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The Effect of Insulin-like Growth Factor-1 on the Quantitative and Qualitative Composition of Phosphoinositide Cycle Components During the Damage and Regeneration of Somatic Nerves

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Abstract: One of the pressing issues in regenerative medicine is the restoration of somatic nerve function after injury. In this study, extraction methods were used to obtain lipids from nervous tissue, followed by chromatographic separation, quantitative analysis via densitometry, and qualitative and quantitative analyses of the fatty acid composition through gas chromatography. The results showed that nerve cutting results in the accumulation of all forms of phosphoinositides and a decrease in diacylglycerol (DAG) levels in both the proximal and distal segments of the nerve conductor. This phenomenon is likely attributable to the inactivation of phosphoinositide-specific phospholipase C and the activation of lipolytic enzymes, particularly phospholipases A_1 and A_2, resulting in an increase in the amount of free fatty acids (FFAs). The intramuscular administration of insulin-like growth factor-1 (IGF-1) was associated with enhanced phosphoinositide metabolism, increased DAG levels, reduced FFA levels, and a redistribution of fatty acids within the studied lipid fractions. The registration method of action potentials demonstrated the restoration of nerve conduction in the proximal segment of somatic nerves following the introduction of IGF-1. This correlates with our findings regarding alterations in the lipid fraction composition of damaged nerve conductors in response to the drug's effects. Most likely, IGF-1 exerts its effects through activation of the phosphoinositide-specific phospholipase C and phosphatidylinositol-3 kinase signaling pathways, which are necessary for axonal regeneration and the restoration of functioning damaged nerve conductors.

Keywords: somatic nerves; nerve regeneration; phosphoinositides; diacylglycerol; free fatty acids; insulin-like growth factor-1; signaling pathways

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1. Introduction

One of the pressing issues in regenerative medicine is the restoration of somatic nerve function after injury [1]. It generates interest in studying various pathways for activating axonal regeneration by applying biological stimulators to restore the functional activity of damaged nerve fibers. The literature increasingly reports the involvement of growth factors, particularly IGF-1 (insulin-like growth factor-1), in regulating nerve cell proliferation and differentiation processes [2,3]. One of the key components of the phospholipid composition of cell membranes is known to be phosphoinositide (PI), which plays an active role in regulating cellular processes. It acts as a source of secondary messengers in signal transduction from receptors inside the cell and is involved in the regulation of Ca^{2+} ion transport [4]. In addition to the changes in the content of individual PI classes, the fatty acid composition of these components is also of significant importance, as pathological processes are accompanied by oxidative stress, resulting in the activation of lipid peroxidation (LPO) and disrupting normal cell membrane function [5]. The changes in

the levels of FFAs (free fatty acids)—lipid metabolites produced by phospholipase A_2—are also an important indicator of the intensity of LPO processes [6]. It should be noted that there are currently insufficient data on the fatty acid composition of PI cycle components in the literature. One significant product of phosphodiester bond hydrolysis is diacylglycerol (DAG), which activates protein kinase C. This activation enhances the signal from the activated cell surface receptor to effector proteins and serves as a precursor for arachidonic acid, which is essential for synthesizing prostaglandins and other physiologically active compounds [7]. Studying the composition and intensity of the metabolism of PI cycle components during the transection and regeneration of damaged nerve fibers will elucidate the role of these components in regulating intracellular mechanisms necessary for restoring the function of damaged somatic nerves and the targeted effects of physiological substances, particularly IGF-1, on specific elements of metabolic signaling pathways involved in these processes.

Therefore, this study aimed to investigate the effect of IGF-1 on the quantitative and qualitative changes in PI cycle components during the damage and regeneration of somatic nerves. To achieve this goal, we completed the following tasks: we studied the effect of IGF-1 on changes in the levels of individual PI fractions, DAG, and FFA in the proximal and distal segments of the sciatic nerve after transection; investigated the changes in the fatty acid composition of phosphatidylinositol fractions, DAG, and FFA in the proximal and distal ends of the rat sciatic nerve after injury and IGF-1 treatment; and determined the role of PI cycle components in regulating the regeneration processes of damaged nerve fibers under the influence of IGF-1.

2. Materials and Methods

This study focused on the sciatic nerves of Wistar rats. The rats had an average weight of 250 $\pm$ 50 g. We used 10 rats in each series of experiments. In one experimental group, the sciatic nerve was transected at the mid-thigh level. The nerve trunk was accessed by dissecting the skin and subcutaneous fat of the hindlimb using blunt branches. The fascia was dissected in layers, and the hip region muscles were dissected along the posterior limb surface. The nerve was transected into proximal and distal sections, each averaging 1.4 cm, in the lower third of the thigh at the site of its bifurcation into the common fibular and tibia nerves. In the second group, after nerve transection, IGF-1 (recombinant human insulin-like growth factor type 1) (*E. coli*) (SIGMA-ALDRICH, Saint Louis, MO, USA) was administered intramuscularly daily at 50 and 75 ng/kg concentrations. The proximal and distal ends of the nerves were extracted on days 7, 14, 21, and 28 and placed in Ringer's solution, consisting of 136 mM sodium chloride, 2.7 mM potassium chloride, 1.8 mM calcium chloride, 2.4 mM sodium bicarbonate, and 5.55 mM glucose. Intact animals served as controls. Lipid extraction from nerve tissue was performed using the Bligh–Dyer method [8]. PI was separated using the Prokhorova method [9], employing two-dimensional chromatography on silica gel with solvent systems n-propanol/4N ammonia (2:1) and chloroform/methanol/4 N ammonia (9:7:2). To separate DAG and FFAs, a heptane/diethyl ether/ice-cold acetic acid (60:40:1 by volume) system was used [10]. To visualize individual lipid fractions, a reagent for staining plates was pre-prepared as follows: 20 g of copper sulfate pentahydrate was dissolved in 200 mL of distilled water, followed by the addition of 8 mL of sulfuric acid (98%) and 8 mL of orthophosphoric acid (85%). After separation in a solvent system, the plate was placed in a dye for 15 s and dried in the air. After that, it was heated on a tile at 140 °C for 30 min, and brown staining of lipid fractions was observed. Individual lipid fractions were identified using Rf (ratio of fronts) values, specific staining agents, and standards. Quantitative lipids were determined using densitometry on an automated CAMAG TLC Scanner 4 (Muttenz, Switzerland). The qualitative and quantitative composition of fatty acids (FA) was determined using a SHIMADZU GC-2010Plus AF gas chromatograph (Kyoto, Japan), with prior fatty acid esterification according to the Morrison and Smith method [11]. Bioelectrical activity was recorded for a proximal nerve segment with extracellular recording under the following

