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Research Article

Bacterial Melanin Favors Regeneration after Motor Tract and Peripheral Nerve Damage

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Abstract. Experiments were performed on 48 albino rats. All experimental animals were initially trained to a balancing instrumental conditioned reflex (ICR). Unilateral bulbar pyramidotomy performed in 24 rats caused contralateral hemiparesis. On the next day following the operation 12 rats (first group) were injected intramuscularly with bacterial melanin (BM) solution. Recovery periods of ICR and paralyzed hindlimb movements were registered for melanin injected rats ($n = 12$) and for operated rats, not treated with melanin ($n = 12$, second group). In rats injected with bacterial melanin the posttraumatic recovery is shorter than in animals not treated with melanin. Morphohistochemical examination was carried out to confirm the results of behavioral and electrophysiological experiments. Medulla slices were prepared to trace the regeneration of nerve fibers. Examination of transection area revealed that bacterial melanin increases vascularization, dilates the capillaries in nervous tissue and stimulates the process of sprouting. Ischiadic nerve transection was performed in third and fourth groups of rats (12 rats in each group). Third group animals were injected with BM on the next day of surgery. ICR was used to assess the recovery of movements after nerve damage. Method for Ca^{2+}-dependent acidic phosphatase activity measurement was used to examine sections of nerve fibers and to trace the recovery of the nerve and limb movements after its injury. Acceleration of the instrumental conditioned reflex recovery and data from morphohistochemical study showed that bacterial melanin has neuroprotective action and facilitates recovery of limb movements after peripheral nerve or motor tract lesions.

Keywords: instrumental conditioned reflex; corticospinal tract; melanin; sciatic nerve damage, recovery of movements, morphohistochemical study.

1. Introduction

In the experiments on laboratory animals (white rats) with brain surgical trauma it was revealed that BM facilitated the recovery of instrumental conditioned reflexes after unilateral ablation of sensorimotor cortex that had caused paresis of limbs. Low doses of BM accelerated the recovery of physiological functions lost because of nervous tissue damage [1]. The proposed by us concept of the effect of bacterial melanin on regeneration of nervous cells is innovative and earlier has not been found in literature. The investigations of the past two decades have radically changed specialists' notion on inability of neurons of the central nervous system (CNS) to regenerate [2]. Key researchers in the field of neurobiology in their literary reviews consider in detail mechanisms of axon regeneration in mammalians' CNS [3], regeneration in the spinal cord [4], formation of glial cicatrix [5], neuroglia activation in the damaged brain [6], strategy of axon regeneration maintenance or assistance [6], regeneration of peripheral nerve subjected to damage [7].

These reviews also dwell upon the possibilities of application of physiologically active compounds regulating cascade of processes involved in nervous tissue regeneration and promoting optimization of this process. Agents catalyzing autooxidation processes are known to provoke some specific pathological symptoms: diskynesia, deafness, pigmentation disorders, skin ageing, inflammatory/fibrosis processes, arthritis, kidney lesions, cardiomyopathy, diabetes, *etc.* All these conditions are common for senescent organism [8] with decreased level of melanin pigment production [9, 10]. Melanin is believed to prevent the development of these symptoms. In this connection, the interest of researchers to melanin as potential pharmacological preparation is well founded. For the first time melanin-synthesizing strain with high level of pigment synthesis - *Bacillus Thuringiensis* was obtained. The ecologically safe technology of biosynthesis, isolation and purification of the bacterial melanin (BM) has been elaborated. High biological activity of melanin was shown both on animals and plants [1, 2, 11–13].

