Infusion of Mg in Humans Acutely Reduces Serum Insulin Levels: a Pilot Study

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Abstract

Background: infusion of Mg for therapeutic purposes is still a matter for debate. Dosages vary considerably, yet subclinical effects on normal physiology are largely ignored. In human and animal models, interactions between Mg and insulin exist, thus we have investigated the effect of infusing Mg on serum insulin, ionised Mg (Mg^{2+}) and Ca (Ca^{2+}) and plasma glucose in human volunteers.

Methods: six male volunteers were infused with magnesium sulphate ($MgSO_4$) dissolved in normal saline, using a high-dose "loading" bolus, followed by a lower-level "maintenance" period.

Findings: serum Mg^{2+} rose rapidly throughout the bolus infusion, declined during the maintenance phase, but remained higher than pre-infusion levels throughout the experimental period; serum Ca^{2+} rose when serum Mg^{2+} was highest. Infusion of $MgSO_4$ had no effect on heart rate or blood pressure, but caused a rapid, pronounced drop in circulating fasting insulin ($p < 0.0005$), which slowly recovered to basal values during the course of the maintenance infusion. A slight, transient rise in plasma glucose ($p < 0.05$) concomitant with the decline in serum insulin was also observed.

Interpretation: it is possible that the effect of Mg^{2+} on insulin may have been due to antagonism of Ca^{2+} entry in pancreatic beta-cells, the insulin decline causing a subsequent rise in circulating glucose levels. We suggest that these effects of $MgSO_4$ infusions should be considered where the aim is to achieve high doses of blood Mg^{2+} levels by clinical intervention.

Keywords: Magnesium, intravenous, insulin, human

Introduction

An acute infusion of Mg has been used therapeutically in a wide range of clinical circumstances including acute myocardial infarction [1;2], stroke [3], sub-arachnoid haemorrhage [4], stent implantation [5], post-operative cardiac arrhythmias [6], pre-eclampsia [7], and tocolysis [8] (table 1). Subclinical systemic effects unrelated to the original therapeutic targets of Mg, and which arise from infusion of supraphysiological levels of the divalent cation remain largely undocumented, although some evidence suggests a potential interaction with insulin: *in vitro*, elevating external Mg decreased calcium uptake into islets isolated from rats [9] or *ob/ob* mice [10], whereas in humans, hypermagnesaemia induced by Mg infusion led to a reduction in the level of insulin reached during an intravenous glucose-tolerance test [11]. In lactating and non-lactating sheep, infusion of Mg decreased circulating insulin levels, and in the lactating animals, impaired glucose disposal during an intravenous glucose-tolerance test [12]. Finally, in a rat model of thyrotoxicosis, parenteral Mg infusion decreased insulin secretion [13]. Thus it is possible that when used therapeutically, supraphysiological dose of Mg used have significant effects on insulin secretion and hence the ability to maintain adequate uptake of glucose by tissues and organs at a time when changes in energy status or an ability to utilise glucose may be severely detrimental to the well-being of the individual. With this in mind, we have measured blood insulin, glucose, ionised Mg (Mg^{2+}) and Ca (Ca^{2+}) levels in volunteers given an infusion of $MgSO_4$ at doses comparable to those used therapeutically (table 1).

Table 1 here

Methods

All chemicals were Analar grade or better, and were purchased from Sigma, Dorset, UK. Sterile solutions for $MgSO_4$ (heptahydrate salt) or physiological saline (0.9%) infusions were

