# High-Dose Porcine Galanin Infusion and Effect on Intravenous Glucose Tolerance in Humans

STEPHEN G. GILBEY, JUDITH STEPHENSON, DOMHNALL J. O'HALLORAN, JACQUELINE M. BURRIN, AND STEPHEN R. BLOOM

**The neuropeptide galanin inhibits glucose-stimulated insulin release in dogs and rodents and has been proposed as having a role in the control of insulin release in humans. The effect of infused galanin on intravenous glucose tolerance in humans was investigated by giving an intravenous glucose tolerance test (0.5 g glucose/kg body wt) alone and with infusions of synthetic porcine galanin at high-dose levels (80 and 160 pmol · $kg^{-1}$ · $min^{-1}$) to seven healthy male volunteers. The results showed no effect of galanin infusion on plasma glucose or serum insulin, although a rise in serum growth hormone even in the face of the intravenous glucose load confirmed the potent growth hormone–stimulating effect of galanin. These results suggest that caution should be exercised in extrapolating a physiological role for galanin in humans from the results of animal studies.** ***Diabetes*** **38:1114–16, 1989**

Galanin is a 29–amino acid peptide first isolated from pig intestine in 1982 (1). Galanin is widely distributed in the central nervous and gastrointestinal systems (2,3).

Galanin is not normally detectable in plasma, and there is no known stimulus for the release of galanin into the circulation. However, there is strong circumstantial evidence that galanin is a neurotransmitter and that it may play a physiological role in the control of carbohydrate metabolism at pancreatic and hypothalamic levels. Galanin also stimulates feeding in rats when injected into the hypothalamus (4). Studies in rats and dogs have shown that galanin inhibits pancreatic insulin release in response to a number of stimuli including oral and intravenous glucose, intravenous tolbutamide, and arginine infusion (5–9). Galanin receptors have been identified in the islet (10), and a putative mode of action for galanin inhibition has been suggested (11).

These findings, in conjunction with the presence of galanin in canine islet cells (12), have led to speculation about a possible physiological role for galanin in the regulation of insulin secretion in humans (13,14). However, preliminary studies suggested that small doses of infused galanin did not significantly affect plasma insulin concentrations in humans (15).

Because of the apparent discrepancy between animal and human studies, we undertook in normal volunteers a study of the effect of infusion of porcine galanin, at higher dosages than have previously been used in humans, on intravenous glucose tolerance and plasma growth hormone levels.

## RESEARCH DESIGN AND METHODS

**Subjects.** Seven male volunteers were recruited from the hospital staff (mean ± SD age 30 ± 3 yr). All were in good health and taking no medicine. All gave informed, written consent, and the study was approved by the Hammersmith Hospital ethical committee.

**Infusion protocol.** All infusions were undertaken with the subjects recumbent with indwelling cannulas inserted into the antecubital fossae of both arms: one for infusion and one for blood sampling. Sterile, endotoxin-free synthetic galanin was used (Institut Armand-Frappier, Laval, Quebec), reconstituted immediately before infusion in 1.5 ml of the subject's own heparinized plasma with 5000 U aprotinin and diluted in normal saline.

The subjects were studied on three separate occasions at least 1 wk apart at 0900. On each occasion, they underwent an intravenous glucose tolerance test (IVGTT); baseline blood samples were taken at −15 and −10 min. At time 0, 0.5 g/kg body wt of glucose (20% solution) was given over ≤1 min, and blood was taken at 3, 5, 7.5, 10, 15, 20, 25, 30, 40, 50, and 60 min. This was combined with one of three infusions (in random order) between −10 and 30 min. The three infusions included an infusion of normal saline, an infusion of 160 pmol · $kg^{-1}$ body wt · $min^{-1}$ galanin, and an

From the Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London, United Kingdom.

Address correspondence and reprint requests to Professor S.R. Bloom, Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 ONN, UK.

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infusion of 80 pmol · kg$^{-1}$ body wt · min$^{-1}$ porcine galanin.

**Measurements.** Serum growth hormone was measured with a specific double-antibody radioimmunoassay with an automated system (Kemtek, Burgess Hill, Sussex, UK) as previously described (16), with a detection limit of 1 mU/L and within- and between-assay coefficients of variation of 6 and 8%, respectively. Insulin was measured with an in-house double-antibody radioimmunoassay, and plasma glucose was measured with a glucose oxidase method (Beckman glucose analyzer, Galway, UK). When galanin was infused, blood was taken for plasma galanin measurement with an established radioimmunoassay method (15).

