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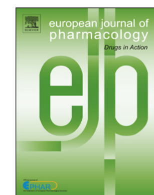

Neuropharmacology and analgesia

Neurobehavioral effects of liraglutide and sitagliptin in experimental models

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Glucagon-like peptide (GLP-1) receptor agonists and dipeptidyl peptidase 4 (DPP-4) inhibitors are two currently approved therapies for type 2 diabetes mellitus (T2DM). Present study evaluated the effect of liraglutide (a long-acting GLP-1 agonist) and sitagliptin (a DPP-4 inhibitor) on nociception, anxiety, depression-like behavior and cognition in rats or mice.

Nociception was assessed using tail-flick test; anxiety-behavior in open-field test and elevated plus maze (EPM) test while depression-like behavior was evaluated in forced swim test (FST) and tail-suspension test (TST). Cognition was assessed in EPM and Morris water maze (MWM) following memory deficit induced by pentylenetetrazole (PTZ) or scopolamine.

In tail-flick test sitagliptin (6 mg/kg) produced transient nociceptive effect. Liraglutide (200 μg/kg) reduced peripheral square crossings by rats in open field test as well as reduced closed arm entries in the EPM, indicating a decline in exploratory behavior. In FST and TST models for depression, the duration of immobility with sitagliptin (6 mg/kg) was reduced significantly in comparison to control group suggesting its antidepressant effect. Liraglutide did not show any antidepressant action. In EPM test for cognition, liraglutide and sitagliptin ameliorated the increase in transfer latency caused by PTZ in a dose-dependent manner. In MWM liraglutide and sitagliptin prevented the scopolamine-induced increase of the escape latency.

This study shows that sitagliptin has mild antinociceptive effect and anti-depressant effect in the animal models of depression while liraglutide did not have such an effect. Liraglutide showed anxiogenic effects in the animal models. Both liraglutide and sitagliptin produced cognitive improvement in the animal models.

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1. Introduction

Modulation of the incretin systems has provided a novel treatment option in type 2 diabetes mellitus (T2DM). Glucagon-like peptide (GLP)-1, an incretin hormone exhibits diverse actions including insulinotropic effects, neogenesis, differentiation and anti-apoptotic preservation of pancreatic β-cells (Baggio and Drucker, 2006; Drucker, 2003). GLP-1 acts through GLP-1 receptors (R). GLP-1R stimulation enhances pancreatic islet beta-cell proliferation, insulin secretion and decreases blood glucose and food intake in patients with type 2 diabetes mellitus.

Endogenous GLP-1 has a half-life of a few minutes as it is broken down by endopeptidase enzymes such as dipeptidyl peptidase 4 (DPP-4) (Vilsboll et al., 2003). Thus it is unsuitable for routine clinical use on account of its short half-life. Drugs with a highly increased half-life acting either by stimulation of GLP-1 receptors (GLP-1 receptor agonists) or by restoring the endogenous GLP-1 pool by inhibiting its DPP-4 mediated breakdown are developed to obtain or maintain high levels of GLP-1 (Drucker, 2003). Growing evidence has shown that GLP-1 is also produced in the brain (Alvarez et al., 1996), particularly from the nucleus of the solitary tract (Larsen et al., 1997), area postrema and caudal brain stem (Hamilton and Holscher, 2009). In the brain, it acts as a growth factor. GLP-1 has been shown to enhance neurite outgrowth and to protect against oxidative injury in cultured neuronal cells (Perry et al., 2007). In addition, GLP-1R is widely expressed in many regions of the CNS and plays an important role in regulating neuronal plasticity and cell survival. Mice overexpressing GLP-1R in the hippocampus developed increased neurite growth and showed improved learning (During et al., 2003).

Substantial amount of evidence supports neurotrophic and neuroprotective potential of GLP-1 and GLP-1R stimulation in an increasing array of cellular and animal neurodegeneration models

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as well as in neurogenesis (Holscher, 2012; Salcedo et al., 2012). Hence, in recent years, research involving GLP-1 and its receptors has shifted from T2DM to focus upon various neurodegenerative disorders (Bertilsson et al., 2008; Martin et al., 2009). Activation of incretin pathway has been shown to stimulate neuronal cell proliferation and prevented cell death (Li et al., 2010). Inhibition of GLP-1 degradation with the DPP-4 inhibitor is also associated with neuroprotection in the diabetic rat, independent of any changes in glycemia (Jin et al., 2009).

In recent studies, depression is also characterized by enhanced neurodegeneration (Maes et al., 2009) and hence GLP-1 could have a role in depression. In addition, the potential of GLP-1 receptors in animal models of pain (Gong et al., 2014) and DPP-4 in degradation of substance P and its influence on pain pathway is described (Grouzmann et al., 2011). Also, some studies have shown the anxiogenic potential of exogenous GLP-1 (Kinzig et al., 2003).

Liraglutide, a long-acting GLP-1R agonist and sitagliptin, a DPP-4 inhibitor are approved drugs for T2DM. Both liraglutide and sitagliptin have been shown to reverse the deleterious effect on learning and memory in mice fed with high fat diet (Gault et al., 2015; Porter et al., 2010).