prepared by the hospital pharmacy department. The protocol was approved by the Lothian Research Ethics Committee, reference number LREC/2000/3/27; participants gave written informed consent. Infusion rates used in this study were based on those previously used for stroke patients [3]. Since the effect of magnesium on serum insulin levels was the major interest in this study, a power calculation using information based on the precision of the insulin ELISA indicated that to detect a change of 15% in paired insulin levels, six subjects would be required ($\alpha = 0.05$, power = 0.8); our previous experience [12] indicated that the fall in insulin was likely to be much larger than this, so six subjects were deemed sufficient for the study. Six healthy male volunteers (aged 28 – 43) were recruited from staff of the Hannah Research Institute and Royal Infirmary of Edinburgh, and were free from hypertension, overt renal or liver disease, or diabetes. The initial infusion protocol for each subject was chosen randomly, followed by the remaining infusion after a washout period of at least two weeks. After fasting overnight, subjects were admitted the following morning; volunteers were supine for at least 15 min prior to the start of the infusion, and remained supine until after the last sample had been collected. Blood samples were removed from the antecubital vein *via* an indwelling cannula in one arm, and infusions carried out using a similar cannula in the other arm. The infusion protocols were as follows: either a) saline alone (0.9% NaCl in sterile distilled water) for 75 min, or b) $MgSO_4$ (heptahydrate salt) in sterile saline: a bolus dose of 15.6 mmol Mg (12.5 ml of 1.25 M $MgSO_4$ in saline, 50 ml/h for 15 min) was given followed by an infusion of 42 mM $MgSO_4$ in saline at the rate of 50 ml/70 kg/h for 60 min (= 2.1 mmol Mg infused/70 kg). Samples and measurements were taken at: -30 min, then -15, 0, 7.5, 15, 30, 45, 60, 75, 105, 135, and 165 min (0 min indicates the start of the 15 min bolus infusion, 15 and 75 min are the start and end of the maintenance infusion respectively). Blood samples were taken at each time-point for analysis of glucose (plasma), and ionised Mg^{2+}, Ca^{2+}, or insulin (serum). Plasma was prepared by dispensing whole blood (10 ml) into standard lithium-heparin tubes (Sterilin, Ltd.,

UK), on ice, which were centrifuged within 60 min of collection at 1,720 x g at 4ºC for 20 min; the plasma was removed and frozen and -20ºC until required. To prepare serum, whole blood (10 ml) was collected into polystyrene tubes free of anticoagulant (Sterilin, Ltd., UK), and allowed to clot at room temperature for at least 2 h; after this time, the samples were centrifuged at 9,500 g for 5 min at room temperature, and the supernatant serum frozen at –20˚C until required for assay. For measurement of serum Mg^{2+} or Ca^{2+}, samples were analysed on an AVL 988-4 ion analyser (Roche-AVL, Staffs, UK) following HEPES-buffering to compensate for the loss of CO_2 from serum and subsequent alkalinisation on freezing [14]: briefly, 200 µl of serum were added to 50 µl of 0.5 M HEPES-TRIS solution (pH 7.4) which buffered the samples to approximately pH 7.4 ± 0.5. The tubes were vortexed, and equilibrated for 45 min at room temperature before analysis on the AVL for Mg^{2+} and Ca^{2+}. Insulin and glucose levels were measured in by ELISA (Mercodia Kit, Diagenics, Ltd., UK) and enzymatic reaction respectively [15]. All results are mean values ± SEM. To minimise variability in the analysis of the response curves, graphs were expressed as percentages of mean pre-infusion (basal) levels [12], and analysed by repeated measures 1-way ANOVA, with Bonferroni's Multiple Comparison correction for comparisons between multiple points. Differences between basal values and those occurring at maximum serum Mg^{2+} were examined by Student's paired *t* test. Blood pressure and heart rate were taken throughout by automatic sphygmomanometer to monitor for Mg-induced hypotension. Finally it must be borne in mind that the sample size was determined by the original primary outcome of the effect of hypermagnesaemia on serum insulin levels, and is thus likely to be underpowered for many of the other parameters. To assess the impact of hypermagnesaemia on these fully, further studies would be required where appropriate power calculations are carried out for the parameters of interest.

Results

Mean Basal (pre-infusion) values are shown in tables 2 and 3, together with values measured when serum Mg^{2+} was highest (15 min from start of $MgSO_4$ infusion). For analytes measured pre-infusion, there were no significant differences between the saline or $MgSO_4$ treatments. There were no significant changes in either heart rate or either systolic or diastolic blood pressure during the infusions (table 2).

Table 2&3 here

Serum ionised magnesium and calcium

Serum Mg^{2+} rose significantly ($p < 0.001$) when the ion was infused (Figure 1a), with the peak value occurring at +15 min. All the serum levels of Mg^{2+} reached at time-points after 7.5 min were significantly different from pre-infusion values (all $p < 0.001$); there were no significant changes in the corresponding control infusion. Similarly, serum Ca^{2+} showed a slight but significant transient rise ($p < 0.005$) during $MgSO_4$ infusion (Figure 1b), with only the values at +15 and +30 min being different from the pre-infusion Ca^{2+} levels ($p < 0.05$ and $p < 0.01$ respectively). Peak Ca^{2+} was reached at 30 min after the start of the $MgSO_4$ infusion (1.39 ± 0.04 mM). There was a much greater variability in values obtained for Ca^{2+} in the control, but again, there were no significant changes throughout the infusion or sampling periods thereafter.

