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Actions of prolonged glucagon-like peptide-1 receptor activation on cognitive function in a model of diet-induced obesity

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Liraglutide (Victoza®) is a once-daily glucagon-like peptide-1 (GLP-1) mimetic currently prescribed as a therapy for type-2 diabetes[1]. Liraglutide mimics all of the glucoregulatory, insulin-releasing and extra-pancreatic actions of GLP-1, especially the glucose-dependent stimulation of insulin secretion[2]. Recent studies have shown that Liraglutide crosses the blood-brain-barrier when administered peripherally[3] and GLP-1R deficient mice exhibit impaired memory and learning[4]. Therefore, the present study examined the effects of daily treatment with Liraglutide on the cognitive function in an animal model of diet-induced obesity which exhibits compromised cognitive performance.

Young Swiss *TO* mice (6–8 weeks old; *n* 10 per group) maintained on high-fat diet (45% fat, 20% protein and 35% carbohydrate) for 20 weeks received twice-daily injections of Liraglutide (200 μg/kg bw; *sc*) or saline vehicle over 28 d. An additional group of mice on standard diet (10% fat, 30% protein, 60% carbohydrate) received twice-daily saline injections. Energy intake, bodyweight and plasma glucose and insulin concentrations were monitored at regular intervals. Glucose tolerance, open field assessment, object recognition testing and electrophysiological long-term potentiation (LTP) were performed at the termination of the study.

Treatment with Liraglutide significantly reduced bodyweight (1.1-fold; $P<0.05$) and energy intake (1.5-fold; $P<0.01$), while improving non-fasting glucose (50–230% reduction; $P<0.01$ to $P<0.001$), insulin (30–50% increase; $P<0.05$ to $P<0.01$) and normalising glucose tolerance (40–50% improvement; $P<0.05$) compared to high fat controls. During the object recognition trial, mice on high-fat diet demonstrated a significant decrease in recognition index (RI), whereas mice treated with Liraglutide exhibited a significant increase in RI (1.4-fold; $P<0.05$) indicative of enhanced memory and learning ability. Interestingly, the RI for Liraglutide-treated mice was broadly similar to that observed for healthy age-matched normal mice, highlighting a reversal in the cognitive decline following Liraglutide treatment in this model. *In vivo* hippocampal LTP was completely abolished following high-fat diet. However, daily treatment with Liraglutide ameliorated ($P<0.001$ to $P<0.0001$) the detrimental effects of high-fat diet on LTP formation and maintenance.

In conclusion, this study demonstrates that prolonged GLP-1R activation with Liraglutide exhibits beneficial effects on the cognitive function and hippocampal synaptic plasticity in a mouse model of high-fat diet-induced obesity. Given the increasing awareness of a negative impact of obesity-diabetes on brain function, possible protective effects of GLP-1 mimetics on cognitive parameters need to be assessed in the rising numbers of obese type-2 diabetes patients taking incretin therapeutics.

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