Proceedings of the Nutrition Society (2010), **69 (OCE5)**, E368 doi:10.1017/S0029665110002296

Irish Section Meeting, 16–18 June 2010, Nutrition – Getting the Balance Right in 2010

The metabolic effects of novel peptide-based glucagon receptor antagonists *in vitro* and in high fat fed mice

Z. J. Franklin, N. Irwin and F. P. M. O'Harte
Diabetes Research Group, School of Biomedical Sciences, University of Ulster, Coleraine BT52 1SA, UK

Hyperglycaemia in type-2 diabetes is produced from a combination of impaired insulin secretion, tissue insulin resistance and enhanced secretion of glucagon, the latter resulting in increased hepatic glucose output. Thus, glucagon receptor antagonists have potential to alleviate glucagon-induced hyperglycaemia. In this study, we examined the efficacy of the novel peptide-based glucagon antagonists desHis^{1}(Glu^{9})glucagon and the C-terminal mini-PEGylated form, desHis^{1}(Glu^{9})glucagon[mPEG], on intracellular cAMP production and insulin secretion *in vitro* and glucagon-induced hyperglycaemia *in vivo* in insulin resistant high fat fed mice. Acute (20 min) *in vitro* cAMP production and insulin secretion studies were performed in glucagon receptor transfected HEK293S(GnT1) and clonal pancreatic BRIN-BD11 cells, respectively. *In vivo* studies were performed in National Institutes of Health Swiss mice maintained on high fat diet (45 % fat) for 120 d. Groups of mice (n 8) were fasted for 4 h prior to injection (i.p.) with saline, glucagon alone and desHis^{1}(Glu^{9})glucagon or desHis^{1}(Glu^{9})glucagon[mPEG] with/without glucagon (all at 25 nmol/kg body weight). Blood glucose was measured at 0, 15, 30, 60 and 105 min post injection. Glucagon dose-dependently stimulated cAMP production in HEK293S(Gnt1) cells. However, desHis^{1}(Glu^{9})glucagon and desHis^{1}(Glu^{9})glucagon[mPEG] alone did not stimulate cAMP production. Furthermore, both peptides antagonised glucagon-induced cAMP production *in vitro*. In BRIN-BD11 cells, glucagon dose-dependently (10^{-12}–10^{-6} M) stimulated insulin secretion compared to 5.6 mM glucose control ($P<0.05$ to $P<0.001$). In contrast, desHis^{1}(Glu^{9})glucagon and desHis^{1}(Glu^{9})glucagon[mPEG] did not evoke insulin secretion above control levels. However, both peptides effectively antagonised glucagon-induced (10^{-7} M) insulin secretion *in vitro*. In high fat fed mice, glucagon significantly ($P<0.01$) elevated the overall plasma glucose excursion (0–105 min AUC) compared to saline controls. In contrast, the administration of either desHis^{1}(Glu^{9})glucagon or desHis^{1}(Glu^{9})glucagon[mPEG] did not induce significant changes from saline controls. Moreover, when injected concomitantly with glucagon both analogues significantly ($P<0.01$ to $P<0.001$) lowered individual blood glucose levels when compared to glucagon treated mice. In addition, a combined administration of glucagon and desHis^{1}(Glu^{9})glucagon significantly ($P<0.05$) lowered the overall glycaemic excursion (0–105 min AUC) when compared to glucagon-treated mice. In conclusion, desHis^{1}(Glu^{9})glucagon is a particularly effective glucagon receptor antagonist *in vitro* and *in vivo* and may have potential in alleviation of hyperglycaemia in diabetes.