Figure 1 here

Serum insulin and glucose

Serum insulin levels fell significantly during the $MgSO_4$ infusion (Figure 2a), with time-points +7.5 min, and +15 min, being lower than the basal values ($p < 0.01$ for both). Although the insulin levels during the saline infusion appeared to drift down with time, this effect was not significant ($p=0.09$). Plasma glucose levels (Figure 2b) were slightly but significantly elevated above basal

Figure 2 here

($p < 0.05$) when serum Mg^{2+} levels were highest (+15 min). There were no changes in plasma glucose during infusion of saline.

Discussion

Despite the frequency with which therapeutic infusion of supraphysiological levels of Mg salts are used, there are few reports describing the physiological consequences of such infusions. The present study used an infusion protocol which is comparable to many of those described in the literature (table 1). These levels of Mg were well-tolerated by the subjects, with only two of the six experiencing flushing during the $MgSO_4$ infusion; the peak Mg^{2+} level reached was almost twice that of the pre-infusion value. We have shown that infusion of $MgSO_4$ caused a significant rise in serum ionised Mg (Mg^{2+}), serum ionised Ca (Ca^{2+}), a pronounced, transient, reduction in basal fasting insulin levels, and a brief rise in plasma glucose. Most of these effects of the $MgSO_4$ infusion are associated with the bolus dose, since recovery of Ca^{2+}, insulin and glucose occurred at, or shortly after the end of this phase, even though serum Mg^{2+} was still significantly elevated, and remained so throughout the remainder of the sampling period.

The slight rise in serum Ca^{2+} was unexpected; previous studies of Mg infusions have reported a reduction in blood Ca^{2+} [16-18], thought to be due to Mg-induced inhibition of parathyroid hormone (PTH) secretion [19;20]. However these reported reductions in blood Ca^{2+} occurred several hours after the commencement of Mg infusion, whereas we found a small, rapid increase in serum Ca^{2+} 15 min after the start of the infusion period. This may have been caused by displacement of Ca^{2+} by Mg^{2+} from serum albumin, since variations in the blood concentration of one ion will influence the binding equilibrium of the others as described by the Siggaard-Andersen equation for different concentrations of H^+ (e.g. [14;21-23]). Another mechanism may involve the role of intracellular ions, though these were not measured in this study, but such information would be useful in any further study to assist in clarification of the physiological events. Other groups have suggested that intracellular levels of Ca^{2+} and Mg^{2+} may modulate cellular responses to insulin, with a rise in intracellular Mg^{2+} being followed by a later rise in cytosolic Ca^{2+} [24].

Given the high blood levels of Mg^{2+} obtained in the present study, it is possible that an infusion-induced rise in intracellular Mg^{2+} may also be accompanied by a rise in cytosolic Ca^{2+}, and extrusion of this may contribute to the rise in serum Ca^{2+}.

A relationship exists between insulin and Mg, in that insulin promotes influx of Mg into cells from the extracellular fluid (e.g. [24;25]). As found in sheep [12], the present work demonstrates in humans a reduction in circulating fasting insulin levels following an infusion of $MgSO_4$. This decline in serum insulin may be due to impaired release of the hormone, since insulin secretion requires the presence of external Ca^{2+} [26], and Mg^{2+} is considered to be "Nature's physiologic calcium blocker" [27], and in studies using isolated pancreatic islets or perfused whole organs, inhibition of Ca^{2+} influx by verapamil was also associated with a decrease in insulin secretion in the perfused rat pancreas [28]. Given the pronounced drop in insulin we have observed, it is likely that the rise in glucose is a consequence of the former. Although the insulin reduction is significant, it is also transient, with recovery being complete 30-50 min after the start of infusion; it is not clear what further physiological effects such a brief reduction in insulin would have, although some studies have indicated that insulinopaenia lasting for only a few hours increased endothelial lipoprotein lipase activity in rats [29]. Whilst this may not be significant in the healthy volunteers studied here, Mg infusions are generally carried out in the presence of an existing pathology, and glucose metabolism is abnormal in critically-ill patients [30]. We suggest therefore, that where supraphysiological doses of Mg are being administered therapeutically, consideration is given to the potentially wider physiological sequelae of such treatment for the patient, and further, fuller studies designed to address these interactions.

