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Research Article

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The Study of Exendin-4 for Depression in diabetic rat model

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Abstract

Exendin-4 amplify the sertraline response, as an augmentation strategy for depression in combination with SSRI. Sertraline can also increase anti diabetic activity when co-administered with exendin-4, may be with classic anti diabetic. Exendine-4 blunts the postprandial rise of plasma glucose by increasing glucose-dependent insulin secretion, suppressing inappropriately high glucagon secretion, and delaying gastric emptying. Historically, it was discovered as exendin-4, a protein originally isolated from the venom of *Heloderma suspectum*, that shares 53% sequence identity with GLP-1. The anti diabetic peptide GLP-1 and analogs like Exendin-4 represent alternatives for NIDDM therapy. GLP-1 and Exendin-4 increased basal release of serotonin. As per depression hypothesis serotonin level play an important role in depression SSRI are the preferred choice of drug for treating depression.

Keywords: Exendin-4, depression, Sertraline.

Introduction

Diabetes mellitus is a chronic disease characterized by multiple metabolic abnormalities arising primarily from an inadequate insulin effect. Fifth deadliest disease in the world. 246 Million in 2006 to 380 Million by 2025. Diabetes Long-term macro vascular, neurological, and microvascular complications, such as retinopathy, nephropathy. Depression is a common mental disorder that presents with depressed mood, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, low energy, and poor concentration. Depression is common, affecting about 121 million people worldwide. Depression is among the leading causes of disability worldwide. Fewer than 25 % of those affected have access to effective treatments. Depression represents one of the most common co morbidities in patients with diabetes. Relationship between Depression & Diabetes are unknown. Once in the circulation, GLP-1 has a half life of less than 2 minutes, due to rapid degradation by the enzyme dipeptidy peptidase-4. It is a 37 amino acid peptide produced from proglucagon GLP-1 possess several physiological properties that make it (and its analogs) a subject of intensive investigation as a potential treatment of diabetes mellitus.

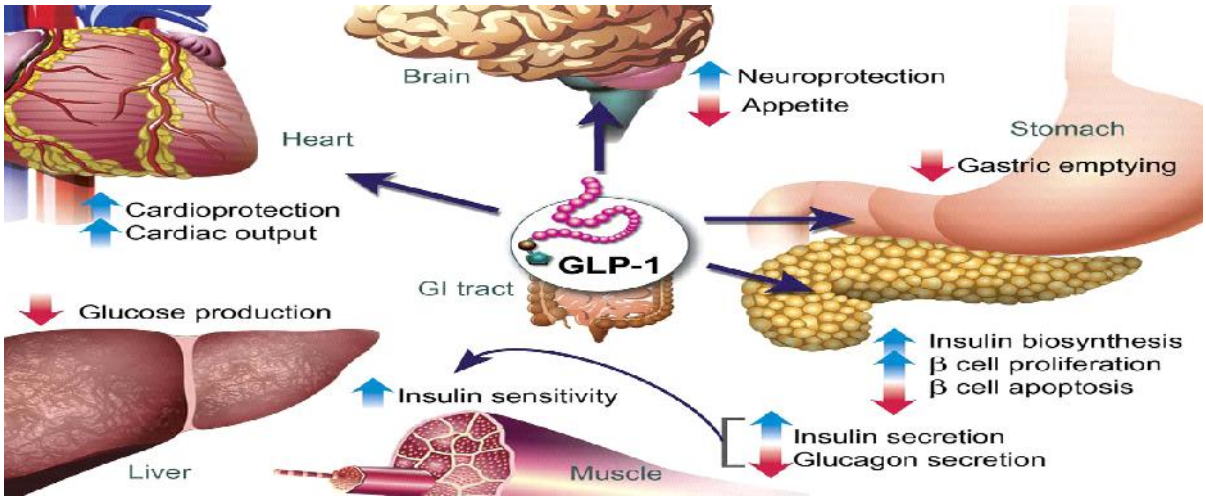

Figure no. 01: **Physiological functions of GLP-1 in insulin synthesis.**

Increases insulin secretion from the pancreas in a glucose-dependent manner and decreases glucagon secretion from the pancreas due to Increases beta cells mass and insulin gene expression. Inhibits acid secretion and gastric emptying in the stomach. Decreases food intake by increasing satiety. Promotes insulin sensitivity.

Mechanism of Action of **Exendin-4:**

- Insulin Release
- Suppress Glucagon.
- Slow Down Gastric Emptying.
- Promote Satiety via hypothalamic receptor.
- Reduce Liver fat Content.

Objective:

- The Aim of present investigation is to evaluate effect of Exendin-4 on co morbid depression (diabetes & depression).
- To evaluate the modulatory effect of Exendin-4 with Sertraline on co morbid depression.

Plan of Work:

- Required chemicals
- Animals and their diet.
- Induction of diabetes by streptozotocin.
- Treatment of Exendin-4 & Sertraline.
- Evaluation of co morbid depression.
- Force Swim test.
- 5- Hydroxy tryptophan potentiation model
- Estimation of blood glucose.
- Interpretation of result by statistical analysis.
- Compilation of data.

