



# Incretin Mimetics Vildagliptin and Exenatide Improve Pedicle Skin Flap Survival in Rats

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## ABSTRACT

Hypoxia and tissue ischemia are the leading factors in the alteration of tissues in many pathological conditions. Prevention and reversion of the effects of local ischemia, which develops during various surgical interventions, is an actual problem of modern medicine. The aim of the present study was to investigate the effect of exenatide and vildagliptin on the survival rate of an isolated pedicle skin flap in sixty adults Wistar rats. Simulation of a pedicle skin graft was performed on the second day of the experiment. After anesthesia under aseptic conditions, a skin graft was cut out: isolated in a plastic bag, the edges of the skin were stitched with interrupted sutures (nylon 3/0). Rats were divided into six groups: control group, exenatide group (10 µg/kg/day subcutaneously for nine days after surgery), vildagliptin group (0.2 mg/kg/day intraperitoneally for nine days after surgery) and pentoxifylline group (100 mg/kg/day intravenously, two hours before the surgical intervention). In the other two groups, glibenclamide (5 mg/kg) were administered before injection of incretin mimetics. On the third, seventh and tenth day, area of the surviving tissue was measured. Subsequently, the survival rate of the skin graft was calculated. The area of the surviving tissue in exenatide and vildagliptin group was 1.5 and 1.7 times more compared to the control group, respectively. Preliminary blockade of ATP-dependent potassium channels by glibenclamide eliminated the protective effect of exenatide and vildagliptin. The increase in the survival of ischemic tissues using exenatide and vildagliptin has been experimentally proved. The current study confirmed the important role of ATP-dependent potassium channels in dermatoprotective properties of incretin mimetics.

**Key words:** Dermatoprotective properties, Exenatide, Ischemia, Pedicle skin graft, Vildagliptin.

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## INTRODUCTION

In the modern view, ischemic-reperfusion injury is the leading cause of most of the critical situations that are somehow associated with ischemia including myocardial infarction, stroke, organ transplantation, and shock of various etiologies (Lankin et al., 2005; Sloth et al., 2014; Sharafeev and Bayazitova, 2016). The resumption of blood flow, occurring after ischemia, paradoxically causes deep tissue damage and further cell necrosis (Savas et al., 2003).

At the same time, none of the proposed methods and their combinations provide guaranteed protection against ischemia-reperfusion injury, in connection with which the search and selection of innovative and promising compounds and preparations of this orientation continue. Preclinical studies at the systemic (Korokin et al., 2014; Peresyphkina et al., 2016; Yakushev et al., 2016), cellular (Danilenko et al., 2016; Kravchenko et al., 2016; Kalmikov et al., 2018), and molecular (Bogus et al., 2018; Dzhimak et al., 2018; Soldativ et al., 2018) levels, including specific activity (Gumanova et al., 2007; Denisyuk et al., 2016; Danilenko, 2018) and toxicology studies (Kolesnichenko et al., 2018) in conjunction with bioequivalence studies (Kalmikov et al., 2018), therapeutic equivalence and effectiveness (Avdeeva et al., 2016) are an integral part of the research of innovative drugs.

Incretin hormones are secreted in response to food intake and stimulate insulin secretion (Gautier et al., 2008). Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted by the small intestine to regulate glucose concentration in the blood. GLP-1 stimulates insulin release by binding to the GLP-1 receptor (GLP-1R) on the beta cells of the pancreas. Moreover, stimulation of GLP-1Rs has cytoprotective and anti-apoptosis effects on tissues cells bearing this receptor (Ban et al., 2010; Anagnostis et al., 2011).

The GLP-1R belongs to class B1 (secretin receptor-like) of the family of G-protein-coupled receptors (GPCR). The interaction of GLP-1 with its receptor is accompanied by activation of adenylate cyclase (AC) and followed by an increase in cyclic adenosine monophosphate (cAMP) level and subsequently leading to activation of protein kinase A (PKA), phosphatidylinositol-3-kinase (PI3K), and protein kinase B (PKB, also known as Akt), thereby realizing the effect of GLP-1 on the functioning of target cells, as well as on the processes of apoptosis and regeneration (Deacon et al., 2006; Ban et al., 2010; Wei et al., 2016) because GLP-10 metabolites with respect to GLP-1R. At the same time, according to some studies, metabolites of incretins have their own physiological effects (Deacon et al., 2006; Saraiva and Sposito, 2014).

