ABSTRACT

THE HYPERGLYCAEMIC EFFECT OF NITRIC OXIDE GENERATING DRUGS S-NITROSOGLUTATHIONE AND S-NITROSO-N-ACETYLPENICILLAMINE - POSSIBLE MECHANISM OF ACTION

Nitric oxide (NO) is an important bioactive signalling molecule that mediates a variety of normal physiological functions which, if altered, could contribute to the genesis of many pathological conditions, including diabetes mellitus. This study investigated the effects of the nitric oxide donors, S-nitrosoglutathione (GSNO) and S-nitroso-N-acetyl-penicillamine (SNAP) on carbohydrate metabolism in clinically healthy dogs and examined the possible diabetogenic effect of these drugs.

Oral glucose tolerance tests (OGTT) revealed an impaired glucose tolerance in GSNO- and SNAP-treated dogs as reflected by elevated postprandial blood glucose levels at the 1.5 h - 2.5 h time intervals ($P < 0.05$). S-nitroso-N-acetyl-penicillamine at low dosages of 10 and 20 mg/kg body weight (i.v.) caused significant hyperglycaemia in dogs accompanied by a concomitant reduction in plasma insulin levels. In contrast, GSNO caused significant hyperglycaemia at higher dosages of 35 and 50 mg/kg body weight accompanied by decreased plasma insulin levels.

Changes in the binding of insulin to its receptor on the cell membranes of erythrocytes and mononuclear leucocytes in response to acute administration of 35 mg/kg of GSNO, 20 mg/kg of SNAP and 20 mg/kg of captopril (the control drug) were also investigated. The captopril-treated dogs exhibited normal insulin binding. Scatchard analysis of the insulin binding data revealed that GSNO and SNAP reduced insulin binding in clinically healthy dogs. The reduction in insulin binding in SNAP-treated dogs was primarily due to a significant decrease in the number of receptors sites per cell ($P < 0.05$) and secondarily to a decrease in the receptor affinity. In contrast, the reduction in GSNO-treated dogs was primarily due to a significant decrease in receptor affinity ($P < 0.05$) and secondarily to a decrease in the number of receptor sites per cell. Scatchard analysis of the binding data resulted in curvilinear plots with characteristics typical of negative cooperativity interactions between receptor sites with reductions in unoccupied site affinity constants in both GSNO- and SNAP-treated dogs.

The elevated postprandial blood glucose was accompanied by an increase in plasma glucagon levels. There is a highly significant positive correlation between the blood glucose concentration and the plasma glucagon concentration ($r = 0.488$, $P< 0.01$). The drugs also lowered the mean arterial pressure and increased heart rate significantly. The modification of these cardiovascular parameters was accompanied by a significant increase in the plasma nitrate/nitrite level that was taken as the biochemical markers of *in vivo* NO formation.

The following conclusions were made from the studies conducted:

(a) Nitric oxide released from GSNO and SNAP caused persistent hyperglycaemia in clinically healthy dogs,

(b) The mechanism by which NO caused the hyperglycaemic effect involved binding abnormalities at the cellular level. Nitric oxide was found to be a negative modulator of the binding of insulin to its receptor on the cell membranes of both erythrocytes and mononuclear leucocytes. This reduction in binding resulted from a decrease in the number of insulin receptor sites per cell and receptor affinity,

(c) Nitric oxide is a positive modulator of glucagon secretion and a negative modulator of insulin secretion. The elevated glucagon and decreased insulin levels contributed to the hyperglycaemic effect,

(d) Ascorbic acid augmented the hyperglycaemic effect by facilitating greater release of NO,

(e) Both SNAP and GSNO significantly decreased mean arterial pressure and increased heart rate, and thus have therapeutic potential in the treatment of hypertension.

Patients with percutaneous transluminal coronary angioplasty and pre-clampsia who are on protracted treatment with nitric oxide generating drugs could be at risk for the development of diabetes mellitus.