stimulation parameters: amplitude 1.5 V, duration 0.3 ms, and stimulation frequency 100 impulses/s using a GW Instek GDS-71042 oscilloscope (Taipei, Taiwan) and laboratory electrical stimulator (ESL-2) (Tomsk, Russia) [12]. The perfused rat sciatic nerves were placed in Ringer's solution at 37 °C with a continuous oxygen flow. The data were statistically processed using Microsoft Excel 2016. The experimental variants were compared using ANOVA, with a significance threshold of 5%.

3. Results and Discussion

PIs are universal signaling molecules that are essential for various cellular functions, specifically the regulation of ionic permeability of the cell membrane through the binding and release of Ca^{2+} ions [13]. Additionally, they can form complexes with various proteins, which leads to the association of numerous proteins on the cell's outer surface. PIs are found in high quantities in nerve tissue, which underscores their crucial role in regulating the physicochemical processes occurring in nerve fibers during their normal functioning [14]. Based on this, in the experiment's first phase, we investigated the changes in the levels of specific PI fractions and their breakdown products—DAG and FFA—in the proximal and distal nerve segments after nerve transection and IGF-1 introduction.

In uninjured rat sciatic nerves, the average concentrations of phosphatidylinositol (MPI), diphosphoinositide/phosphatidylinositol-4,5-diphosphate (DPI), and triphosphoinositide/phosphatidylinositol-3,4,5-trisphosphate (TPI) were 51.4, 6.14, and 7.02 µg phosphorus/mg of total lipids, respectively (Figures 1 and 2). Seven days after sciatic nerve transection, a sharp increase in all PI fractions relative to the control was observed at the proximal end of the nerve. In this experimental condition, the MPI, DPI, and TPI levels were, on average, 84.35, 11.03, and 11.57 µg phosphorus/mg of lipids, respectively (Figures 1 and 2).

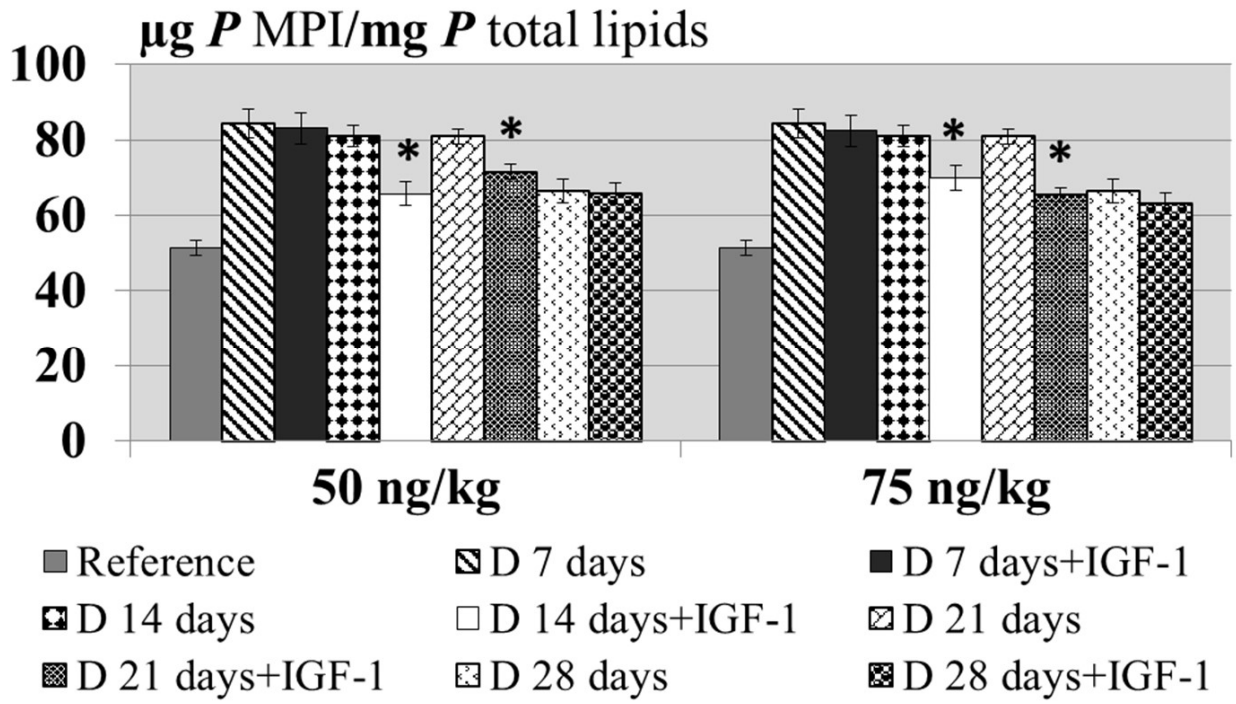

Figure 1. Dynamics of changes in the phosphatidylinositol (MPI) concentration in the proximal end of the rat sciatic nerve after its damage and the action of IGF-1 at concentrations of 50 and 75 ng/kg. D—damage; µg P MPI/mg P total lipids—µg inorganic phosphorus phosphatidylinositol/mg inorganic phosphorus of total lipids (all error bars indicate a standard error of mean (n = 10); *—significant difference compared with damage, $p < 0.05$).