Reconstruction of injured peripheral nerves (PN) is one of the main problems of the modern reconstruction microsurgery. Injury of nervous system causes local reactions in damaged tissue including inflammation, ischemic necrosis, secondary destruction of cells and formation of scar. During the first two weeks axons poorly interact with Schwann cells. Their growth is blocked also by physical changes in microstructure of denervated distal segment [14]. "Crumpled bands of Bungner" are formed and exist for 18 months after the transection [15]. Evidently, nervous regeneration depends more on the application of cells and/or exogenous peptides, than on the most perfect microsurgical technique. That is why the application of physiologically active substances, regulating the cascade of de- and regeneration processes of nervous tissue, is important for the optimization of regeneration process. Damage of the peripheral nerve entails sprouting of motoneuron axons, activates growth factors, neurotrophins, and reaction of glia. Mentioned factors (growth factors, neurotrophins, other peptides) are used to induce rehabilitation efforts and for the treatment after peripheral nerve injury. Bacterial melanin was obtained from the mutant strain of Bacillus Thuringiensis in the Institute of Biotechnology in Armenia. Special attention was paid to the role of bacterial melanin in neurodegeneration [1]. Bacterial melanin has been used in experiments to show its effects on recovery processes after lesions of different CNS structures (corticospinal tract, rubrospinal tract, lateral cerebellar nuclei, sensorimotor cortex) [12]. Bacterial melanin accelerates motor recovery after CNS lesions [16]. We have therefore analyzed functional recovery following transection of rat sciatic nerve using i/m injections of melanin solution.

The objective of the current research is to study the effect of the melanin on axons regeneration in corticospinal tract after its transection and recovery of damaged peripheral nerve.

2. Materials and Methods

Studies were performed on 48 adult white mongrel male rats weighing 180–250 g. All animals were initially trained to an operant conditioned reflex. After the reflex elaboration 24 rats were subjected to unilateral transection of Pyramidal tract. Animals of third and fourth groups were subjected to Ischiadic nerve transection. On the day after surgery animals of the second and fourth groups were given i.m. bacterial melanin at the concentration 6 mg/ml. For administration of melanin, the volume of solutions of the corresponding concentrations given were determined by calculation from the optimally tolerated dose of 0.17 g/kg. Totally five groups of animals were used for the study:

The instrumental conditioned reflex (ICR) was developed as follows: rats were trained to balance on a slowly rotating (9 r/min.) horizontal bar of diameter 2 cm and length 30 cm, located at a height of 90 cm above a soft pillow. Training to the balancing reflex was assessed in terms of the time spent by the animal on the rotating bar, on which the animal balanced exclusively using the hindpaws, which they alternated. At the moment the rats were placed on the bar, they clung to it with their forepaws, but after establishment of body balance they lay calmly on the bar or hung freely from it. Trials were repeated 10 times daily, with intertrial intervals of 60 sec. The criterion for performance of the reflex was a time spent balancing on the rotating bar of at least 250 sec [17, 18].

After elaboration of ICR rats of third and fourth groups were anesthetized with Nembutal (35–40 mg/kg, i.p.) and underwent unilateral transection of n. Ischiadicus in upper femoral area,. ICR testing was resumed one day after the transection.

After elaboration of ICR rats were anesthetized with Nembutal (35–40 mg/kg, i.p.) and underwent unilateral transection of pyramidal tract [19].

After behavioral experiments, all experimental animals were anesthetized with Nembutal (45–50 mg/kg). Animals were decapitated under deep anesthesia, brains were removed and were then fixed in 5% neutral formalin in phosphate buffer (pH = 7.4). Sections of thickness 50–60 μm were then prepared for microscopy.

The morphofunctional state of cellular structures in the animals' medulla oblongata was assessed by performing histochemical and histoangiological studies. A histoangiological method was used to identify the microcirculatory bed [20] and a modified histochemical method was used to identify acid phosphatase activity [21], providing not only a rich morphological picture, but also an assessment of the functional state of the structures themselves.

After behavioral experiments animals of third and fourth groups were decapitated under deep anesthesia, proximal ending of ischiadic nerve was isolated then fixed in 5% neutral formalin in phosphate buffer (pH = 7.4). Thickness of sections prepared for the microscopy was 50–60 m.

The significance of differences on recovery of the operant conditioned reflex and morphometric data was assessed using Student's *t* test.

