Giulio *et al.* 1989). In contrast, decreased noradrenaline and unchanged dopamine levels have been demonstrated in the jejunum of experimentally diabetic rats (Di Giulio *et al.* 1989). While Lincoln *et al.* (1984) reported decreased noradrenaline levels in the ileum of streptozotocin-diabetic rats, La Croix *et al.* (1989) demonstrated an increase in noradrenaline levels in this segment of rat intestine due to alloxan diabetes. Another report indicated unaltered noradrenaline levels in ileum isolated from rats with streptozotocin diabetes (Di Giulio *et al.* 1989). Dopamine levels in rat ileum have been found to be unchanged by experimental diabetes as well (La Croix *et al.* 1989; Di Giulio *et al.* 1989). Decreased activity of monoamine oxidase and tyrosine hydroxylase has also been observed in various brain regions obtained from diabetic animals (Lackovic *et al.* 1990; Gupta *et al.* 1992). As the β-adrenergic responses in all of intestinal segments were decreased as a result of experimental diabetes (Altan *et al.* 1987; Mathison & Davison 1988; Öztürk *et al.* 1990b), it is difficult to imagine that down-regulation of

adrenoceptors resulting from altered catecholamine levels could be responsible for the decreased β-adrenergic responsiveness in the gastrointestinal tract. Alternatively, it may be suggested that diabetes mellitus alters the turnover of β-adrenoceptors in the gastrointestinal tract and that insulin treatment reverses the diabetic changes during turnover. It would, therefore, be of interest to investigate the effects of diabetes mellitus and insulin treatment on turnover of β-adrenoceptors in various tissues in order to understand the mechanism(s) of gastrointestinal diabetic complications as well as other complications accompanying diabetes mellitus.

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