GLP-1 agonist Liraglutide improves animal behavior and cognitive impairment in diabetic rats

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Type 2 diabetes mellitus (T2DM) has negative impact on the central nervous system leading to diabetic encephalopathy and concomitant augmented incidence of cognitive problems(1). None of the known antidiabetic drugs currently used has a proven effect upon cognitive decline. Glucagon-like peptide-1 (GLP-1) receptor agonists, a new class of drugs therapeutically used in diabetic patients, might be a valid alternative for prevention of neurological comorbidity. In addition to its metabolic effects, GLP-1 acts as a growth factor in the brain(2) and is involved in learning and neuroprotection(3). We evaluated the effects of GLP-1 receptor agonist, liraglutide (LIR), on cognitive decline associated with T2DM. Furthermore, we studied the effects of LIR against hippocampal neurodegeneration induced by streptozotocin (STZ), which represents a well-validated animal model of diabetes and neurodegeneration associated with cognitive decline. Diabetes and/or cognitive decline were induced in Wistar rats (6 weeks old) by a single intraperitoneal administration of STZ (65 mg/kg i.p.) or intracerebroventricular injection (1 mg/kg i.c.v.). Age-matched control rats (CTRL) were treated with an equal volume of vehicle for both protocols. Diabetes was verified 48h later quantifying blood glucose levels; rats with blood glucose levels higher than ≥ 300 mg/dl were considered to be diabetic and treated with LIR (300 mg/kg/day subcutaneously) for 4 weeks.

After this period, every experimental group was divided in three subgroups of 14 animals: STZ i.c.v. (LIR or vehicle treated), STZ i.p. (LIR or vehicle treated), CTRL (LIR or vehicle treated). All groups were subjected to behavioral tests: Morris water maze (MWM), Passive avoidance, Forced swimming test (FST), Open field arena (OF), Elevated plus maze (EPM).

Blood glucose values in STZ-LIR group resulted significantly decreased from the second week of treatment in comparison to STZ-vehicle group; instead in CTRL group, LIR treatment did not modify blood glucose levels confirming that LIR has antidiabetic effect only in case of high blood glucose levels.

In FST, the immobility time (IT), directly correlated to depression symptoms, resulted increased in all treated groups with LIR, suggesting a pro-depressive effect.

In OF, only STZ i.p. group showed an increased anxiety in comparison to all other control groups. LIR treatment induced anxiolytic effects in all groups; in particular, the time spent in the center, which is inversely correlated to the level of anxiety/emotionality was significantly ($P < 0.05$) increased by LIR in every group treated (both STZ and CTRL groups). Similar effects were observed in EPM test. STZ administration (i.c.v. and i.p.) induced an impairment of learning and memory, instead all groups LIR-treated showed an improvement of learning and memory; in particular, LIR treatment significantly increased the time latency entering the dark compartment in passive avoidance test. Also in MWM, LIR treatment showed an improvement of learning and memory; in particular, the CTRL-LIR and STZ-LIR group spent less time to reach the platform in comparison to STZ-vehicle group.

In conclusion, LIR significantly reduces glucose blood levels in diabetic rats only. These effects are associated with behavioral anxiolytic properties and a significant improvement in memory and learning, which could be a relevant result in the long-term treatment of diabetic patients. The pro-depressive effect could be related to the LIR anxiolytic effect, which might have influenced FST results. LIR treatment might be a relevant option for cognitive decline prevention in diabetic patients.

References

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