3. Results

In rats of the first and second groups the instrumental conditioned reflex before the operation was elaborated in 2.5±0.8 days. In transected rats, recovery of conditioned reflex after the operation took place in 4.1±0.4 days, whereas in rats, initially trained to ICR and dosed with BM, the recovery of ICR occurred in 1.75±0.95 days (Figure 1). Balancing movements of paralyzed hindlimb recovered in 15,5-17 days in transected rats without treatment and in melanin injected animals after the transection hindlimb movements recovered in 2-4 days. When balancing on the rotating bar the animals usually balance using more their hindlims. Recovery of balancing hindlimb movements is considered complete when the rats balance with hindlimbs continuasly for 250 seconds.

In the first and second groups morphohistochemical study was conducted after the completion of electrophysiological experiments, 6–7 months after the transection. Longitudinal brain sections were prepared in order to track the fibers in the lesion area. 6 rats were selected randomly from transected animals without treatment and 6 transected rats with melanin treatment were also randomly selected. Sections from melanin treated groups were compared with sections from groups transected but not treated with melanin. In morphohistochemical study a new method for detection of Ca^{2+} dependent acid phosphotase was applied, which gives not only an adequate morphological picture, but also an opportunity to study the metabolism of examined structures [21].

Results of morphological examination revealed complete demyelination in lesion area of operated rats not treated with melanin (Figure 2A and 2C) and number of necrotic sites. (Figure 2B). In transected rats not treated with melanin glial cell proliferation leads to scar formation in transection site. On both sides of the scar in lesion area tortuous, swelled and decomposed nerve fibers were revealed. Activity of creatine phosphate is very low in the scar and it has a flat *white line* appearance (Figure 2A). Degenerative changes of nerve cells were apparent. Neuronal cell bodies were massively swollen, the cellular processes were not revealed, few lead phosphate deposits were identified in pericarya. Most of the deposits lyse and thin stria remains along the margins of cell body. Cell nuclei were not revealed. These processes were more explicit in large motoneurons and were revealed clearly in neurons located distally from the transection area. (Figure 2D). Another factor that supports the regeneration is increased vascularization, which in turn reduces scar formation. The possibility of fiber growth in CNS along the newly formed blood vessels was suggested also by other researchers [22]. The growth of new vessels predetermines

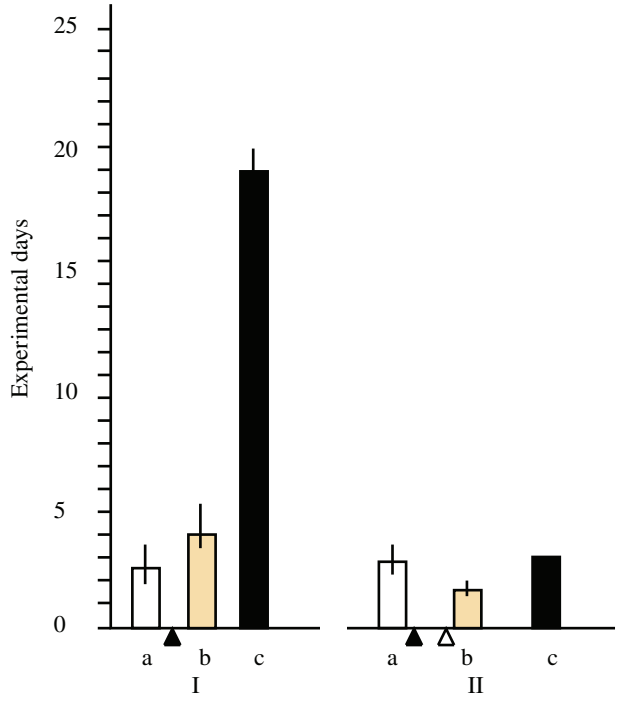

Figure 1: Histogram of instrumental conditioned reflex elaboration and recovery in experimental days. (a) Elaboration of ICR before the operation, (b) recovery period of ICR after the operation and (c) is the recovery period of paralyzed hindlimb movements. Black arrow indicates the operation day, white arrow shows the day of BM injection.

intensity of proliferation, differentiation and formation of new cellular structures.