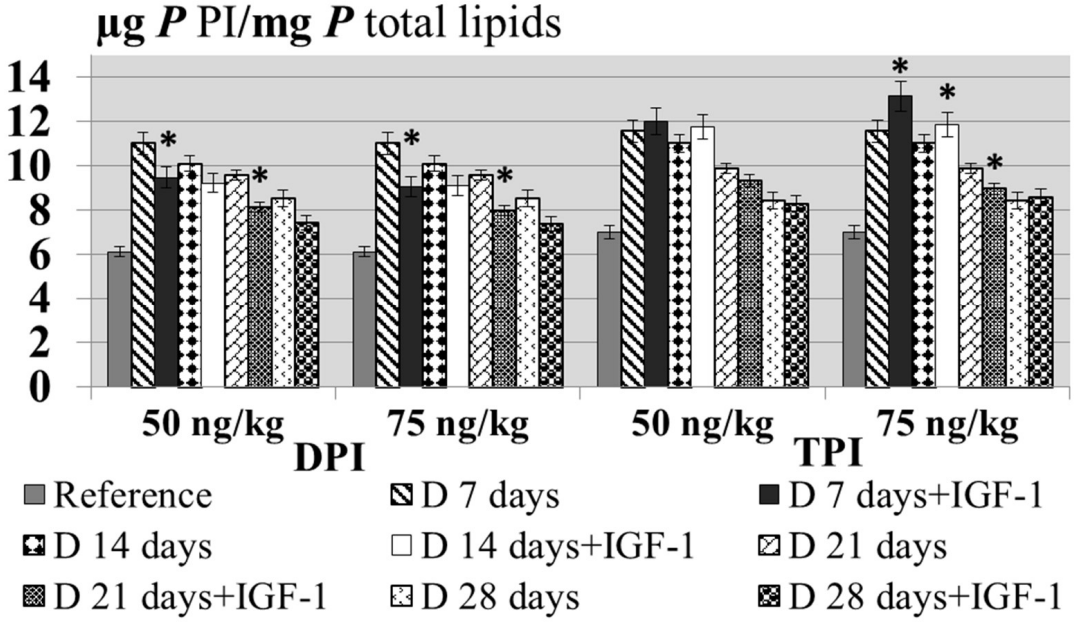

Figure 2. Dynamics of changes in the concentration of diphosphoinositide (DPI) and triphosphoinositide (TPI) in the proximal end of the rat sciatic nerve after its damage. µg P PI/mg total lipids—µg inorganic phosphorus of individual PI/mg inorganic phosphorus of total lipids (all error bars indicate a standard error of mean (n = 10); *—significant difference compared with damage, $p < 0.05$).

In the nerve distal segment, there was a pronounced increase in all studied PI fractions, which were increased on average more than 2.0 times compared with the control (Figures 3 and 4). The obtained data suggest that, following the onset of Wallerian degeneration up to 7 days into the experiment, disintegration of the axoplasmic cytoskeleton occurred due to proteolytic degradation triggered by an elevated influx of calcium ions into the damaged nerve and the activation of signaling pathways related to PI metabolism [13].

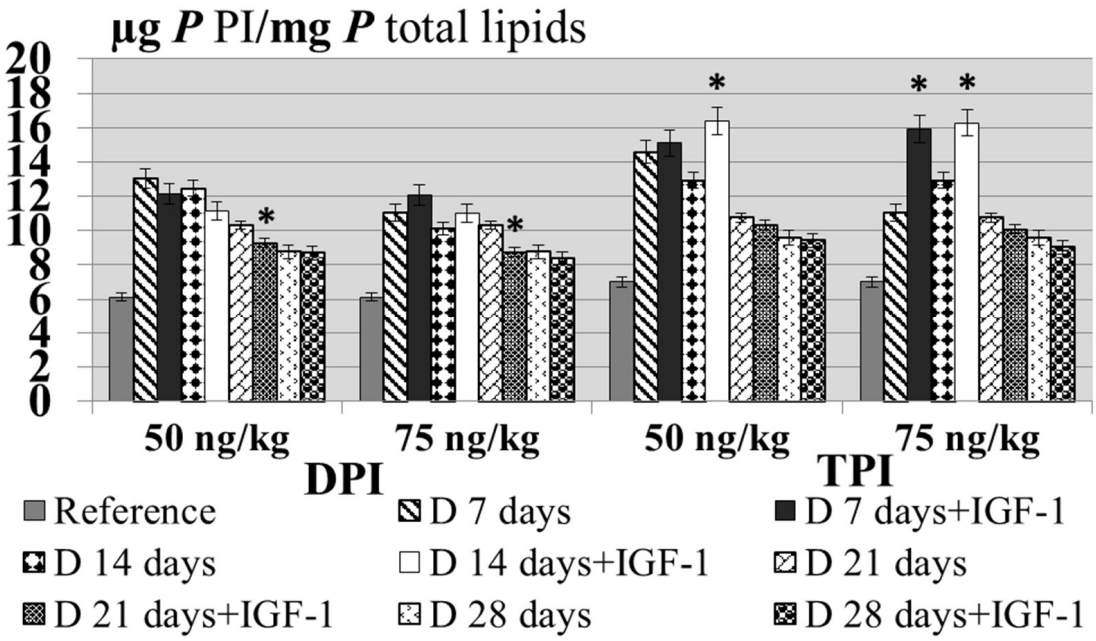

Figure 3. Dynamics of changes in the concentration of diphosphoinositide (DPI) and triphosphoinositide (TPI) in the distal end of the rat sciatic nerve after its damage (all error bars indicate a standard error of mean (n = 10); *—significant difference compared with injury, $p < 0.05$).

