Titel des Beitrags:
Alterations in the hypothalamic melanocortin pathway in amyotrophic lateral sclerosis.

Abstract:
Amyotrophic lateral sclerosis, the most common adult-onset motor neuron disease, leads to death within 3 to 5 years after onset. Beyond progressive
motor impairment, patients with amyotrophic lateral sclerosis suffer from major defects in energy metabolism, such as weight loss, which are well correlated with survival. Indeed, nutritional intervention targeting weight loss might improve survival of patients. However, the neural mechanisms underlying metabolic impairment in patients with amyotrophic lateral sclerosis remain elusive, in particular due to the lack of longitudinal studies. Here we took advantage of samples collected during the clinical trial of pioglitazone (GERP-ALS), and characterized longitudinally energy metabolism of patients with amyotrophic lateral sclerosis in response to pioglitazone, a drug with well-characterized metabolic effects. As expected, pioglitazone decreased glycaemia, decreased liver enzymes and increased circulating adiponectin in patients with amyotrophic lateral sclerosis, showing its efficacy in the periphery. However, pioglitazone did not increase body weight of patients with amyotrophic lateral sclerosis independently of bulbar involvement. As pioglitazone increases body weight through a direct inhibition of the hypothalamic melanocortin system, we studied hypothalamic neurons producing proopiomelanocortin (POMC) and the endogenous melanocortin inhibitor agouti-related peptide (AGRP), in mice expressing amyotrophic lateral sclerosis-linked mutant SOD1(G86R). We observed lower Pomc but higher Agrp mRNA levels in the hypothalamus of presymptomatic SOD1(G86R) mice. Consistently, numbers of POMC-positive neurons were decreased, whereas AGRP fibre density was elevated in the hypothalamic arcuate nucleus of SOD1(G86R) mice. Consistent with a defect in the hypothalamic melanocortin system, food intake after short term fasting was increased in SOD1(G86R) mice. Importantly, these findings were replicated in two other amyotrophic lateral sclerosis mouse models based on TDP-43 (Tardbp) and FUS mutations. Finally, we demonstrate that the melanocortin defect is primarily caused by serotonin loss in mutant SOD1(G86R) mice. Altogether, the current study combined clinical evidence and experimental studies in rodents to provide a mechanistic explanation for abnormalities in food intake and weight control observed in patients with amyotrophic lateral sclerosis. Importantly, these results also show that amyotrophic lateral sclerosis progression impairs responsiveness to classical drugs leading to weight gain. This has important implications for pharmacological management of weight loss in amyotrophic lateral sclerosis.