However, the neurobehavioral effects of liraglutide and sitagliptin are not clear. Therefore, the present study evaluated the effect of liraglutide and sitagliptin on nociception, anxiety and depression-like behavior and cognition in rats or mice. Nociception was assessed using tail-flick test, anxiety-behavior was observed in open-field test and elevated plus maze (EPM) test while depression-like behavior was evaluated in forced swim test (FST) and tail-suspension test (TST). Cognitive behavior was examined in Morris water maze (MWM) and in EPM following memory deficit induced by scopolamine or pentylenetetrazole (PTZ).

2. Material and methods

The present study was approved by the Institutional Animal Experimentation Ethics Committee of Lady Hardinge Medical College (LHMC) and Smt. SK Hospital (SSKH). The care and use of animals in the present study adhered to the 'CPCSEA [Committee for the Purpose of Control and Supervision of Experiments on Animals], India, Guidelines for Laboratory Animal Facilities'.

2.1. Animals

Male Wistar rats or male Swiss albino mice weighing 100–150 g and 25–30 g respectively were used. The rats were housed individually and mice were housed in groups of four to six per cage under a 12 h light–dark cycle and were fed a standard laboratory diet and water *ad libitum*. Animals were acclimatized for at least 1 week before being used in the studies.

2.2. Drugs

Liraglutide injections (VICTOZA, Novo-Nordisk India Pvt. Limited) were obtained as gift samples from the distributor. Sitagliptin phosphate tablets (JANUVIA, Merck Sharp & Dohme, Italy) were purchased from the market. Morphine, lorazepam and imipramine injections were obtained from the hospital supply. Scopolamine (purity ≥ 90%, HPLC) and pentylenetetrazole were purchased from Sigma Chemical Co. (USA).

2.3. Groups

All experiments were performed independently i.e. different set of animals were dosed for each study. The animals (6/group) were intrapertonealy (i.p.) treated as follows: group 1: control (saline), group 2: liraglutide 100 μg/kg, group 3: liraglutide 200 μg/kg, group 4: sitagliptin 3 mg/kg, group 5: sitagliptin 6 mg/kg, group 6: positive control (morphine 2 mg/kg for tail-flick test, lorazepam 1 mg/kg for open-field test and EPM test, imipramine 10 mg/kg for FST and TST). For assessment of learning and memory, the animals (6/group) were treated as follows in EPM tests: group 1: control (saline), group 2: PTZ 200 μg/kg, group 3: PTZ+liraglutide 100 μg/kg, group 4: PTZ+liraglutide 200 μg/kg, group 5: PTZ+sitagliptin 3 mg/kg group 6: PTZ+sitagliptin 6 mg/kg. In MWM test scopolamine 5 mg/kg was used in place of PTZ and only higher dose of liraglutide and sitagliptin was used. Morphine was used as positive control for tail flick test, lorazepam was used as positive control for tests of anxiety (open-field test and EPM test) and imipramine was given as positive control for tests of depression.

2.4. Assessment of nociception

A Techno analgesiometer was used to assess tail-flick latency. The thermal stimulus was applied to the ventral aspect of the mouse's tail and three consecutive readings, at approximately 20 s intervals, were obtained and the average calculated. Care was taken to slightly shift the point of heat application. Animals with tail-flick latency of 4–6 s were included in the study. A cut-off latency of 10 s was set to prevent tissue damage.

2.5. Assessment of anxiety

2.5.1. Open-field test

For open-field test a square open field arena of dimension 68 × 68 × 48 cm divided in 25 square marks measuring 8 × 8 cm each was used. After 30 min of administering saline/test drug, rat was kept in center and its locomotor activity i.e. no. of cental and peripheral squares crossed, was observed for 15 min. Ratio central/total locomotion was calculated to assess anxiolysis.

2.5.2. Elevated plus maze

For elevated plus maze a plus-maze consisting of two open arms (50 cm × 10 cm) and two enclosed arms (50 cm × 10 cm × 40 cm – height) with an open roof, arranged so that the two open arms are opposite to each other was used. The maze was elevated to a height of 50 cm and rat was placed in the center of maze. After 1 h of the treatment with saline/test drug, entries in closed arm, open arm and motor activity were recorded for a period of 5 min (Pellow and File, 1986).

2.6. Assessment of depression

2.6.1. Forced swim test

In forced swim test mice were individually forced to swim inside a vertical plexiglas cylinder (height: 40 cm, diameter: 18 cm), containing water filled up to 15 cm of height. Animals were observed for a total period of 5 min and duration of immobility in the water was recorded.

2.6.2. Tail suspension test

For tail suspension test the mice were suspended on the edge of a shelf, 58 cm above the ground, by adhesive tape placed approximately 1 cm from the tip of the tail of the mice. Mice were considered immobile when they hung passively and completely motionless. This duration of immobility of the mice was recorded for an observation period of 5 min.

Mice were treated for 7 consecutive days with respective treatment before FST/TST. Further, higher dose of each treatment (sitagliptin 6 mg/kg and liraglutide 200 μg/kg) were tested using inclined plane and rotarod tests to assess any motor side-effects. In

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