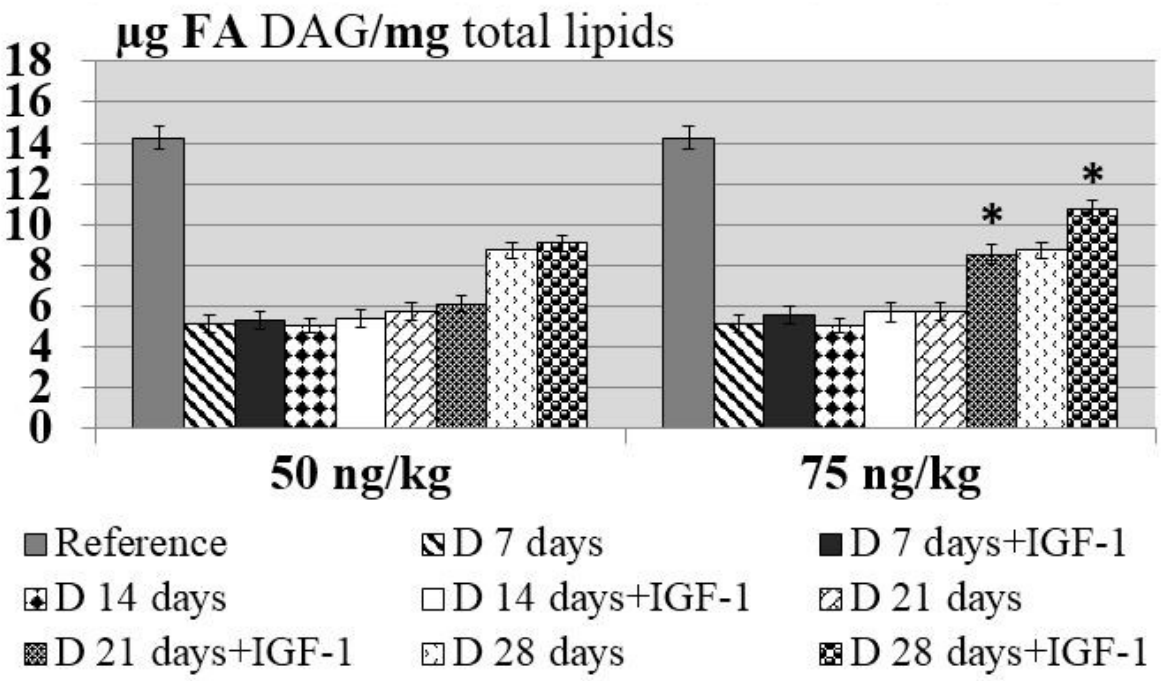

Figure 4. Dynamics of changes in the DAG concentration in the proximal end of the rat sciatic nerve after its damage. µg FA DAG/mg total lipids—µg fatty acids DAG/mg total lipids (all error bars indicate a standard error of mean (n = 10); *—significant difference compared with damage, $p < 0.05$).

Researchers have been increasingly looking for the most effective methods for stimulating axonal regeneration using biologically derived substances. In particular, the IGF signaling pathways, including IGF ligands, their receptors, and binding proteins, form a complex regulatory network of interactions among themselves and other biological modulators of cell growth and survival [15]. On this basis, the next stage of the experiment was to study the effect of IGF-1 on the content changes in individual PI fractions in the proximal and distal segments of the sciatic nerve after its transection. In the proximal nerve segment, the most pronounced changes in the MPI level were observed on days 14 and 21 of the experiment at a drug concentration of 75 ng/kg, resulting in a reduction of 19.0% and 11.5%, respectively, compared with the damage (Figure 1). The administration of the drug at a concentration of 75 ng/kg resulted in a 17.8% reduction in DPI levels by day 7 of observation relative to the injured nerve. Moreover, as the postoperative period reached 21 and 28 days, a nearly identical trend was observed in the reduction in DPI levels in the experimental groups receiving IGF-1 administration at 50 and 75 ng/kg concentrations. The TPI content increases on days 7 and 14 of observation were comparable to the damage with the drug administered at both concentrations, while, by day 21 of the experiment, a trend towards a decrease in its level was observed. The most pronounced changes occurred in the experimental variant with IGF-1 at a concentration of 75 ng/kg, accompanied by a 9.1% reduction in the TPI content relative to transection (Figure 2). The drug's effect was less pronounced in the distal nerve segment compared with its proximal section. At an IGF-1 dose of 75 ng/kg, there was a significant reduction in the DPI level of 15.3% by day 21 of the experiment, along with an increase in the content of TPI fractions of 44.4% and 25.8% by days 7 and 14, respectively, compared with the injured nerve without the drug (Figure 3). In the other experimental variants, no significant changes were observed.

According to some of the literature reports, DAG is known to be a product of breakdown by phospholipase C and plays an important role in regulating the activity of phospholipase A_2, protein kinase C, and Ca^{2+} transport. Additionally, DAG can activate protein kinase C, which amplifies the signal from an activated cell surface receptor to effector proteins and phospholipase A_2, serving as a source of arachidonic acid [16]. On this basis, we studied the content of DAG in the proximal and distal sections of the sciatic nerve after

its transection and the action of IGF-1. The amount of DAG in intact nerves was found to average 14 μg DAG/mg total lipids. Nerve transection was accompanied by decreased DAG levels, with the minimum content observed on day 7. In this experimental condition, the DAG concentration decreased by 63.8% and 93.5% in the proximal and distal segments of the damaged nerve, respectively, compared with the control. As the postoperative period extended to 28 days, the DAG level increased, but it remained, on average, 1.8 times lower than the control value in both segments of the nerve conductor. The experiment showed that the most pronounced changes in DAG levels occurred when the substance was administered at a concentration of 75 ng/kg, with its content increasing on average by 12.4%, 49.3%, and 22.9% on days 14, 21, and 28 after transection, respectively, compared with the damage (Figure 4).

On day 21 of the experiment, the distal segment of the nerve conductor exhibited a 9.4% increase in DAG levels relative to the damaged nerve without drug intervention. No significant changes were observed in the other experimental conditions.