Acknowledgements

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Table 1

Study	Bolus Rate (mmol/min)	Bolus Total (mmol)	Maintenance (mmol/h)	Reference
Atrial Fibrillation	--	--	2.50	[31]
Forearm Bloodflow	--	--	3.96	[32]
Analgesia	--	1.42	2.03	[33]
Myocardial Infarction (LIMIT-2)	1.60	8.00	2.71	[34]
Coagulation Cascade	0.53	8.00	3.00	[35]
Myocardial Infarction (ISIS-4)	0.53	8.00	3.00	[1]
Bleeding Time	0.67	8.00	4.00	[36]
Myocardial Infarction (Magic)	0.54	8.11	2.88	[2]
Stent implantation	0.41	8.12	4.75	[5]
Tetanus	0.38	11.36	8.11	[37]
Stroke (IMAGES)	1.07	16.00	2.71	[3]
Pre-eclampsia	1.62	16.22	4.07	[7]
Subarachnoid haemorrhage	0.67	20.00	3.33	[4]
Tocolysis	0.81	24.32	20.29	[8]
Mean	0.78	10.79	3.94	
Range	0.38 – 1.62	1.42 – 24.32	2.03 – 20.29	
Present Study	*1.11*	*15.60*	*2.10*	

Table 1: Comparison of Mg infusions in previous human studies. It was assumed that the subjects were 70 kg and that the heptahydrate sulphate salt of Mg was used unless otherwise stated in original article; maximum doses are given where a range was used. These figures must not be used experimentally, and the reader is referred to the original publications for confirmation of doses.

Table 2

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Parameter	Pre-infusion (Basal) Levels of CV Parameters			Levels of CV Parameters at Peak Serum Mg (+15 min)		
	Allocated Infusion		p	Infusion		p
	Saline (n = 6)	$MgSO_4$ (n = 6)		Saline (n = 6)	$MgSO_4$ (n = 6)	
Heart Rate (bpm)	69 ± 2	62 ± 1	NS	60 ± 3	65 ± 5	NS
Systolic BP (mm Hg)	128 ± 4	129 ± 2	NS	127 ± 6	130 ± 7	NS
Diastolic BP (mm Hg)	77 ± 1	79 ± 0	NS	73 ± 3	75 ± 6	NS

Table 3

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Analyte	Pre-infusion (Basal) Levels of Analytes — Allocated Infusion			Levels of Analytes at Peak Serum Mg (+15 min) — Infusion		
	Saline (n = 6)	$MgSO_4$ (n = 6)	p	Saline (n = 6)	$MgSO_4$ (n = 6)	p
Mg^{2+} (mmol/l)	0.603 ± 0.012	0.603 ± 0.007	NS	0.594 ± 0.007	1.199 ± 0.047	$p < 0.0001$
Ca^{2+} (mmol/l)	1.38 ± 0.03	1.35 ± 0.01	NS	1.37 ± 0.04	1.39 ± 0.01	$p < 0.02$
Glucose (mmol/l)	4.82 ± 0.21	5.03 ± 0.17	NS (p=0.09)	4.80 ± 0.22	5.32 ± 0.14	$p < 0.05$
Insulin (ng/ml)	4.36 ± 0.99	4.52 ± 1.0	NS	3.94 ± 0.73	2.85 ± 0.46	$p < 0.02$

Figure Legends

Figure 1. Effect of infusing saline (open circles), or $MgSO_4$ (closed circles) on serum ionised a) Mg^{2+}, and b) Ca^{2+}. The solid line shows the duration of infusions; for Mg, the upper line represents the bolus, the lower, the "maintenance" infusion. Asterisks denote difference from preinfusion values: * = $p < 0.05$, *** = $p < 0.0001$.

Figure 2. Effect of infusing saline (open circles), or $MgSO_4$ (closed circles) on a) serum insulin and b) plasma glucose . The solid line shows the duration of infusions; for Mg, the upper line represents the bolus, the lower, the "maintenance" infusion. Asterisks denote difference from preinfusion values: * = $p < 0.05$, ** = $p < 0.0005$.

