COLLOQUIA IN CELLULAR SIGNALLING

Venue: Medical University Vienna, Center for Physiology and Pharmacology,
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Friday **25.04.2014 11:00 s.t.** **Thomas Scherer** **(host: Ch. Österreicher)**

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"The role of brain insulin action in regulating hepatic lipid content"

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Abstract:
Hepatosteatosis and dyslipidemia are hallmarks of the metabolic syndrome and plasma triglycerides (TG) correlate with insulin resistance (IR). Since hepatic lipogenesis is increased in the IR state, TG secretion must not be too low in order to prevent steatosis. Insulin action comprises of direct effects on peripheral organs e.g. liver and the adipose, but also of indirect effects that are mediated via the central nervous system[1]. Systemic insulin decreases very low-density lipoprotein (VLDL) production by the liver, yet it is unknown whether brain insulin can independently regulate VLDL flux. To study the role of brain vs. systemic insulin signaling on hepatic VLDL secretion, we performed tyloxapol infusion studies in male Sprague Dawley rats during systemic or isolated brain hyperinsulinemia, which was accomplished by infusing insulin or vehicle for 4 hrs into the 3rd ventricle (ICV). ICV insulin infusion increased hepatic VLDL secretion compared to controls (2.59□0.28 vs. 1.80□0.2 µmol/kg/min; P=0.039; n≥11 per group). To the contrary, a hyperinsulinemic euglycemic clamp decreased TG flux (0.85□0.05 µmol/kg/min; P=0.020; n=4), which is in agreement with prior reports[2]. Plasma lipid profiling in these animals demonstrated that ICV insulin increased the accumulation of TG associated FAs such as palmitate and oleate (+30%; P<0.05). Conversely, mice that lack the insulin receptor in the whole brain had reduced hepatic TG flux compared to littermates, which was again assessed by tyloxapol studies (154□6 vs. 126□12 µmol/kg/h; P = 0.038; n≥9 per group). Furthermore, chronic continuous low-dose ICV insulin treatment over 4 weeks using stereotaxic cannulae connected to subcutaneously implanted osmotic mini pumps, reduced hepatic TG content independent of changes in body weight and food intake. While systemic hyperinsulinemia and isolated loss of neuronal insulin signaling both suppress TG flux, ICV insulin infusion increases VLDL secretion and reduces hepatic lipid load. We speculate that the liver fat accumulation that is commonly seen in the obese state may be due to brain insulin resistance or in other words a failure to increase VLDL export from the liver in order to compensate for the caloric excess and unrestrained hepatic *de novo* lipogenesis in the IR state.

1 Scherer, T. *et al.* Brain insulin controls adipose tissue lipolysis and lipogenesis. *Cell Metab* **13**, 183-194, doi:S1550-4131(11)00009-X [pii] 10.1016/j.cmet.2011.01.008 (2011).

2 Grefhorst, A. *et al.* Acute hepatic steatosis in mice by blocking beta-oxidation does not reduce insulin sensitivity of very-low-density lipoprotein production. *Am J Physiol Gastrointest Liver Physiol* **289**, G592-598, doi:10.1152/ajpgi.00063.2005 (2005).