According to the literature, FFAs regulate the activity of ion channels and ATPases, G-proteins, and protein kinases, modulating the PI and sphingomyelin cycles, acting as secondary messengers, and mediating the effects of many other bioactive molecules [17]. According to our findings, the FFA content in the nerves of the control animals averaged 20 μg FA/mg total lipids. After nerve transection, significant changes were observed in the FFA levels in the proximal segment of the nerve conductor. The maximum accumulation occurred on day 7 of the experiment, reaching 51.76 ± 2.44 μg FA/mg total lipids. Subsequently, the FFA level displayed a propensity to decrease. Extending the post-injury period to 28 days decreased FFA levels, although the level remained significantly higher than that of the control, averaging 1.4 times greater (Figure 5). Similar dynamics were observed in the distal segment of the nerve conductor, but these changes were more pronounced due to extensive degenerative processes along its entire length. When IGF-1 was administered at a concentration of 75 ng/kg in the proximal segment of the nerve, there was a decrease in FFA levels. The amount of FFA decreased by 15.7% and 35.6% relative to injury on days 14 and 21, respectively, and, following an increase in the post-injury period to 28 days, the FFA level decreased by a factor of 1.4 compared with the transection series (Figure 5).

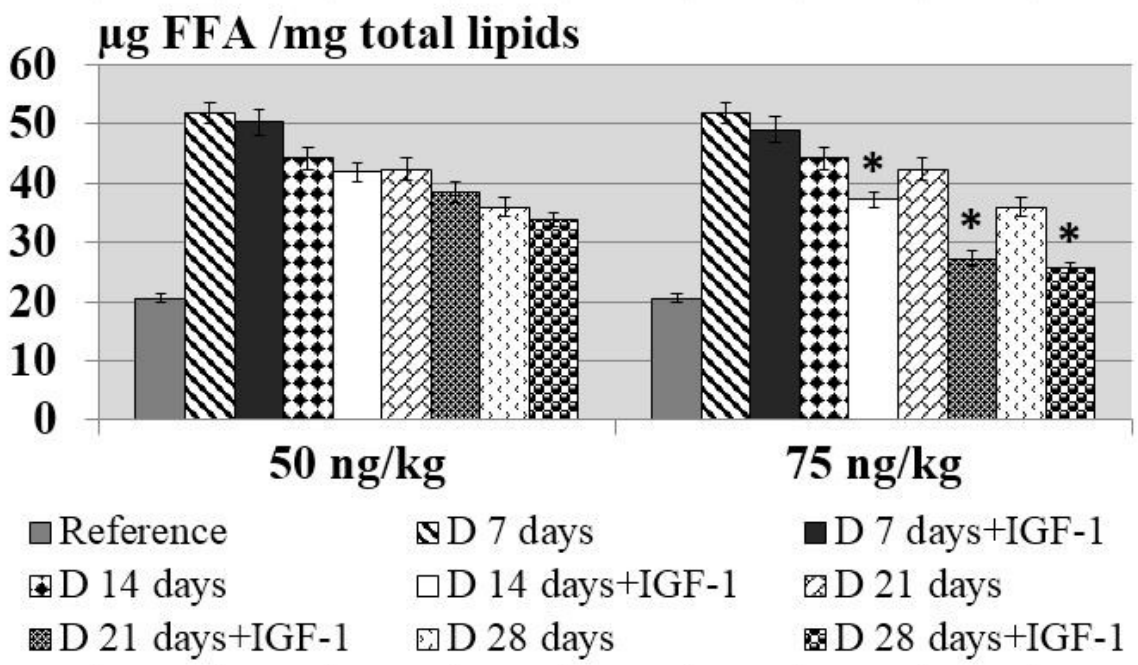

Figure 5. Dynamics of changes in the FFA concentration in the proximal end of the rat sciatic nerve after its damage. μg FFA/mg total lipids—μg FFA/mg total lipids (all error bars indicate a standard error of mean (n = 10); *—significant difference compared with damage, $p < 0.05$).

In the distal segment of the nerve conductor, there was a slight decrease in FFA levels by day 21 of observation under the experimental condition using the drug at its maximum concentration. In other experimental conditions, no significant changes were observed.

The lipid composition of the nerve conductor is known to be one of the most important indicators of its functional state. Fatty acids play a role in forming the hydrophobic zone of the membrane and determining its phase state. The presence of unsaturated fatty acids in membrane lipids makes them susceptible to various influences, including lipid peroxidation. Intensification of lipid peroxidation processes leads to various disruptions at the level of individual enzyme systems and the entire cell [18]. Therefore, it was interesting to study the quantitative distribution of fatty acids within the phosphatidylinositol fraction, saturated fatty acids, and diacylglycerides following transection and the action of a physiologically active substance (IGF-1).

The following fatty acids were found in the fatty acid composition of phosphatidylinositol, FFA, and DAG: C10:0 (decanoic acid); C11:0 (undecanoic acid); C12:0 (lauric acid); C13:0 (tridecanoic acid); C14:0 (myristic acid); C14:1 (myristoleic acid); C15:0 (pentadecanoic acid); C15:1 (cis-10-pentadecenoic acid); C16:0 (palmitic acid); C16:1 (palmitoleic acid); C17:1 (cis-10-heptadecenoic acid); C18:0 (stearic acid); C18:1 (oleic acid); elaidic acid (18:1n9t); C18:2 (linoleic acid); C20:0 (arachidic acid); C18:3 (alpha-linolenic acid); C21:0 (heneicosanoic acid); C20:2 (cis-11,14-eicosadienoic acid); C22:0 (behenic acid); C20:3 (cis-8,11,14-eicosatrienoic acid); C20:4 (arachidonic acid); C24:0 (lignoceric acid); and C24:1 (nervonic acid).

Nerve damage was found to cause a redistribution of fatty acids in both segments of the nerve conductor. Seven days after the transaction, the FA composition of the phosphatidylinositol fraction changed. The changes were manifested by an increase in the content of saturated fatty acids relative to the control by 18.6% at the proximal nerve end, mainly due to undecanoic, tridecanoic, pentadecanoic, palmitic, and stearic acids. At the same time, the content of unsaturated fatty acids decreased, and the saturation index (the ratio of saturated fatty acids to unsaturated ones) increased to 0.5. This trend continued; although, by day 28 of the experiment, the saturation index still exceeded the control value by, on average, 2.0 times. Administering IGF-1 to the test animals at a concentration of 75 ng/kg caused noticeable changes in FA redistribution, manifested by a decrease in the content of saturated fatty acids and an increase in unsaturated fatty acids. By days 21 and 28 of observation, the saturation index decreased by 20% and 28%, respectively, compared with the condition with nerve damage. In the distal segment of the damaged nerve, the saturation index increased by, on average, 4.0 times over 14 days of the experiment. With prolonged damage exposure, the indicator decreased but still exceeded control values by 2.4 times by day 28 of observation. Using the drug at its maximum concentration helped normalize the saturation index, accompanied by decreases of 36.8% and 28.3% on days 21 and 28, respectively, compared with the damage condition (Figure 6).