Figure 1a

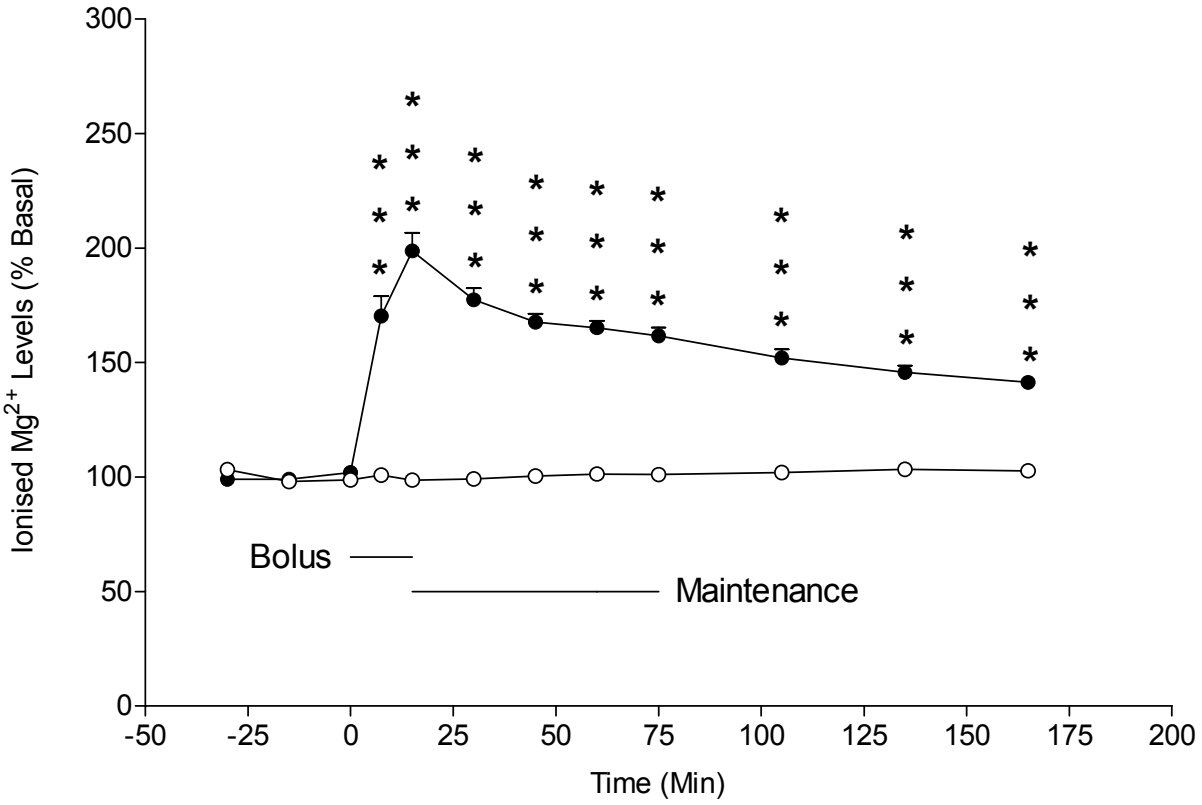

Ionised Mg^{2+} Levels (% Basal)
300
250
200
150
100
50
0
-50
-25
0
25
50
75
100
125
150
175
200
Time (Min)
Bolus
Maintenance