In addition to the hypoglycemic effect, there is evidence that GLP-1R agonists and DPP-4 inhibitors have pleiotropic effects (Ban et al., 2008; Vlasov et al., 2016). Due to the fact that the pancreas, brain, heart and other organs have exactly the same type of GLP-1R, it is reasonable to assume that the cytoprotective effect will extend to all types of tissues including skin tissue (Tyurenkov et al., 2017). In this regard, the present study intended to evaluate the efficacy of the incretin mimetic agents including exenatide and vildagliptin in preventing and ameliorating the consequences of ischemia-reperfusion injury.

## MATERIALS AND METHODS

The present study were conducted in laboratory of Medical Institute of Belgorod State University, Belgorod, Russia. The experiments were carried out on 60 adult male rats of the Wistar line weighing 200-250 g. All rats were divided into six groups of 10 animals. Simulation of an isolated pedicle skin flap was performed on the second day of the experiment, according to the findings of Kolesnik (2010). On the abdomen of the rat, the skin was cut off and stepping back 1 cm from the xiphoid process along the white line of the abdomen. A skin graft was cut off (1 × 4 cm) while maintaining the supply vessel. It was placed in an insulated plastic bag and sewn to the skin. Operations were performed under anesthesia with chloral hydrate (300 mg/kg, intraperitoneally).

To study the cytoprotective effect of exenatide and vildagliptin on the model of an isolated skin graft on the pedicle, all experimental animals were divided into six groups. In the control group, rats did not receive any treatment. In exenatide group, exenatide (10 µg/kg/day) was injected subcutaneously for 9 days after the operation, rats in vildagliptin group received vildagliptin (0.2 mg/kg/day) intraperitoneally for 9 days after the operation. In the other group, pentoxifylline as a drug reference was injected intravenously at a dose of 100 mg/kg/day 2 hours before the experiment.

To determine the role of ATP-dependent potassium channels in the implementation of the mechanism of action of incretin mimetics, 5 mg/kg glibenclamide were injected intragastrically through a probe to animals, 30 minutes before drug administration. The areas of surviving tissue were measured on third, seventh and tenth days and eventually, the survival rate of the skin graft was calculated (the ratio of the area of the surviving tissue to the initial area of the graft × 100%).

### Ethical approval

All of the experimental process was conducted in according to “modern ethical requirements for animal experiments” (Kopaladze, 1999).

## RESULTS AND DISCUSSION

In the control group, the area of the surviving tissue on the fifth day was  $1.62 \pm 0.02 \text{ cm}^2$ , which is 41% of the original area ( $4 \text{ cm}^2$ ). The administration of exenatide and vildagliptin led to an increase in the area of the surviving tissue to  $2.68 \pm 0.03 \text{ cm}^2$  and  $2.41 \pm 0.09 \text{ cm}^2$ , respectively. In the group of pentoxifylline (100 mg/kg/day), surviving graft area was  $1.81 \pm 0.07 \text{ cm}^2$ , which is 1.1 times more than the control group, but less than in exenatide and vildagliptin.

When simulating a skin graft on the pedicle, both studied incretin mimetics contributed to a significant increase in the area of the surviving tissue in comparison with the control group at 3, 7, and 10 days (Table 1). According to the obtained results, vildagliptin had more beneficial effects on graft survival rate compared to the control group.

In the present study, it was revealed that Preliminary blockade of ATP-dependent potassium channels by glibenclamide eliminates the protective effect of incretin mimetics when simulating a pedicle skin graft in rats. The survival of the skin graft in experimental animals with the administration of glibenclamide did not differ from that of the control group, which confirms the fact that glibenclamide at the applied dose does not affect the survival of ischemic tissues (Table 2). When using glibenclamide before the administration of exenatide and vildagliptin, the area of the surviving tissue was 1.3 and 1.4 times less than with their isolated administration, respectively.

The GLP-1R has been identified in the skin of mice; in cultured skin cells, GLP-1 activates the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathway associated with cell proliferation, differentiation, and cytoprotection (List and He, 2006). In this regard, many recent studies have demonstrated the beneficial role of GLP-1 analogs such as exenatide and DPP-4 inhibitors such as vildagliptin in patients with diabetes (Lee and Lee, 2017), as well as promote ulcers healing on the feet (Long et al., 2018) and the healing of diabetic wounds in rodents (Roan et al., 2016). In addition, DPP-4 expression is increased in dermal fibroblasts of mouse muscle after skin damage (Schürmann et al., 2012) and is a prerequisite for fibroblast migration and proliferation, indicating the role of regional incretins in regulating fibroblast functions and, possibly, wound healing. Recent experimental findings indicated the possible role of incretins in promoting tissue regeneration and, therefore, their ability to stimulate the migration of endothelial cells (Kang et al., 2013) to inhibit apoptosis (Favaro et al., 2012) and reduce inflammation and oxidative stress during ischemia (Gurtner et al., 2008).

