Using sheep as a model for the study of insulin-insensitivity in obesity

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In humans, Type II or non-insulin-dependent diabetes is generally associated with obesity. The reasons for such an association are not clear. It is understood that the responsiveness to stimuli and the capacity of the pancreatic β cells to secrete insulin, the rate of delivery of both insulin and glucose to insulin-sensitive tissues of the body and the rate of uptake and utilisation of glucose by these tissues are all important determinants of the rate of clearance of glucose from the circulation. This study is the first of a series undertaken, using sheep as the experimental model, to examine these determinants in obesity. While it has been suggested that sheep muscle might be less sensitive to insulin than is the muscle of the rat or human, the animal, because of its size, provides a potentially convenient and useful in vivo experimental model for the study of the glucose/insulin complex.

Twelve Merino wethers, aged 2 yrs, were fed the same diet of lucerne and corn but at different levels so that six wethers became obese while the others remained relatively lean. Chronic indwelling catheters were installed in both the external jugular veins of each animal. The animals were fasted for 24 hrs then were each given an intravenous bolus of glucose (50% solution) at the rate of 0.3 g/kg live weight. A week later, this procedure was repeated but the bolus of glucose was followed 20 mins later by a bolus of insulin at the rate of 0.03 IU/kg live weight.

	Lean	Obese	P
Live weight (kg)	28 ± 0.9	44 ± 0.9	0.000
Body fat (%)	18 ± 0.7	29 ± 1.0	0.000
Fasting plasma glucose (mM)	4.8 ± 0.4	5.0 ± 0.3	0.29
$t\frac{1}{2}$ (min)			
Glucose only	84 ± 7.0	113 ± 10.0	0.0177
Glucose + insulin	40 ± 2.0	61 ± 4.0	0.0017

Although the sheep were all of the same age, the lean group had a mean live weight and body fat content of 63 and 62% of those of its obese counterpart. The basal glucose concentrations in plasma in the two groups were not significantly different but were relatively high probably due to the corn in the diet.

The lean sheep cleared glucose from the circulation more quickly than did the obese sheep. The rate of glucose clearance was increased in both groups by the addition of exogenous insulin. While the mechanisms underlying the differences between the two groups of sheep in the way they disposed of glucose are not clear, it would seem that there was a limitation in the rate of insulin secretion in the two groups of animals. Furthermore, the difference between the two groups would suggest a basic difference in the way in which respective insulin-sensitive tissues took up and metabolised glucose and/or in the rate of delivery of insulin and glucose to these tissues.

It is concluded that the difference in the rate of glucose disposal between the two groups of sheep was large enough to suggest that the lean and obese sheep may be successfully used as experimental models to study, in vivo and at the tissue and cellular levels, the reasons for the generally observed insulin insensitivity in obesity.

Effect of habitual diet on platelet phospholipid polyunsaturated fatty acids

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Dietary arachidonic acid (AA) can increase platelet AA level, leading to increased production of thromboxane A_2 (TXA_2), a known vasoconstrictor and a potent intiator of platelet aggregation. Omega-3 polyunsaturated fatty acids (PUFA), particularly eicosapentaenoic acid (EPA) have beneficial effects in the area of thrombosis, by reducing platelet AA levels and producing an alternative form of thromboxane (TXA_3), which is relatively inactive in promoting platelet aggregation and vasoconstriction (1). The aim of this study was to examine how the platelet phospholipid (PL) PUFA profile was influenced by habitual dietary intake. According to available research results, we hypothesised that habitual meat eaters would have a higher level of platelet PL AA, than vegetarians, since meat is a major dietary source of AA.

We recruited 143 male healthy subjects aged 20-55 years from the metropolitan area of Melbourne. According to their habitual dietary intake, they were divided into four groups: vegan (n = 18), ovolacto vegetarian (n = 44), moderate-meat-eaters (n = 61, <300 g meat/day) and high-meat-eaters (n = 20, >300 g meat/day). Venous blood was collected into citrate vacutainers from which plasma was prepared. Platelets were isolated using a metrizoate concentration gradient method. Lipid extraction, phospholipid separation, fatty acid methylation and separation were carried out by standard methods. Results (% of total fatty acids) are shown in the table.

	Vegan[1]	Ovolacto[1]	Moderate-meat[1]	High-meat[1]
18:2n-6	6.3 ± 0.5	6.2 ± 0.9	5.2 ± 0.6 *ach, bch*	5.4 ± 0.7 **h,adh, bdh*
20:3n-6	1.5 ± 0.4	1.5 ± 0.4	1.5 ± 0.3	1.5 ± 0.3
20:4n-6	23.0 ± 1.7	23.8 ± 1.4	24.5 ± 1.2 *acg, bcf*	24.3 ± 1.5 **h, adf*
20:5n-3	0.2 ± 0.1	0.3 ± 0.2	0.4 ± 0.1 *ach, bcg*	0.4 ± 0.1 **h,adh, bdg*
22:4n-6	2.7 ± 0.5	2.6 ± 0.5	2.5 ± 0.3	2.3 ± 0.3 **f, adg, bdg*
22:5n-6	0.2 ± 0.1	0.3 ± 0.1	0.3 ± 0.2	0.2 ± 0.0
55:5n-3	1.5 ± 0.4	1.9 ± 0.5	1.9 ± 0.3 *ach*	1.9 ± 0.3 **g, adg*
22:6n-3	0.9 ± 0.3	1.3 ± 0.5	1.7 ± 0.4 *ach, bch*	1.4 ± 0.4 **h, adh*
n-3	2.7 ± 0.5	3.5 ± 0.8	4.0 ± 0.5 *ach*	3.76 ± 0.5 **h, adh*
n-6	33.8 ± 2.2	34.3 ± 1.6	33.9 ± 1.2	33.7 ± 1.9
n-3/n-6	0.08 ± 0.01	0.10 ± 0.03	0.12 ± 0.02 *ach, bcg*	0.11 ± 0.02 **h, adh*

[1] mean ± SD; *Anova: $^{f}P<0.05$. $^{g}P<0.01$. $^{h}P<0.001$. [ac] vegan vs moderate-meat. [ad] vegan vs high-meat. [bc] ovolacto vs moderate-meat. [bd] ovolacto vs high-meat. T-test.

The propotion of linoleic acid (18:2n-6) in the platelet PL of both the vegan and ovolacto vegetarian groups was significantly higher than in the two meat-eating groups (P<0.001). Adrenic acid (22:4n-6) was significantly higher in the vegan than in the high-meat-eater group (P<0.05). However AA was significantly lower in the vegan group than in either meat-eating groups (P<0.01). There was no significant difference between the four groups in total n-6 fatty acids. The proportion of EPA, docosapentaenoic acid (22:5n-3) and docosahexaenoic acid (22:6n-3) were greater in both of the meat-eating groups than in the vegan and ovolacto vegetarian groups.

Our findings indicate that vegan diets containing no long chain (LC) PUFA result in lowered platelet AA levels relative to meat eaters, which may predispose meat eaters to a higher thrombotic risk. However, the increased proportion of LC n-3 PUFA in the platelet PL of meat eaters relative to vegans and vegetarians may provide a protective effect.

1. Needleman P, Raz A et al.. Triene prostaglandins: Prostacyclin and thromboxane biosynthesis and unique biological properties. Proc Natl Acad Sci USA 1979;76(2):944-8.