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ORIGINAL ARTICLE

Beneficial effects of certain phosphodiesterase inhibitors on diabetes mellitus in rats

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Abstract The present study is conducted to investigate the possible antidiabetic effect of certain phosphodiesterase inhibitors. Diabetes mellitus was induced in 18 h-fasted male wistar albino rats by intraperitoneal injection of streptozotocin (STZ) in a single dose (50 mg/kg). Gliclazide (Glcl) as a reference standard in a dose of 10 mg/kg, sildenafil (Sild) in 3 doses (5, 10, 20 mg/kg) as PDE5 inhibitor and vinpocetine (Vinp) in 3 doses (10, 20, 40 mg/kg) as PDE1 inhibitor were injected intraperitoneal daily for 2 weeks. Their effects were assessed at different time intervals namely; 2 h after first dose, 1 week and 2 weeks after drug administration. In the present study, STZ significantly elevated serum blood glucose (SBG) level, lowered serum insulin, C-peptide levels and decreased liver glycogen content (LGC). Glcl significantly elevated serum insulin and C-peptide levels accompanied by reduction in serum glucose level and raised LGC. Vinp and Sild elevated serum insulin, C-peptide levels, LGC and decreased SBG level. The antidiabetic effect of Glcl was significantly higher than that of Vinp or Sild. It could be concluded that Vinp possibly produced its insulin stimulatory action via inhibition of PDE1 while Sild stimulated insulin secretion through inhibition of PDE5. The increase in serum C-peptide indicated that Vinp and Sild stimulated synthesis of insulin in the β-cells and Vinp is more potent than Sild in this respect due to the difference in their mechanism of action.

1. Introduction

Diabetes mellitus (DM) is a metabolic disorder with chronic hyperglycemia resulting from defects in insulin secretion, insulin action or both.[1] Diabetes mellitus is classified into 4 subtypes namely; type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), gestational diabetes mellitus (GDM) and other specific types.[2]The pathophysiology of T2DM is primarily due to insulin impairment accompanied by beta-cell failure resulting from prolonged and increased secretory demand.[3]

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Table 1 Effect of Glcl, Sild and Vinp individually on SBG level of STZ-induced diabetic rats after 2 h of drug administration.

Drugs and doses	Parameters Serum glucose level	
	Absolute value $\ddot{X}$ ± S.E. (mg %)	% of diabetic control
Normal control (citrate buffer)	100.5 ± 4.552	23.67
Diabetic control (streptozotocin 50 mg/kg, I.P.)	424.5[*] ± 26.13	100
Gliclazide (10 mg/kg, I.P.)	64.86[a] ± 5.383	15.28
Sildenafil (5 mg/kg, I.P.)	384.7[b] ± 33.79	90.62
Sildenafil (10 mg/kg, I.P.)	354.5[ab] ± 25.13	83.51
Sildenafil (20 mg/kg, I.P.)	324.7[ab] ± 20.25	76.49
Vinpocetine (10 mg/kg, I.P.)	373.4[b] ± 12.24	87.96
Vinpocetine (20 mg/kg, I.P.)	111.4[ac] ± 9.065	26.24
Vinpocetine (40 mg/kg, I.P.)	118.3[ac] ± 8.731	27.86

The number of animals in each group ranges between 6 and 8.
Data are expressed as mean ± S.E.
Statistical analysis was carried out by one way ANOVA followed by Post-test Newman–Keuls multiple comparison test.
[*] Significantly different from normal control at $P < 0.05$.
[a] Significantly different from diabetic control at $P < 0.05$.
[b] Significantly different from gliclazide at $P < 0.05$.
[c] Significantly different from sildenafil (20 mg/kg) at $P < 0.05$.

Table 2 Effect of Glcl, Sild and Vinp individually on SBG level of STZ-induced diabetic rats after 1 week of daily drug administration.

Drugs and doses	Parameters Serum glucose level	
	Absolute value $\ddot{X}$ ± S.E. (mg %)	% of diabetic control
Normal control (citrate buffer)	95.10 ± 4.781	20.80
Diabetic control (streptozotocin 50 mg/kg, I.P.)	457.2[*] ± 18.31	100
Gliclazide (10 mg/kg, I.P.)	142.9[a] ± 10.09	31.25
Sildenafil (5 mg/kg, I.P.)	442.8[b] ± 26.34	96.85
Sildenafil (10 mg/kg, I.P.)	380.0[ab] ± 34.30	83.11
Sildenafil (20 mg/kg, I.P.)	141.3[a] ± 9.525	30.90
Vinpocetine (10 mg/kg, I.P.)	166.5[a] ± 8.371	36.41
Vinpocetine (20 mg/kg, I.P.)	146.8[a] ± 12.17	32.1
Vinpocetine (40 mg/kg, I.P.)	138.0[a] ± 9.862	30.18

The number of animals in each group ranges between 6 and 8.
Data were expressed as mean ± S.E.
Statistical analysis was carried out by one way ANOVA followed by Post-test Newman–Keuls multiple comparison test.
[*] Significantly different from normal control at $P < 0.05$.
[a] Significantly different from diabetic control at $P < 0.05$.
[b] Significantly different from gliclazide at $P < 0.05$.

The complications of diabetes include cardiovascular disease, peripheral vascular disease, and cerebrovascular disease.[4] Moreover, there is a relation between diabetes and growing different types of cancer.[5] The commonly used classes for management of diabetes have adverse effects such as increased risk of hypoglycemia, gastrointestinal problems, heart failure[6] and vomiting leading to their incompliance.[7]

Consequently, it deemed of importance to seek for antidiabetic drugs with more efficacy and less side effects.

Vinpocetine (Vinp) is a classic PDE1 inhibitor which elevates intracellular levels of cGMP and cAMP.[8] Vinp blocks voltage dependent Ca^{2+}/Na^{+} channel.[9,10] Vinp is a cerebral vasodilator commonly used in ischemic stroke.[11] While sildenafil (Sild) is a selective PDE5 inhibitor which elevates intracellular level of cGMP, commonly used in erectile dysfunction.[12] Vinp and Sild show antioxidant activity[13–15] which are expected to have potential effects on carbohydrate metabolism.

The aim of the present study is to investigate the beneficial effects of PDEIs on DM.

2. Materials and methods

2.1. Animals

Adult male wistar albino rats weighing 200–250 g were used. They were obtained from animal house of Faculty of