This study showed that in the DAG fraction, the content of saturated fatty acids was 67% and that of unsaturated fatty acids was 33%. The saturation coefficient was 2.03. Seven days after nerve transection, the DAG fraction showed a reduction in the saturation coefficient by an average of 1.6 times compared with the control. The introduction of IGF-1 led to an average increase in this indicator by 27% in the proximal end of the nerve compared with the injury at both drug concentrations. The tendency continued, and by 28 days, the indicator approached control values. In the distal segment of the injured nerve, the DAG fraction showed the maximum reduction in the saturation coefficient relative to the control by day 7 of the experiment, reaching 0.77. Administering the drug to the test animals at a dose of 75 ng/kg resulted in a slight increase in the saturation coefficient by days 21 and 28 of observation. No significant changes were observed in the other experimental conditions (Figure 7).

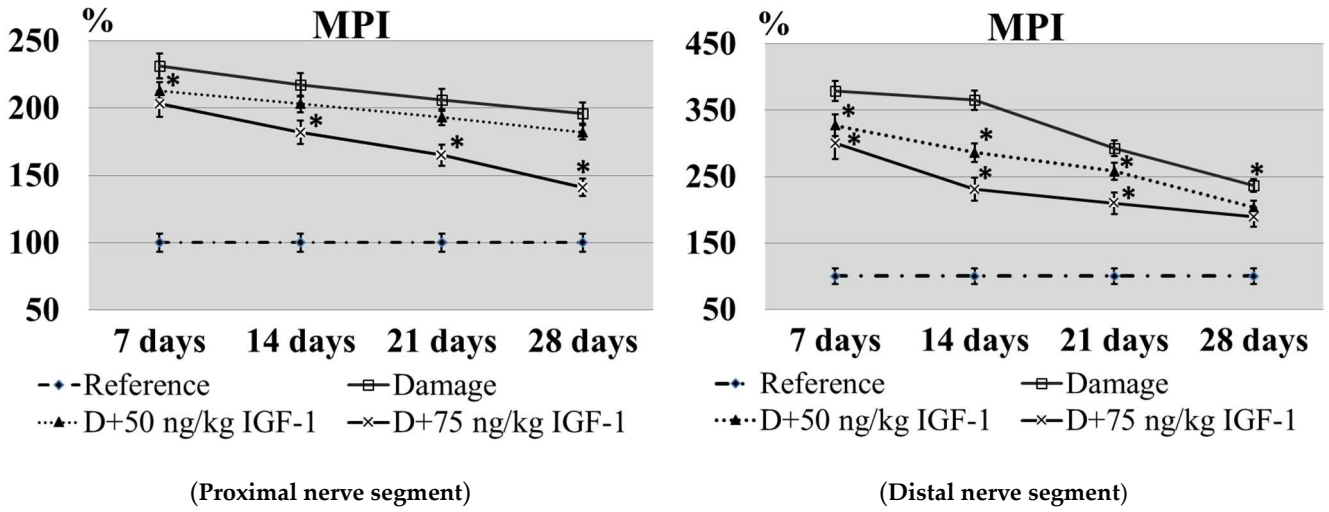

Figure 6. The effect of IGF-1 on the change in the saturation coefficient of phosphatidylinositol (MPI) in the rat sciatic nerve after its damage (in % of the reference; all error bars indicate a standard error of the mean (n = 10); *—significant difference compared with damage, $p < 0.05$).

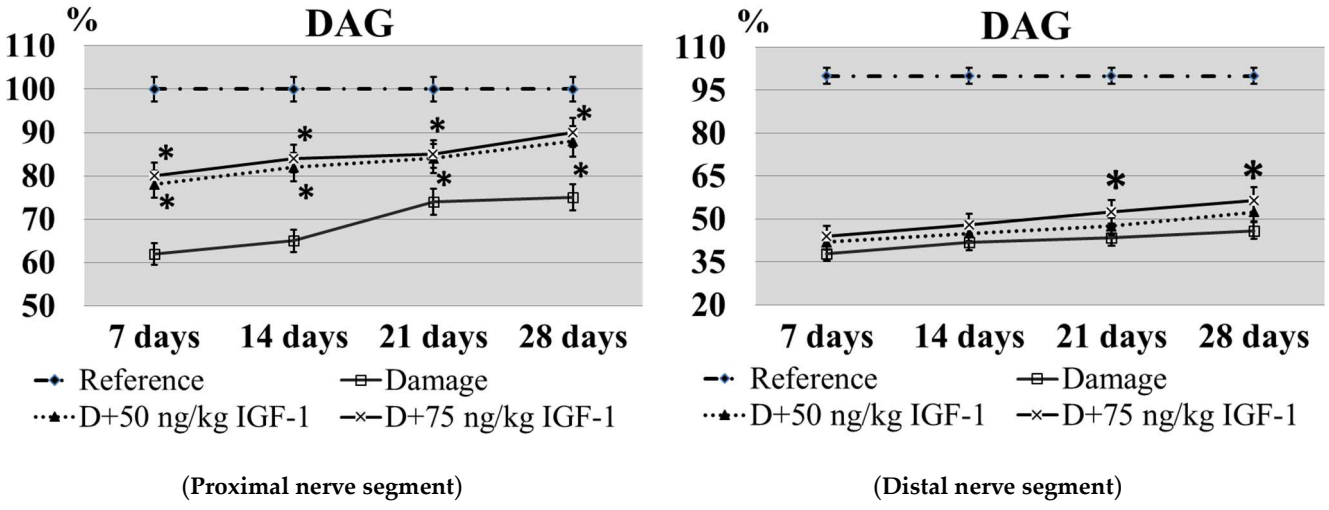

Figure 7. The effect of IGF-1 on the change in the saturation coefficient of DAG in the rat sciatic nerve after its damage (in % of the reference; all error bars indicate a standard error of the mean (n = 10); *—significant difference compared with damage, $p < 0.05$).

