PROGRAMMA DI RICERCA STM – RELAZIONE CONCLUSIVA

Visiting professor: Paula Macedo, Department of Physiology, Faculty of Medicine, New University of Lisbon, Portugal.

CNR hosting institute: Istituto di Ingegneria Biomedica, Corso Stati Uniti 4, Padova; investigator: Andrea Mari.

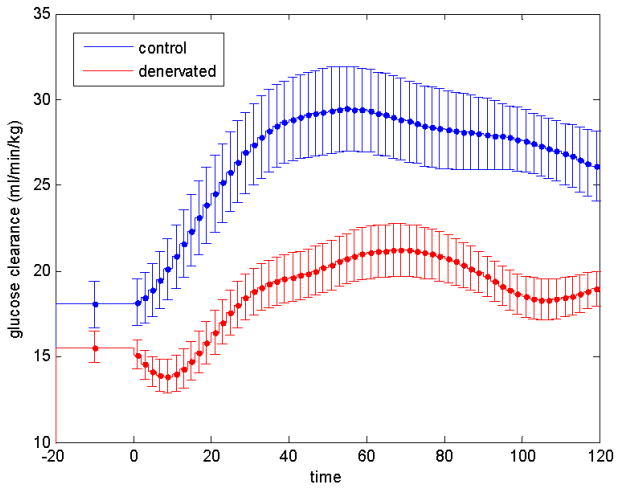
Visit period: October 3-14, 2011.

Program title: Exploring new factors contributing to glucose tolerance: the central nervous system and insulin clearance.

Planned objectives: The objective of this visit was to strengthen the existing collaboration between the Department of Physiology of the New University of Lisbon and ISIB-CNR on the use of mathematical models for the analysis of in vivo metabolism, with focus on two main topics: 1) the analysis of glucose fluxes based on tracer modeling methods in animal experiments performed to assess the role of the central nervous system in glucose homeostasis; 2) the assessment of insulin clearance in humans, its determinants and its role in glucose tolerance.

Activity report

Topic 1. The double tracer method for the assessment of glucose absorption, production and utilization during an oral glucose load has been reviewed. The model-based calculation methods developed at ISIB (1) have been explained in detail, enabling Prof Macedo to apply these methods to rat experiments for which double tracer data were available (2). These experiments were performed in Lisbon in two groups of rats: a group in which the hepatic nerves were surgically removed and a group of sham-operated rats. A liquid meal containing glucose, fat and proteins was administered through an intraenteric cannula. An intravenous and a meal stable-isotope tracers were used; tracer enrichments were analyzed by mass-spectrometry at the University of Coimbra, in collaboration with Prof John Jones. The tracer data were analyzed during Prof Macedo's visit, using the methods developed at ISIB. The analysis has shown that denervation produces a decrease in glucose clearance (see figure), which was more evident during the administration of the liquid meal, implying an involvement of the central nervous system in glucose homeostasis, as previously suggested (3). Unfortunately, some difficulties were encountered in the calculation of glucose production and oral glucose absorption, due to problems related to the oral tracer. These problems are currently under investigation. It has been planned to complete the tracer analysis upon solution of the tracer problem and to draft a manuscript.



Topic 2. During Prof Macedo's visit, the issue of insulin clearance has been reviewed under several aspects, in view of the analysis of the data of the RISC study (4). First, a summary of the literature has been performed considering both in vivo and in vitro studies on the subject. In vivo studies have shown rather consistent relationships between estimates of insulin clearance and obesity and insulin resistance. However, due to the potential dependence of insulin clearance on insulin levels and the well-established relationships between obesity, insulin resistance and insulin secretion, whether the observed relationships are mediated by insulin levels themselves or reflect control mechanisms remains unclear. Second, the methods for the calculation of insulin clearance have been reviewed in depth, to appreciate the characteristics and limitations of the approaches used in the literature.

Regression Coefficients
slope vs. 3 Independents

	Coefficient	Std. Error	Std. Coeff.	t-Value	P-Value
Intercept	-1.324	.291	-1.324	-4.554	<.0001
isi	-.281	.022	-.366	-13.052	<.0001
bmi	.606	.063	.247	9.583	<.0001
isrt	.118	.028	.111	4.252	<.0001

Multiple regression model showing the dependence of a new estimate of insulin clearance (dependent variable "slope") on insulin sensitivity (isi), body mass index (bmi) and total insulin secretion during an OGTT (isrt). This models shows that insulin sensitivity and obesity are independent correlates of insulin clearance, also when total insulin secretion is taken into account.

Based on this background, the analysis of the RISC study has started by first obtaining classical and new estimates of insulin clearance, which have been possible owing to the rich database (5). The analysis has proven to be quite complex due to the large number of variables of the database. An important first result has been that insulin sensitivity and obesity are independent correlates of insulin clearance, and that the observed relationships are not mediated by total insulin secretion during an OGTT (see table). Although during Prof Macedo's visit it has not been possible to complete the analysis, the main characteristics of insulin clearance have been outlined and a plan for additional analysis has been drafted. During Prof Macedo's visit, Prof Andrea Natali, from the coordinating center of the RISC study at the University of Pisa, has joined us to discuss this issue and make a plan for a manuscript draft.

Overall evaluation and future plans. Prof Macedo's visit has been fully successful and all goals, except the complete analysis of the tracer data in Topic 1, have been achieved. The plans for the next future are as follows. *Topic 1:* 1) examine the tracer problem to find a solution. 2) Upon solution of the tracer problem complete the tracer analysis and draft a manuscript. *Topic 2:* complete the analysis of insulin clearance and draft a manuscript.

In addition to the topics of the project discussed here, Prof Macedo's visit has been important to discuss possible future collaborations. It has been in particular envisaged to develop an experimental and data analysis model for the assessment of insulin secretion and beta-cell function in rats, based on C-peptide analysis as in human subjects (6,7). Prof Macedo will explore the possibility to perform experiments in rat for the assessment of C-peptide kinetics, the core of the method.

References

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Padova, 27/10/2011

Andrea Mari