After complete elaboration of the ICR unilateral transection of sciatic nerve (n. Ischiadicus) was performed in third and fourth group rats. On the next day after the operation part of the animals was injected intramuscularly with the bacterial melanin solution at a concentration of 6 mg/ml. The concentration was determined by calculation from the optimally tolerated dose of 170 mg/kg. Two days after the operation clinical testing was performed to check the animals' ability to use the operated limb in locomotion. Then the ICR testing was resumed, and the process of its recovery was studied in postoperative experimental testing. The testing showed that all animals on the third day after the transection of sciatic nerve started using the operated hind limb in locomotion. Both, the control rats and animals administered with bacterial melanin used the operated limb in locomotion, putting it on the floor and holding the paw vertically to the floor. The hind limb and paw phalanxes were paralyzed in all rats. In that time period movements of rats administered with bacterial melanin were faster compared with control animals. The control animals were trying to put their knee on the rotating bar, but without success, and in 5–10 seconds they were falling down. Rats injected with BM were able to put their knees on the rotating bar, but in 10 seconds the limb

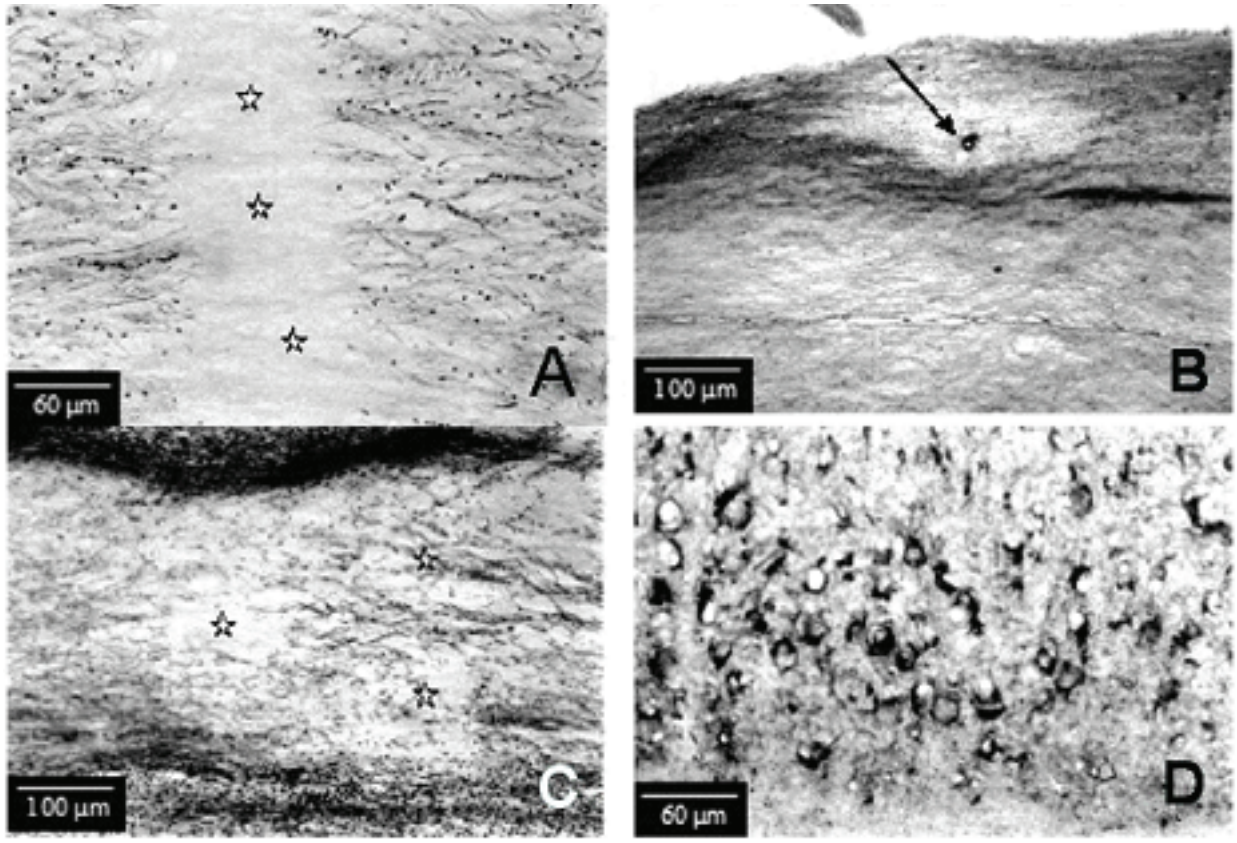

Figure 2: (A–D) Brain stem horizontal sections of pyramidotomized rats, not treated with melanin (white arrow indicates the area of transection, the rectangle shows fibrous scar); (A–C) Picture of demyelination (arrow indicates focus of necrosis, asterisks show area where nerve fibers are not revealed); (D) A distal area of spinal cord where extreme swelling of motoneurons was revealed. Detection of Ca^{2+}-dependent acid phosphatase activity.

slid of the bar and hanged down. However these rats kept the balance on the rotating bar for considerably longer period (30–50sec.) than control animals. Moreover, for the whole testing period they were trying to put back the hanging limb. Not always the animals succeeded in their efforts to hold the operated limb on the bar, and after balancing on the bar for 100–120 seconds they were falling down. Paralyzed