Experimental Design

- **Animals and treatments:**

- **Procurement of Animals:** Albino wistar rats (170–200 g) issued from animal house of Institute of pharmaceutical education and research, Wardha. All animals were maintained under controlled conditions of temperature (22±2 ◦C), and illumination (12 h light–dark cycle), with free access to food (lab diet) and water.

- **Drugs :**

  Streptozotacin (50mg/kg,ip), Exendin-4 (100mcg/kg), Sertraline (30mg/kg) .

- **Drug solutions and administration**: Exendin-4 (Sigma, St. Louis, MO) was dissolved in DMSO & then dissolved in isotonic saline and administered intraperitonially (ip) in a volume of 0.4ml/rat. The sertraline were administered in normal saline.

Experiment: The Experiment was conducted for a period of 12 days. All animals were divided into eight experimental groups of six each. Animals were grouped as follows

- **Group 01:** saline (control)
- **Group 02:** diabetes + saline
- **Group 03:** standard (diabetic+ Sertraline)
- **Group 04:** Test I (diabetic +Exendin-4)
- **Group 05:** Test II (diabetic +Exendin-4+sertraline)
- **Group 06:** control + sertraline
- **Group 07:** control + Exendin-4
- **Group 08:** control + Exendin-4 + sertraline

Diabetes induced by Streptozotocine at a dose of 50 mg/kg (i.p.), dose of sertraline (30mg/kg). Force swim test were perform 13th day. Glucose estimation were carried out 1ST & 13th day of dosing.

Results

FST in Normal:

Table no. 01: Force swim test in Normal

Group no.	Treatment	Immobility(sec.)
1	Normal	65.66± 0.76
2	Normal+Sertrline	36.66± 1.08***
3	Normal+Exendin-4	45.16 ± 0.6**
4	Normal+Exendin-4 +Sertraline	27.5 ± 0.99***

Values expressed as mean ± SEM., n=6, One way ANOVA followed by Dunnett t test. All groups were compared with normal control, (*** P <0.001, **P <0.01,*P <0.05).

FST in Diabetic:

Table no. 02: Force swim test in Diabetes

Group no.	Treatment	Immobility(sec.)
1.	Saline	65.66± 0.76
2.	Diabetic (control)	80.5±1.11$^{\#}$
3.	Diabetic+ Sertrline	44.5±0.84**
4.	Diabetic+Exendin-4	61.83±0.6*
5.	Diabetic+Exendin-4 +Sertraline	35.66±1.11***

Values expressed as mean ± SEM., n=6, single ANOVA followed by Dunnett t test. All groups were compared with control, (*** P <0.001, **P <0.01,*P <0.05). Diabetic grup compared with saline ($^{\#}$P<0.001).

Blood Glucose in Diabetic:

Table no. 03: Blood Glucose level in Diabetes:

Group no.	Treatment	Blood Glucose (g/dl)
1.	Saline	82±2.8
2.	Diabetic	238±7.4$^{\#}$
3.	Diabetic+ Exendin-4	97.66±2.58***
4.	Diabetic+Sertraline	179.66±3.14*
5.	Diabetic+Exendin-4 +Sertraline	83.33±3.07***

Values expressed as mean ± SEM., n=6, ANOVA followed by Dunnett t test. All groups were compared with control, (*** P <0.001, **P <0.01,*P <0.05). Diabetic group compared with saline ($^{\#}$P<0.001).

Blood Glucose in Diabetic

Group No.	Treatment	HTR
1	Diabetic	100±0.76
2	Diabetic +Sertraline	301±0.9**
3	Diabetic +Exendin-4	220±1.1*
4	Diabetic+Exendin-4 +Sertraline	388±0.7***

Values expressed as mean ± SEM., n=6, One way ANOVA followed by Dunnett t test. All groups were compared with control, (*** P <0.001, **P <0.01,*P <0.05). Diabetic group compared with saline ($^{\#}$P<0.001).

Discussion

NIDDM is a metabolic disorder that affects up to 5% of the worldwide population and is currently considered a major disease. Depression represents one of the most common co morbidities in patients with diabetes depression significantly increases the risk of developing Diabetes. The anti diabetic peptide GLP-1 and analogs like Exendin-4 represent alternatives for NIDDM therapy. GLP-1 and Exendin-4 increased basal release of serotonin. As per depression hypothesis serotonin level play a important role in depression SSRI are the preferred choice of drug for treating depression. In a previous study showed that Sertraline decreases glucose overload. Administration of STZ (50 mg/kg i.p.) effectively induced diabetes in normal fasting rats. Exendin-4 showing less immobility in the model of FST as compare to control. Immobility shown by sertraline(std.) are less as compare to exendin-4. Exendin-4 amplify the sertrline response, as an augmentation strategy for depression in combination with SSRI, Sertraline can also increase anti diabetic activity when co-administered with exendin-4 or may be with classic anti diabetic.

Conclusion

The results of the present study, we can conclude that exendin-4 shows anti-depressant activity in diabetic rats. Exendin-4 completely augment the antidepressant effect of sertraline. Sertraline increases the antidiabetic activity of exendin -4.

Future Scope

Receptor level studies required to confirm the activity of Exendin-4 and Sertraline in comorbid depression. Clinical studies required for Exendin -4 and Sertraline in comorbid depression.

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