Figure 1b

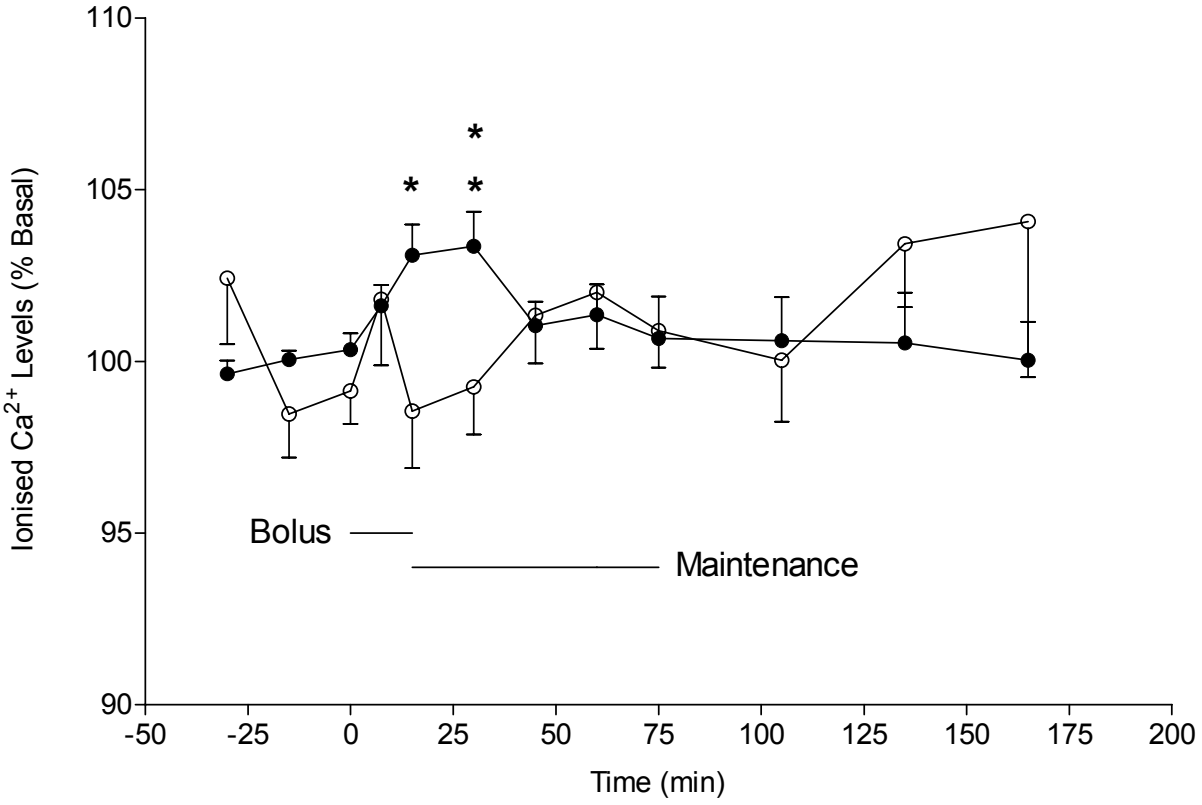

110
105
100
95
90
Ionised Ca2+ Levels (% Basal)
*
*
*
Bolus
Maintenance
-50
-25
0
25
50
75
100
125
150
175
200
Time (min)