paw and phalanxes of rats administered with melanin became active after the 23-rd experimental day, and after 54 testing days (testing the animal 10 times daily) balancing movements of the operated hind limb were close to normal. At that time the animals were able to hold the limb on the bar and put the phalanxes on it, only for some short episodes the limb slid of the bar, but the rats were able to put the limb back keeping the balance till the testing period was over (250 sec.).

The testing time period of the ICR for the control animals, or the balancing time for their injured hind limb in 54 testing experiments gradually increased, but the activity of the paw and phalanxes wasn't changed. The paw and phalanxes gradually became atrophied and at the end of the experiments were almost shriveled.

Thus, the criteria for the recovery of motor activity of hind limb after the transection of sciatic nerve were not only the rat's ability to hold the injured limb with paw and phalanxes on the rotating bar but also to keep balance by moving them. Only the animals injected with BM managed to complete the task, whereas in control rats the balancing movements of injured limb didn't recover for the whole period of study.

After the completion of behavioral experiments all experimental animals were anesthetized with Nembutal and sciatic nerve was dissected. From dissected sections microscopic preparations were made for morphohistochemical study. Analysis of morphohistochemical data revealed absence of regeneration processes in transection area of control animals (Figure 3A). As a rule, the distal segment has a stub end, because of necrosis and destruction of afferent and efferent fibers, separated from cell bodies. After the nerve transection secondary degeneration occurs, characterized by diameter irregularity of nerve fibers, structural changes in the form of swelling and delamination in number of fibers.

Thickening, convolution, vacuolization and in some areas fragmentation is revealed in axons. Along with degeneration processes, at the nerve proximal segment insignificant proliferation of Schwann cells was revealed. Cell mass is formed around the transected nerve ending, which has a smaller size and progressively narrows, but never reaches the

