Acute effects of rimonabant, a CB1 receptor antagonist, on IMCL and plasma parameters in fed Wistar rats – a 1H-MRS study

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Introduction Physiological and pharmacological studies for monitoring energy homeostasis focus predominantly on food intake, body weight and body composition, because these parameters are easily measurable in biomedical research. In acute preclinical studies cannabinoid CB1 receptor antagonists demonstrated an important reduction of food consumption and body weight (1-3). Until now rimonabant is the best characterized CB1 receptor antagonist and has been unequivocally proven to be pharmacological active in humans to reduce body weight and to improve metabolic parameters (4). In contrast to effects on food intake, metabolic tissue parameters like intramyocellular lipids (IMCL) are more difficult to measure but are also important due to their impact in lipid metabolism and insulin resistance. In the present study we therefore investigated the acute pharmacological activity of rimonabant on metabolic plasma parameters and IMCL in fed Wistar rats.

Materials & Methods:
Exp. protocol. Male Wistar rats (HsdCpb:WU) with a body weight of 280-320 g were housed in groups of 3 to 4 at 20-22°C and on a 12-h light-dark cycle with ad libitum access to standard rat chow and water. Animals were divided into three groups, a control group, a treated group and an additional pair-fed control group to separate the effect of rimonabant from that which was caused by reduced caloric intake (n=6-7 each group). Rimonabant was administered orally in 0.5% hydroxymethylcellulose/0.2% Tween 80 suspension at a dose of 30 mg/kg body weight p.o. and IMCL and serum parameters (FFA, triglycerides) were measured against a control and pair-fed control group during the next day.

NMR-groups: IMCL in white tibialis anterior muscle (glycolytic), and soleus muscle (oxidative) were determined by in vivo ^{1}H-MRS as described previously (5). Briefly, in vivo MRS studies for about 1h in isoflurane-anaesthetized rats were performed on a 7 Tesla Biospec system (Bruker BioSpin, Ettlingen, Germany). Measurement of IMCL started 20h after single administration of rimonabant using a single voxel spectroscopy sequence and the results were expressed as IMCL/tCr ratio.

Results: Apart from an approximate 50% reduction in food consumption over 20h, rimonabant caused a slightly more pronounced body weight reduction compared to the pair-fed control group (Fig.1). Serum levels of FFA were increased by rimonabant and even more in the pair-fed controls, while serum triglyceride levels were even more reduced in the treated group compared to the pair-fed controls (Fig.2). In spite of higher FFA levels compared to the control group, IMCL contents were normalized or slightly reduced by rimonabant, in contrast to elevated IMCL levels of the pair-fed control group (Fig.2) indicating in addition to the reduced serum triglyceride levels a reduction of fatty acids in skeletal muscle.

Discussion: Rimonabant caused a slight dose-dependent increase in basal lipolysis from fat tissue (increased FFA). Principally, increased levels of FFA are involved in insulin resistance due to ectopic lipid accumulation in non-adipose tissues like skeletal muscle and liver. Surprisingly, 20h after a single administration of rimonabant, IMCL levels were already similar to controls and even significantly lower than pair-fed controls, demonstrating that rimonabant caused a redistribution of fatty acids into that tissue, which can effectively oxidize them. We conclude that in addition to the well-investigated effect to reduce body weight due to reduced caloric intake, rimonabant increased lipid oxidation driven by persistently increased lipolysis from fat tissues, which might significantly contribute to the weight reducing effect of rimonabant. Furthermore, the reduction of IMCL in glycolytic muscle might demonstrate an important insulin-sensitizing activity of rimonabant.

References: 1. Colombo, G. et al., Life Sci 1998; 63. **2.** Hildebrandt, AL et al., Eur J Pharmacol 2003; 462. **3.** Vickers, SP et al., Psychopharmacology 2003; 167. **4.** van Gaal, LF et al., Lancet 2005; 365. **5.** Kuhlmann, J et al., Diabetes 2003, 52.

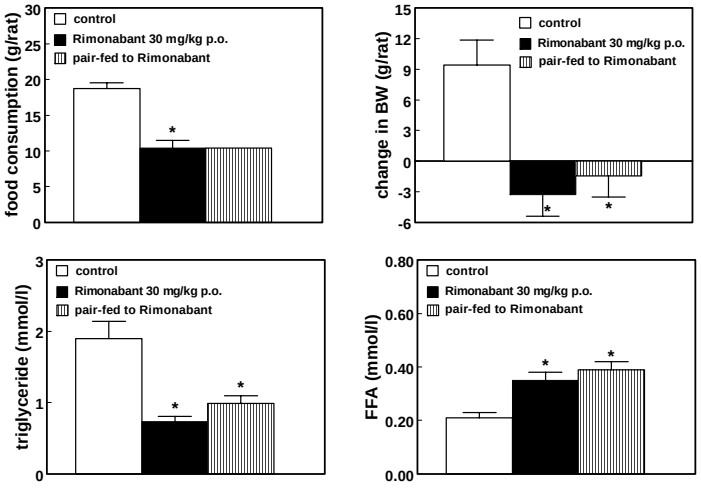

Fig. 1 Acute effects of rimonabant 20h after a single administration in comparison to pair-fed controls on food consumption and change in body weight in Wistar rats. Values are mean ± SEM, n=6-7, *p<0.05 vs control.

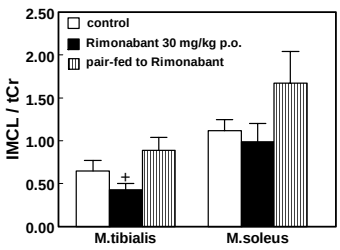

Fig. 2 Acute effects of rimonabant 20h after a single administration on FFA, serum triglyceride and IMCL levels in M. tibialis anterior and M. soleus. Values are mean ± SEM, n=6-7, *p<0.05 vs control, +p<0.05 rimonabant vs. pair-fed control.