Figure 2a

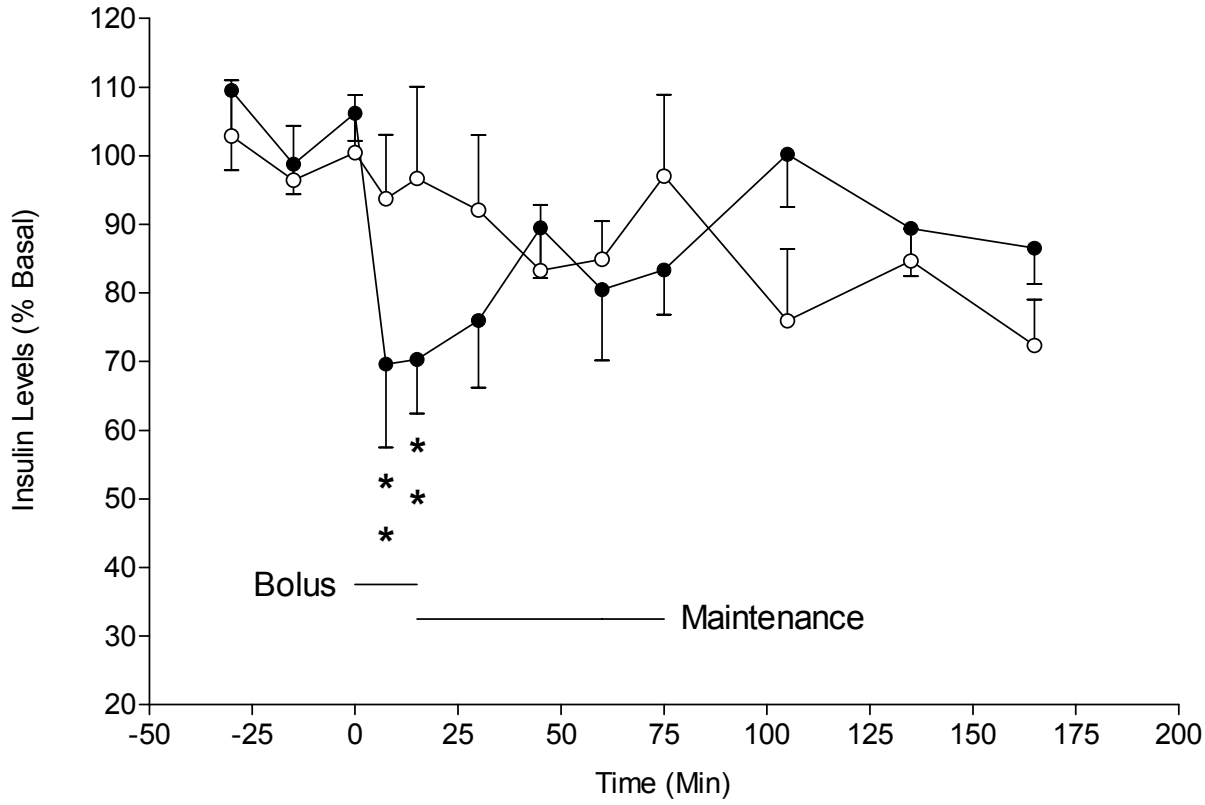
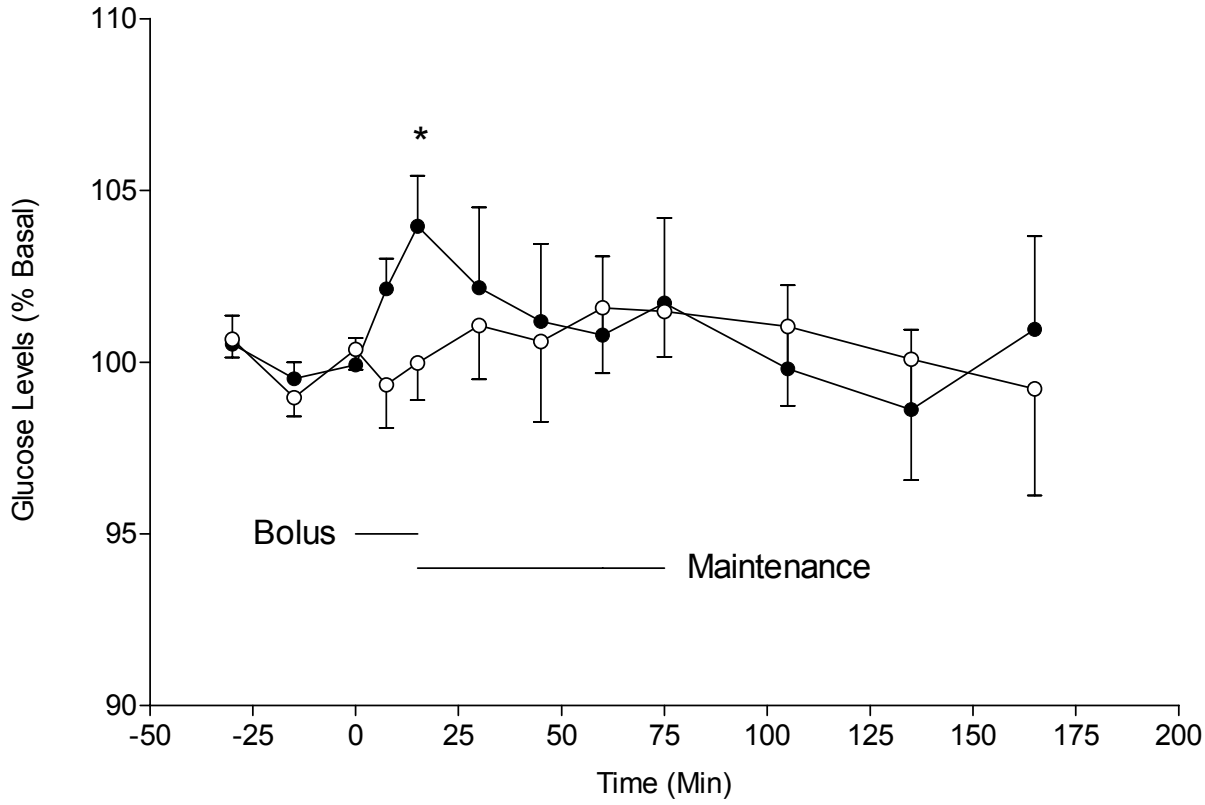

Insulin Levels (% Basal)
Time (Min)
Bolus
Maintenance
120
110
100
90
80
70
60
50
40
30
20
-50
-25
0
25
50
75
100
125
150
175
200
*
*
*
*

Figure 2b


110
105
100
95
90
*
Glucose Levels (% Basal)
Bolus
Maintenance
-50
-25
0
25
50
75
100
125
150
175
200
Time (Min)

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