**Statistical analysis.** Results were compared with Friedman's nonparametric analysis for two-way analysis of variance and Student's *t* test for individual comparisons. Incremental area under the curve (AUC) was calculated by use of the trapezoidal rule, and with the mean of the values at −15 and −10 min as baseline, the statistical significance of the differences found was then tested with Student's *t* test. $P \leq .05$ was defined as statistically significant. Results are given as means ± SE unless stated otherwise.

## RESULTS

All subjects commented on the unpleasant metallic taste produced by galanin infusion; two also reported mild epigastric discomfort. One declined to have his second galanin infusion because of this and therefore did not receive 160 pmol · kg$^{-1}$ body wt · min$^{-1}$.

**Plasma glucose and serum insulin.** Galanin infusion at either dose level had no effect on the levels of plasma glucose or serum insulin reached during the IVGTT (Figs. 1 and 2). Glucose elimination constants ($K_g$ [17]) were 2.01 ± 0.14%/min for the IVGTT alone, compared to 2.7 ± 0.25%/min for the IVGTT with 80 pmol · kg$^{-1}$ body wt · min$^{-1}$ galanin, and 2.3 ± 0.2%/min with 160 pmol · kg$^{-1}$ body wt · min$^{-1}$ galanin.

**Serum growth hormone.** Growth hormone levels during the baseline IVGTT did not rise (AUC 18 ± 19 U). Galanin infusion at 80 and 160 pmol · kg$^{-1}$ body wt · min$^{-1}$ led to a rise in growth hormone levels (Fig. 3). Peak values were 18.4 ± 3.7 mU/L and 22.6 ± 3.1 mU/L at 40 min, and AUC was 651 ± 166 U and 826 ± 185 U, respectively. Both rises

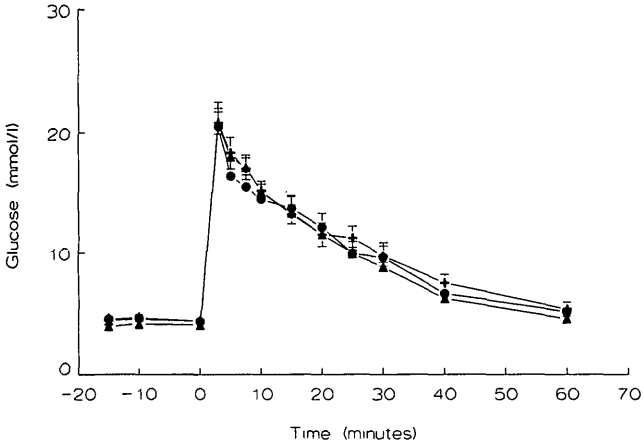


**FIG. 1. Plasma glucose levels during intravenous glucose tolerance test with infusion of 0 galanin (●), 80 pmol · kg$^{-1}$ body wt · min$^{-1}$ galanin (▲) from −10 to 30 min, and 160 pmol · kg$^{-1}$ body wt · min$^{-1}$ galanin (+).**

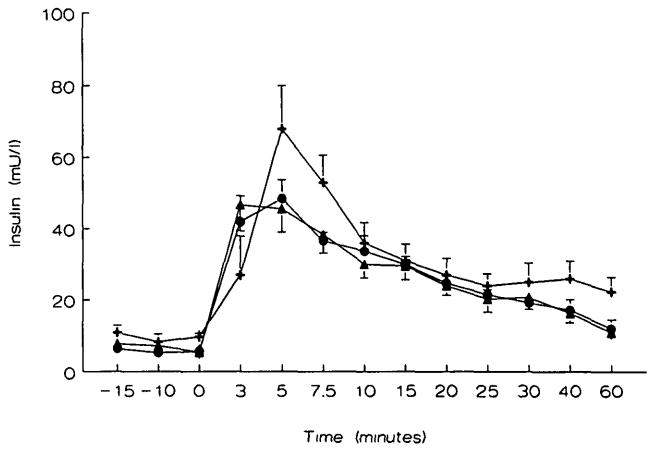


**FIG. 2. Serum insulin levels during intravenous glucose tolerance test with infusion of 0 galanin (●), 80 pmol · kg$^{-1}$ body wt · min$^{-1}$ galanin (▲) from −10 to 30 min, and 160 pmol · kg$^{-1}$ body wt · min$^{-1}$ galanin (+).**

were statistically significant compared with the baseline IVGTT ($t$ = 3.7, $P$ = .003 for 80 pmol/kg galanin; $t$ = 7.9, $P < .00001$ for 160 pmol/kg). Although the rise in growth hormone levels was greater after the 160 than after the 80 pmol · kg$^{-1}$ body wt · min$^{-1}$ infusion, this was not statistically significant ($t$ = 0.43, $P$ = .8).