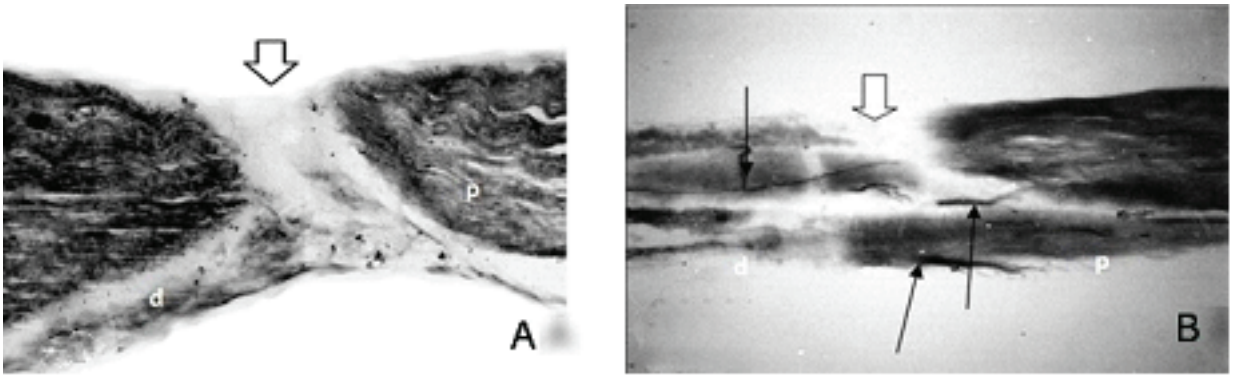

Figure 3: Longitudinal sections of sciatic nerve of a control (A) and bacterial melanin injected (B) rats prepared 2 months after the transection (transection area – white arrow; D – distal and P proximal parts of the transected nerve; black arrows – blood vessels). Method for the eduction of Ca^{2+} dependent acid phosphotase. Magnification power: oc.10, ob.6,3 (A); 2,5 (Б).

distal segment and especially doesn't grow into it. Influence of bacterial melanin preserves the enzyme activity along almost the whole length of the nerve, with an insignificant prevalence in proximal segment (Figure 3B). In the area of compression random alternation in the activity of creatine phosphate is revealed, which is manifested with weak or strong staining of nerve fibers. In the middle and distal parts dilated blood vessels respond. Morphohistochemical data of the present study indicate that the influence of bacterial melanin induces regenerative efforts in damaged peripheral nerve.

4. Discussion

The data obtained on the recovery times of the instrumental conditioned reflex and balancing movements in the paralyzed limb after transection of pyramidal tract in animals of the first and second groups lead to the conclusion that melanin plays a clear protective role, accelerating compensatory recovery in central nervous system after trauma. Other investigators have observed similar effects in studies of the effects of melanocyte-stimulating hormone [23]. The effect of bacterial melanin in the brains of experimental animals appear to be the primarily enhancement of trophic processes due to improved vascularization, which promotes rapid restoration of impaired motor functions. Recovery of instrumental conditioned reflexes after unilateral transection of bulbar Pyramids also started in animals not treated with melanin, but limb movements here recovered very late. The main reason for recovery of movement deficit in transected rats, not treated with melanin, is believed [12, 18, 24] to be the ability of the corticorubrospinal tract to take over the functions of the lesioned corticospinal tract. These two motor tracts interact via numerous branches at the cortical and stem levels and also have projections to several spinal cord levels [12]. When transection was followed by removal of the inhibitory influence of the pyramidal tract on the corticorubrospinal pathway, the rubrospinal system, by means of rubro-olivary projections [18], assumed the control, supporting the performance of the previously acquired operant reflex, thus compensating for the function of the corticospinal tract. Thus, the different recovery periods of the operant conditioned reflex in transected animals treated and not treated with melanin provide evidence of acceleration of this process as a result of treatment with bacterial melanin. It remains possible that this involves acceleration of the processes of sprouting and new synapse formation [25].

Recovery of instrumental conditioned reflexes after unilateral transection of sciatic nerve also started in animals not treated with melanin, but limb movements in this group didn't recover and rats were not able to complete the ICR task. Thus, the different recovery periods of the operant conditioned reflex in animals after Ischiadic nerve, transection treated and not treated with melanin, provide evidence of acceleration of recovery process as a result of treatment with bacterial melanin. It remains possible that this involves acceleration of the processes of sprouting or nerve invasion. Morphological results from the sections of experimental animals also showed that administration of the melanin doses used here with the aim of facilitating clinical recovery after peripheral nerve damage probably involves activation of a whole series of trophic processes favoring regeneration [26]. The main challenge in the facilitation of nerve regeneration is the prevention of scar tissue formation in lesion area [27]. Melanin stimulated vascularization, caused dilation of capillaries. Nerve sections of melanin treated animals contained more newly developed nerve fibers and less scar tissue than the sections of control rats. Thus, bacterial melanin appears to improve directional growth of regenerating axon sprouts and the therapeutic application perspective needs further study.

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