In the FFA fraction, the content of saturated fatty acids was 59%, while unsaturated fatty acids accounted for 41%. Among the detected fatty acids, palmitic and stearic acids comprised the largest proportions at 46.8% and 27.0%, respectively. Seven days after nerve transection, there was an increase in the proportion of unsaturated fatty acids, primarily linolenic and arachidonic acids. At the same time, the saturation index decreased by 2.8 times compared with the control. Extending the post-injury period to 28 days changed the saturated-to-unsaturated fatty acids' ratio, which remained 1.7 times lower than the control's. The administration of the drug at its maximum concentration altered the fatty acid composition of the FFA fraction. The saturation index 7 days after injury in the experimental group receiving IGF-1 at a concentration of 75 ng/kg increased 1.6 times compared with that in the series of experiments with injury, mainly due to a decrease in the levels of linoleic, cis-8,11,14-eicosatrienoic, and arachidonic acids. Under these conditions, with the post-injury period extended to 28 days, the content of unsaturated fatty acids was 65.5% lower compared with the injured nerve without drug treatment. In the distal segment

of the nerve conductor, there were no significant changes in the fatty acid composition of the FFA fraction due to IGF-1 treatment (Figure 8).

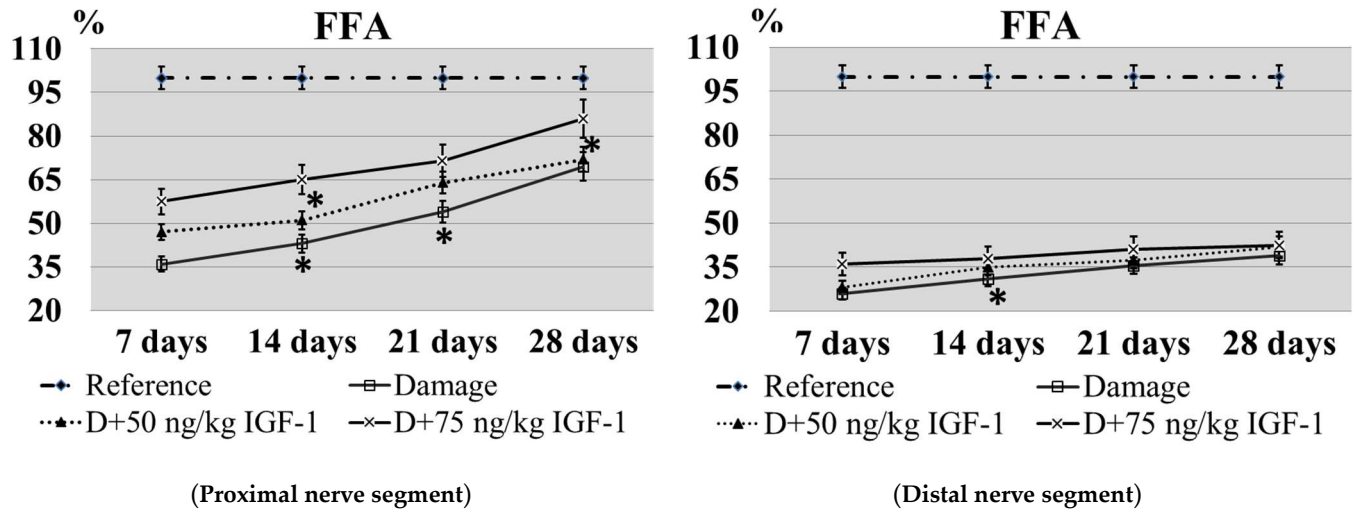

Figure 8. The effect of IGF-1 on the change in the saturation coefficient of the FFA fraction in the rat sciatic nerve after its damage (in % of the reference; all error bars indicate a standard error of the mean (n = 10); *—significant difference compared to damage, $p < 0.05$).

According to the literature, calcium ions and the structural changes occurring in the plasma membrane of the nerve fiber during excitation are known to activate phosphoinositide-specific phospholipase C, resulting in a DAG content increase [19]. Additionally, the changes in the quantitative content of FFA and the fatty acid composition of MPI and DAG interrelate and correlate. Thus, it can be hypothesized that FFA forms due to the metabolism of PI and from the products of their breakdown—DAG. Our experiments confirmed this, establishing that a decrease in the number of individual fatty acids in the FFA fraction led to an increase in their content in the MPI fraction. Thus, our study demonstrated that the introduction of IGF-1 was accompanied by the breakdown of PI, as evidenced by the DAG accumulation and the redistribution of fatty acids within the MPI, DAG, and FFA fractions.

It was found that, when the drug affected the damaged nerve conductor, there was an intensive renewal of the phosphate groups of PI cycle components and the fatty acids within them. The obtained data indicate that the high turnover rate of PI cycle components, along with the presence of various fatty acids determining the physical state of the bilayer and its oxidation capacity, was associated with their active participation in regeneration processes under the action of IGF-1. The findings correlate with restoring functional activity in damaged somatic nerves in response to the drug. It was shown that because of the injury, nerve conductivity was significantly reduced in its proximal segment and completely lost in the distal segment of the nerve conductor. With an increase in the duration of the damaging effect up to 28 days, the recovery of action potential (AP) conduction originated from a summation of action currents occurring in many nerve fibers, with a small amplitude noted only in the proximal segment of the nerve, which is explained by the preservation of central innervation and partial restoration of neuromuscular transmission. In the experimental condition with damage, the amplitude of the AP decreased by an average of 1.4 compared with the control by day 28 of observation. In contrast, the intramuscular administration of IGF-1 at a concentration of 75 ng/kg was accompanied by a restoration of conductivity in the proximal nerve segment to an average of 1.5 times compared with the damage (Figure 9, Table 1).

