Systemically active NGF mimetic GK-2 demonstrates antidiabetic activity on C57Bl/6 mice

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Background

Original dimeric dipeptide mimetic GK-2 (hexamethylenediamide bis-(N-monosuccinyl-glutamyl-lysine) was synthesized based on the structure of β-turn of NGF loop 4 at the V.V. Zakusov Institute of Pharmacology [2].

Aim

The purpose of this study was to investigate whether GK-2 affects the effects of diabetogenic toxin, streptozotocine (STZ).

Methods

Experiments were carried out on 45 C57Bl/6 mice divided into 4 groups:

1. - passive control treated with saline;
2. - active control treated with STZ 100 mg/kg;
3. - animals treated with GK-2 in doses of 0.5 mg/kg i.p. for 14 days before and 14 days after STZ;
4. - animals treated with 5 mg/kg of GK-2 per os at the same schedule.

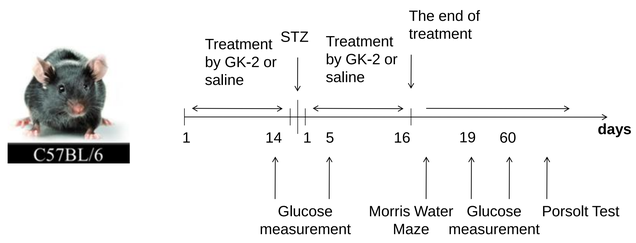

Fig.1 Design of the experiment

Non-fasting blood glucose was measured one day before the STZ injection, at days 5, 19 and 60 after the STZ injection.
Body weight was measured every three days.

Percentage of animals able to find the invisible platform in Morris water maze on 2-7 days of testing [3] and the immobility duration in Porsolt test [1] have been registered, using Realtimer.

The content of MDA in plasma as a sign of oxidative stress was measured by the colorimetric thiobarbituric acid assay.

The design of the experiment is presented on figure 1.

Results

GK-2 was shown to be able to overcome the well known metabolic effects of STZ: hyperglycemia (Fig.2), body weight loss and MDA accumulation.

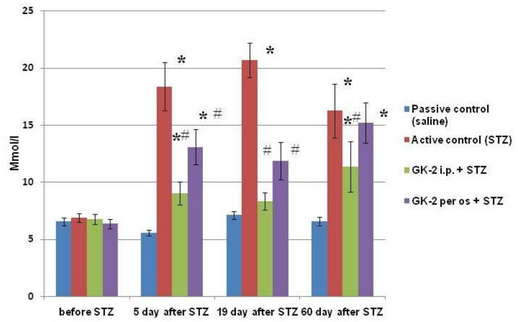

Fig.2 Blood glucose level (Mmol/l)
***** - statistical differences (P<0.05) between the STZ-treated and control groups
# - statistical differences (P<0.05) between the STZ-treated and GK-2 +STZ treated groups

While STZ diminished the % of mice able to find the hidden platform to 9% comparing to 14% in passive control, GK-2 treated mice demonstrated the figures as high as 27.3 and 50% for i.p and p.o routes of administration correspondingly (Fig.3) already on the second day of testing. The same was true for others testing days.

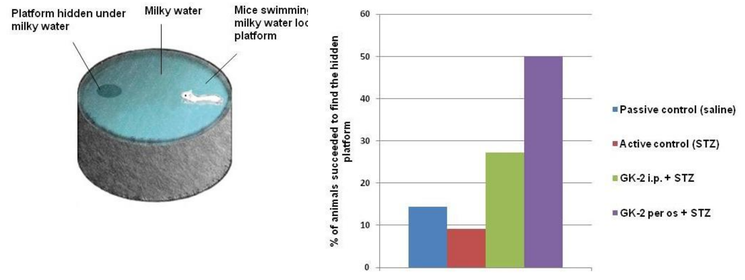

Fig.3 Morris Water Maze test
GK-2 increased the % of animals succeeded to find the hidden platform on the second day of testing

STZ increased significantly the immobility duration in Porsolt test. GK-2 was revealed to ameliorate this sign of depression (Fig.4).

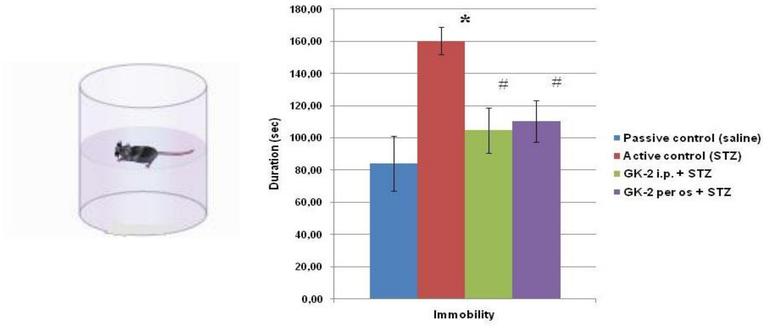

Fig.4 Porsolt test
While STZ was shown to increase the duration of immobility (sec), Gk-2 overcomes this effect.
***** - statistical differences (P<0.05) between the STZ-treated and control groups
# - statistical differences (P<0.05) between the STZ-treated and GK-2 +STZ treated groups

Conclusion

1.In whole correspondence with literature data STZ was shown to provoke the hyperglycemia, body weight loss, MDA accumulation combined with depressive-like conditions and memory disturbances.

2.Original dimeric dipeptide mimetic GK-2 was firstly revealed to antagonize main biochemical effects of STZ as well as above listed behavioral deficits.

3.Efficiency of GK-2 both in case of intraperitoneal and peroral routes of administration should be underlined as the important difference from native NGF.

4.These effects lasted after discontinuation of treatment.

References

1. Porsolt R.D., Bertin A., Jafre M., *European Journal of Pharmacology*, 51, 291-294 (1978).
2. Seredenin S., Gudasheva T., RF patent 2410392.
3. Vorhees C.V., Williams M.T., *Nat Protoc*, 1(2), 848-858 (2006).

Acknowledgments

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