Soutenance de thèse présentée par : Christopher Taveau

Directeur de Thèse : Nadine Bouby

Le Vendredi 26 Septembre 2014

Role of vasopressin in glucose metabolic disorders: possible impact about diabetes development

Abstract

Key words: Vasopressin; V1a receptor antagonist; V1b receptor antagonists; Glucose metabolism; insulin resistance; liver steatosis

It is well established that vasopressin (AVP) level is high in both human and experimental diabetes. Since the 1970s, it is known that administration of AVP transiently increases glycaemia in humans and rodents. This action of vasopressin may be related to an increase in hepatic glycogenolysis and gluconeogenesis through V1a receptors. V1b receptors seem to be involved in the regulation of glucose homeostasis through a glucose-dependent stimulation of insulin and glucagon pancreatic secretions. In humans, several recent studies have shown an association between copeptin (biomarker of AVP secretion) and the occurrence of diabetes mellitus or hyperglycemia, metabolic syndrome and obesity. Our team has shown a reverse association between water consumption and the risk of hyperglycemia in the general population (D.E.S.I.R cohort).

The aim of my thesis was to determine the role of vasopressin and fluid intake in glucose homeostasis in healthy rats and in a rat model of metabolic syndrome. For this, we used physiological and pharmacological approaches. Circulating levels of vasopressin have been modified either by continuous infusion of vasopressin through Alzet minipumps or by increasing the water intake (which induces a decrease in the vasopressin secretion). The respective roles of V1a and V1b receptors were studied using specific antagonists. Vasopressin, administered acutely in healthy rats, induces dose-dependent effects on the blood glucose levels. Hyperglycaemic effects are mediated by the V1a receptors. V1b receptor activation does not influence insulin secretion but stimulates moderately basal glucagon production by the pancreas. In healthy rats, a high concentration of vasopressin increases long-term blood glucose level and this effect is reversed by a V1a receptor antagonist. These effects were observed in two strains of rats (Sprague Dawley and Zucker Lean). In obese Zucker rats, a high vasopressin level worsens fasting hyperinsulinaemia and glucose intolerance evaluated by glucose and insulin tolerances and response to pyruvate load. A low vasopressin concentration does not affect glucose tolerance but drastically reduces hepatic steatosis, the content of cholesterol and triglycerides in liver and expression of genes involved in hepatic lipogenesis. These effects are independent of the percentage of body fat, and plasma osmolarity which did not changed with the different treatments.

In conclusion, these studies show for the first time, that long-term high vasopressin levels aggravate glucose tolerance whereas a highly hydrated diet is protective. These results, in agreement with our epidemiological data, demonstrate a causal link between vasopressin and/or hydration and glucose metabolism disorders.