Biological Aspects of Actovegin’s Action

A.Yu. Nikolchenko (ORCID: 0009-0004-2679-4459); L.M. Tynynyka (ORCID: 0009-0001-7887-1143);
T.O. Kudryavtseva (ORCID: 0000-0002-1636-5704)

Private Institution of Higher Education «Kharkiv International Medical University», Kharkiv, Ukraine

Abstract Actovegin is a protein-free hemodialysate derived from calf blood, containing low-molecular-weight peptides, nucleotides, oligosaccharides, and metabolic intermediates with molecular weights below 5 kDa. This article analyzes the biological mechanisms underlying Actovegin’s pharmacological action, with particular emphasis on its insulin-like metabolic effects. Experimental data demonstrate that Actovegin enhances cellular uptake and utilization of glucose and oxygen, stimulates pyruvate dehydrogenase activity, and improves aerobic energy metabolism without interacting with insulin receptors. Its action occurs at the post-receptor level, allowing efficacy even under insulin-resistant conditions. The active fraction also exhibits cytoprotective, angioprotective, antioxidant, and anti-inflammatory properties, contributing to improved tissue repair, wound healing, and recovery in ischemic and hypoxic conditions. These findings support the broad therapeutic potential of Actovegin in metabolic, vascular, neurological, and musculoskeletal disorders.

Keywords: Actovegin; hemodialysate; insulin-like activity; glucose transport; hypoxia; energy metabolism.

Actovegin is a hemodialysate obtained from the cell mass of blood or tissue of calves (cows) by filtration and deproteinization. In addition to inorganic electrolytes and other microelements, it contains 30% organic substances, such as peptides, aminoacids, intermediate products of carbohydrate and animal metabolism, and lipids. Actovegin's active fraction consists of low-molecular-weight peptides and nucleotides with a molecular weight of less than 5 kDa, and contains oligopeptides, nucleotides, and nucleosides (ATP, GTP, CTP, etc.) [1,2]. These components readily penetrate cells and stimulate the transport and utilization of oxygen and glucose, improving metabolism.

Using various chromatographic methods, it was demonstrated that the active fraction isolated from Actovegin exerts an insulin-like effect on isolated rat adipose tissue adipocytes. Lipid biosynthesis can increase fivefold, depending on the drug dose. Administration of adipocytes containing the active fraction causes a concentration-dependent stimulation of pyruvate dehydrogenase (PDH) activity. Approximately 60% of total PDH activity is transferred to the active form, which corresponds to the stimulation provided by physiological insulin concentrations. Actovegin's insulin-like mechanisms of action differ significantly from those of insulin administration alone, as under these conditions, lipogenesis, lipolysis, and glucose transport are not inhibited by anti-insulin antibodies [1,2,3].

Furthermore, it was noted that hemodialysate does not affect insulin receptor phosphorylation or insulin dependence on its receptor. This suggests that Actovegin signals are not transmitted to insulin receptors but rather occur at the post-receptor level [4]. The active fraction isolated from hemodialysate increases 3-O methylglucose (3-OMG) transport in a dose-dependent manner by 5-fold. The use of 3-OMG is an instrumental glucose analog that allows for the separation of transport from metabolism, since measuring 3-OMG uptake by cells allows for the assessment of the rate and nature of glucose transport. This makes it possible to distinguish between Na^+-dependent and Na^+-independent glucose transport, since 3-OMG passes through both types of glucose transporter—Na^+-dependent and independent [3,4]. The duration of action of Actovegin's active fraction is the same as that of insulin. Both agents begin to act within 1 minute and reach their maximum after 5 minutes. Stimulation of 3-0 methylglucose transport by the active fraction does not result in an increase in cytocholasin-B in the plasma fraction. The active fraction apparently acts independently of glucose transport. Stimulation of transport occurs through modulation of the intrinsic activity of the glucose carrier. This explains Actovegin's independent insulin-like effect on glucose transport and utilization, resulting in improved cellular energy status [4,5].

It was found that the active fraction of Actovegin does not affect either receptor phosphorylation or insulin binding to its receptor. Analysis of sugar before and after hydrolysis revealed that the active fraction contains sugar in the precipitate, but not in monomeric form, but as oligosaccharides. Further analysis of the active components of the active fraction was investigated using chemical modification [5,6]. It was found that loss of activity occurs after shortening and oxidation of the polysaccharide chain, i.e., under conditions that alter the sugar. A partially purified active fraction of Actovegin was tested for its ability to stimulate lipogenesis. It was shown that the active fraction of Actovegin mimics insulin-like effects, such as stimulation of lipogenesis, inhibition (induced by isoproterenol) of intracellular cAMP formation, lipolysis, and stimulation of glucose transport [6].