Most researchers talk about the connection of the GLP-1R with the most important intracellular signaling cascades - PI3K/PKB (Akt), AC/PKA/MAPK, PKB (MAPK)/NF- $\kappa$ B and PKB (PKA)/eNOS. GLP-1R agonists (including liraglutide and exenatide) are able to have an endothelium protective effect in diabetes mellitus, reducing the activation of many pro-inflammatory mediators and adhesion-enhancing factors (including TNF $\alpha$ , PAI-1, VCAM-1, ICAM-1, MCP-1 and E-selectin) which stimulate adhesion and infiltration of the vascular wall by monocytes and macrophages and are associated with endothelial dysfunction and atherogenesis (Stewart et al., 2015; Jiang et al., 2018).

Nevertheless, there is no consensus in the literature in explaining the mechanism of the cytoprotective action of incretin mimetics. A number of studies suggest the implementation of a protective effect of incretin mimetics according to the type of ischemic preconditioning, where the mitochondrial ATP - dependent potassium channels can be considered as the final effector link, the activation of which directly leads to an increase in resistance during ischemia (Tamareille et al., 2011; Ussher and Drucker, 2012).

**Table 1.** Indicators of skin graft survival rates when using exenatide, vildagliptin, and pentoxifylline in male rats.

Medicaments (dose; number of members)	Necrosis area of the skin graft (%)		
	Day 3	Day 7	Day 10
Control group (saline)	30.98 $\pm$ 3.2	65.76 $\pm$ 2.4	84.55 $\pm$ 3.3
Exenatide (10 $\mu$ g/kg/day; 10)	27.37 $\pm$ 3.1*	52.9 $\pm$ 4.4*	61.8 $\pm$ 3.5*
Vildagliptin (0.2 mg/kg/day; 10)	24.1 $\pm$ 2.8*	44.3 $\pm$ 3.1*	59.1 $\pm$ 2.4*
Pentoxifylline (100 mg/kg/day; 10)	36.9 $\pm$ 1.9*	39.5 $\pm$ 3.8*	67.8 $\pm$ 2.4*

\*significant different (p<0.05) compared to the control group. Values are expressed as mean  $\pm$  standard deviation

**Table 2.** Protective effect of exenatide and vildagliptin in the background of glibenclamide on skin graft survival rate.

Medicaments (dose; number of members)	Necrosis area of the skin graft (%)		
	Day 3	Day 7	Day 10
Control group: saline (10)	30.9 $\pm$ 3.2	65.7 $\pm$ 2.4	84.5 $\pm$ 3.3
Exenatide (10 $\mu$ g/kg/day; 10)	27.3 $\pm$ 3.1*	52.9 $\pm$ 4.4*	61.8 $\pm$ 3.5*
Glibenclamide (5 mg/kg; 10)	31.0 $\pm$ 2.2	64.3 $\pm$ 3.1	83.9 $\pm$ 2.7
Glibenclamide (5 mg/kg) + Exenatide (10 $\mu$ g/kg/day) (10)	29.1 $\pm$ 2.04	61.7 $\pm$ 2.53	82.5 $\pm$ 3.21
Vildagliptin (0.2 mg/kg/day; 10)	24.1 $\pm$ 2.8*	44.3 $\pm$ 3.1*	59.1 $\pm$ 2.4*
Glibenclamide (5 mg/kg) + Vildagliptin (0.2 mg/kg) (10)	31.2 $\pm$ 2.12	64.71 $\pm$ 2.59	84.5 $\pm$ 3.13

\*Significant different (P<0.05) compared to the control group. Values are expressed as mean  $\pm$  standard deviation

## CONCLUSION

The obtained results in the present research testify the protective effect of exenatide and vildagliptin incretins when simulating a pedicle skin graft, which was accompanied by a decrease in the severity of ischemic tissue damage. The blockade of ATP-dependent potassium channels by glibenclamide on a pedicle skin graft reduced the effects of exenatide and vildagliptin. There is a necessity for further experimental and clinical studies to explain the mechanism for implementing the protective effects of incretins on various models.

## DECLARATIONS

### Authors' contributions

All of authors had equal roles in writing, editing, and experimental process and finally checked and approved the last edition of article.

### Competing interests

The authors have declared that no competing interest exists.

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