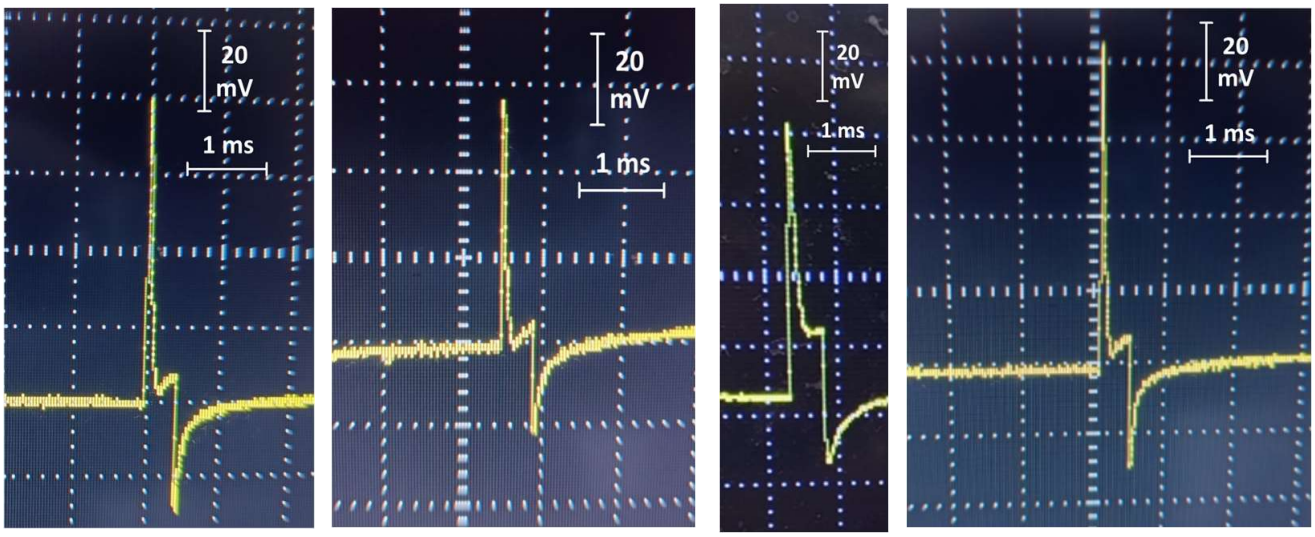

Figure 9. The AP of the rat sciatic nerve: (**A**) control nerve; (**B**) proximal nerve section 28 days after damage; (**C**) proximal nerve section 28 days after damage and administration of IGF-1 at a concentration of 50 ng/kg; and (**D**) proximal nerve section 28 days after damage and administration of IGF-1 at a concentration of 75 ng/kg.

Table 1. Parameters of the AP of the rat sciatic nerve (all error bars indicate a standard error of mean (n = 10).

Parameters	Control Nerve	Proximal Nerve Section 28 Days After Damage	Proximal Nerve Section 28 Days After Damage and Administration of IGF-1 at a Concentration of 50 ng/kg	Proximal Nerve Section 28 Days After Damage and Administration of IGF-1 at a Concentration of 75 ng/kg
Amplitude of AP, mV	80.00 ± 2.00	56.00 ± 2.00	80.00 ± 3.00	88.00 ± 3.00
Duration of AP, ms	1.00 ± 0.03	0.80 ± 0.02	0.80 ± 0.02	0.80 ± 0.03

4. Conclusions

This study revealed nerve transection to be accompanied by all forms of PI accumulation and a decrease in the DAG level in both proximal and distal segments of the nerve conductor. This is most likely explained by the inactivation of phosphoinositide-specific phospholipase C. Intramuscular administration of IGF-1 was shown to promote the intensification of PI metabolism, DAG accumulation, and decreased FFA levels. Our findings are consistent with the literature data indicating that IGF-1 can initiate several signaling pathways associated with forming lipid metabolites. One of these pathways is mediated by the activation of phosphoinositide-specific phospholipase C, leading to a decrease in the quantitative content of phosphatidylinositol-4,5-diphosphate. This signaling pathway regulates physiological functions such as cell growth, proliferation, and differentiation [20–22]. Additionally, the binding of IGF-1 to IGF receptor type 1 initiates the phosphatidylinositol-3-kinase signaling pathway, resulting in the phosphorylation of phosphatidylinositol-4,5-diphosphate to phosphatidylinositol-3,4,5-trisphosphate, which, in turn, stimulates cytoplasmic factor PDK1 (3-phosphoinositide-dependent protein kinase 1) in this signaling pathway, leading to Akt (protein kinase B) activation and increased

expression of various transcription factors necessary for axonal regeneration and recovery of the function of damaged somatic nerves [23]. The obtained data also correlate with the restoration of the ability of somatic nerves to conduct action potentials under the influence of IGF-1, indicating effective regeneration processes in the injured nerve conductors. Thus, IGF-1 promotes the intensification of PI metabolism in damaged somatic nerves through the activation of the signaling pathways mediated by phosphoinositide-specific phospholipase C and phosphatidylinositol-3-kinase, leading to the formation of lipid metabolites acting as active regulatory molecules necessary for the recovery of functional activity in damaged nerve conductors.

Author Contributions: Conceptualization, M.P. and V.R.; methodology, M.P., V.R. and E.C.; investigation, E.C., I.M., E.P. and A.Z.; data curation, M.P., E.C., E.R. and A.Z.; writing—original draft preparation, M.P.; writing—review and editing, V.R. and E.R.; supervision, V.R.; project administration, M.P. and V.R.; funding acquisition, V.R. and M.P. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The animal study protocol was approved by the Ethics Committee of the Ogarev Mordovia State University (Protocol No. 89 dated 12 September 2023) for studies involving animals.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data are presented within this study.

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