It is possible that the active substances are released from the plasma membranes of cellular components during the manufacturing process and are contained in the product in a concentrated form, since Actovegin is produced from whole blood after its autohydrolysis. A series of inhibition experiments were conducted with various sugars, alcohols, and amino sugars to determine which component of the active fraction is responsible for the various insulin-like effects. It was found that none of these substances exerted any effect on the active fraction's stimulation of glucose transport, intracellular cAMP formation, or lipolysis [3,4,5]. However, stimulation of lipogenesis by the active fraction can be inhibited by glucosamine, mannose, and inositol monophosphate. Inhibition of lipogenesis by the addition of mannose, glucosamine, or inositol monophosphate demonstrates that oligosaccharides act through a receptor on a cellular effector during lipogenesis. Compounds containing mannose, glucosamine, or inositol monophosphate mimic signaling molecules that typically bind to cell surface receptors. For example, mannose can interact with mannose receptors on the membranes of endothelial and adipocytes. Glucosamine is involved in hexosamine pathways, influencing protein O-glycosylation. Inositol monophosphate mediates phosphoinositide signaling cascades and regulates intracellular calcium and lipogenesis. Oligosaccharides do not directly enter the nucleus to regulate enzymes. They can bind to specific membrane receptors, triggering intracellular signaling cascades, for example, through G proteins, phosphoinositides, or ion channels. Oligosaccharides can also modulate the activity of lipogenesis enzymes such as acetyl-CoA carboxylase and synthase [4,5].

Thus, lipogenesis is regulated by external signals acting through membrane receptors. These data confirm the important role of oligosaccharides in Actovegin as secondary carriers of insulin-like activity. Hemodialysate has been shown not only to improve glucose transport and oxygen uptake but also to stimulate their utilization, which improves oxygen metabolism. This mechanism ensures clinical

efficacy in conditions of transient stress and tissue hypoxia associated with peripheral arterial disease [5,6,7].

Actovegin's effect on glucose utilization is particularly significant, as glucose is the single most important substrate for energy production in peripheral arterial diseases. Furthermore, recent studies have shown that patients with these diseases exhibit insulin resistance and carbohydrate metabolism [3,4,5]. These deficiencies can be eliminated or partially reversed by Actovegin's insulin-like action. Due to Actovegin's stimulating effects on both glucose transport and PDH, positive results can also be achieved in cases of insufficient cerebral supply. Hemodialysate has been shown to have a positive effect on impaired cerebral metabolism during ischemia, manifested by changes in glucose, ATP, and lactate accumulation. In addition to general cerebral ischemia, hemodialysate has been used to improve cellular energy status in hippocampal lesions [4,5]. Currently, active research into the structures of Actovegin's active components is ongoing by scientists worldwide.

Hemodialysate has been used for wound healing in a number of studies by many authors. Granuloma activation has been demonstrated not only morphologically but also by an increase in DNA levels at the wound site. Clinical studies have demonstrated accelerated wound healing in cases of pressure ulcers, leg ulcers (venous and venous-arterial), second- and third-degree burns, and radiation injuries [3,4]. Carbohydrate metabolism after injury is characterized by hyperglycemia and glycosuria. Hyperglycemia results from glucose accumulation, while the relative reduction in glucose utilization due to insulin resistance results. Oxidizable glucose initially accumulates in the burn zone, but glucose assimilation is simultaneously reduced due to insulin resistance. As aerobic glycolysis becomes increasingly impaired, a switch to anaerobic glycolysis occurs, which in turn causes lactate accumulation. These severe metabolic disturbances lead to reduced endogenous glucose accumulation. Actovegin's stimulating effect on wound healing is explained by improved glucose utilization even in the presence of insulin resistance, as Actovegin does not affect glucose transport via insulin receptors [5,7].

Scientists found that wound healing in gangrene is achieved only if blood glucose levels are returned to normal in a series of experiments with laboratory animals and clinical studies of diabetic patients with type 2 diabetes [6]. These studies clearly demonstrate that glucose utilization plays a central role in wound healing. This is especially important for patients with type 2 diabetes with complications such as gangrene, where wound healing is slowed by insulin resistance [3,6].

The potential of Actovegin for use in a completely different area of therapy—sports medicine—was also studied. This treatment is used for acute muscle injury (muscle rupture and strain). A prospective randomized trial was conducted on 103 patients to compare the results of protein-free hemodialysate (Actovegin) and placebo [8]. The hemodialysate group included 68 patients. Acute muscle injury is characterized by muscle pain and loss of muscle function. Patients received three injections into the injured muscle every three to four days. They were examined three months after the start of treatment. Full athletic activity was restored in the hemodialysate group after 5.5 weeks, and in the non-hemodialysate group after 8.3 weeks. Significant differences were observed in the rehabilitation of the calf and thigh muscles. The results demonstrated high statistical significance. In sports medicine, acute paratendinitis of the Achilles tendon was also treated using Actovegin, resulting in a significant improvement in the patients' condition [8].

Thus, the active fraction of Actovegin exerts a metabolic effect, enhancing glucose and oxygen transport into cells, and improves aerobic energy metabolism by increasing ATP synthesis. The active fraction of Actovegin also has a cytoprotective effect, which reduces cell damage during hypoxia and ischemia and stimulates the regulation of membrane potential and intracellular Ca^{2+}. It also has an

angioprotective and microcirculatory effect, which is realized by increasing capillary elasticity and permeability while improving microcirculation in damaged tissues. Actovegin also exhibits antioxidant and anti-inflammatory properties, helping to reduce the formation of free radicals and attenuating the response of phagocytes to oxidative stress.

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