**Plasma galanin.** Circulating levels of plasma galanin at 30 min were 1.4 ± 0.5 pmol/ml during the 80 pmol · kg$^{-1}$ body wt · min$^{-1}$ infusion and 2.7 ± 0.8 pmol/ml during the 160 pmol · kg$^{-1}$ body wt · min$^{-1}$ infusion (means ± SD).

## DISCUSSION

This study investigated in detail the effect of infusion of porcine galanin on intravenous glucose tolerance in humans; a preliminary study suggested that galanin influenced glucose disposal after an intravenous bolus of glucose but not plasma insulin or peak plasma glucose levels (15). Much higher doses of galanin were given than was the case in previous studies, and our results showed that these pharmacological doses of galanin had no effect on glucose tolerance or insulin release, although galanin markedly stimulated growth hormone release even in the face of an intravenous glucose load.

The lack of an effect of galanin on glucose tolerance and insulin release is at variance with the results from animal studies, which have shown that galanin inhibits insulin release in vivo (5–9). There are a number of possible interpretations of this including *1*) galanin does not play a role in the regulation of insulin secretion by the human islet cell, in contrast to dogs or rats; *2*) galanin has a part to play but in a paracrine role that is not necessarily simulated by the infusion of galanin into the systemic circulation, however high the levels reached; and *3*) the lack of effect in this study is solely because of differences in amino acid composition between porcine and human galanin.

Species differences in the distribution and physiological action of galanin could explain these findings. Although there is convincing evidence that galanin inhibits the insulin response to many insulin secretagogues in rats and dogs, the ease with which this can be demonstrated in both species indicates that this action should have been evident in humans during this study. Species differences have already

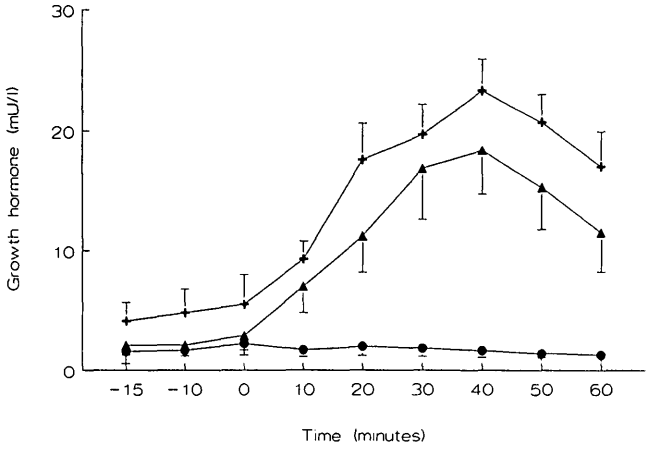


**FIG. 3. Serum growth hormone levels during intravenous glucose tolerance test with infusion of 0 galanin (●), 80 pmol · $kg^{-1}$ body wt · $min^{-1}$ galanin (▲) from −10 to 30 min, and 160 pmol · $kg^{-1}$ body wt · $min^{-1}$ galanin (+).**

become apparent in other respects: studies in dogs that have shown an effect on glucose tolerance have failed to show an effect on growth hormone levels, whereas galanin stimulates pituitary growth hormone secretion in humans (15) and rats (18), probably by an indirect action on the hypothalamus (19).

Differences in the amino acid composition of porcine and human galanin might provide an explanation for our findings; the sequence of human galanin is unknown. However, the effects on growth hormone in our human subjects were unequivocal and provided useful confirmatory evidence that adequate levels of biologically active circulating galanin were achieved. Previous studies showed that infusion of porcine galanin in humans at a dose as low as 10 pmol · $kg^{-1}$ body wt · $min^{-1}$ causes a release of growth hormone, whereas 40 pmol · $kg^{-1}$ body wt · $min^{-1}$ also produces a dramatic inhibition of gastrointestinal mobility (20). Indeed, the results of this study confirm that galanin induces a rise in circulating growth hormone even in the face of an intravenous glucose load, which normally suppresses basal (21) and growth hormone–releasing hormone–mediated growth hormone release (22). In conclusion, results from this study cannot be used in support of animal evidence for an inhibitory effect of galanin on β-cell function.

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