

## PART II

# Study of the Mechanism of Action of Eleutherococcus Extract

### SOME ASPECTS OF THE MECHANISM OF ACTION OF ELEUTHROCOCCLUS EXTRACT

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#### **1. BIOLOGICAL ACTION RANGE OF ELEUTHROCOCCLUS EXTRACT**

Adaptogens (primarily eleutherococcus extract), are the main remedies of the pharmacology of health. Adaptogens as well as muscle exercise can speed up the transmission of energy and positive information that provide for the optimization of the energy and plastic potential of the tissues. Raising the level of the physiological adaptation still more, they promote rapid mobilization of the body's energy and plastic resources under extremal conditions and their rapid recovery following stress.

Numerous experimental data on the adaptogenic action of eleutherococcus were supported by extensive surveys over the health status of large population groups at big enterprises of the Soviet Union.

These data have been already presented in this collection. It should be indicated, in addition, that the data by Galanova (1977) and subsequent research performed by this author at the Volga Automobile Plant in Togliatti made it possible to carry out further observations of 3000 truck drivers performing long-term interurban runs. The systematic intake of eleutherococcus for 6 years progressively reduced disease incidence. As compared with 1973, the incidence of influenza in 1979 reduced 15 times, that of hypertension 10 times and of ischemic heart disease 33 times. At the same time, certain physiological functions improved: the latent time of the visual and motor reactions dropped, the number of errors decreased, attention improved, which is very important for traffic safety. As regards subjective sensations, the test subjects noted that eleutherococcus intake improved the well-being and working

capacity, favoring a less painful settling of disputed matters at work and at home.

Patients experience acute or chronic stresses more frequently. Therefore the administration of eleutherococcus to them is fairly desirable. The literature contains much data on a beneficial effect of eleutherococcus extract used in combined treatment of patients suffering from neurasthenia, chronic brain injuries and some other illnesses. This drug is successfully used for the preoperative preparation of surgical patients, including those with cancer. It is known that operation injury provokes severe stress, which promotes metastasis of malignant tumors in oncological patients (Yaremenko and Mokalik, 1978). Eleutherococcus extract in combination with radiotherapy was successfully employed for the treatment of lip carcinoma, and in combination with radical surgery, radiotherapy was successfully employed for the treatment of lip carcinoma, and in combination with radical surgery, radiotherapy and antitumor drug thiophosphamide for the treatment of breast cancer (Gvamichava et al., 1966). The ability of eleutherococcus preparations to speed up the recovery of energy and plastic resources after experimental stressful effect is successfully realized by administering the extract to patients convalescing after different illnesses, surgical interventions, tuberculosis, infectious diseases, etc.

The concepts of modern medicine of causal therapy do not grasp the broad range of the biological action of eleutherococcus extract. This circumstance demanded the large-scale research into the mechanisms of its physiological action.

Study of eleutherococcus by the classical pharmacological methods in acute experiments on animals or on isolated organs did not provide any substantial data explaining the wide range of the drug biological action. In the pharmacology of

eleutherococcus, attention should be called to its regulatory effect on different body's systems with functional shifts. It has been demonstrated, in particular, that eleutherococcus extract increases the duration of the animals' muscle work and that glycosides obtained from the roots of this plant are more active than extract by a magnitude of about two orders. It has also been demonstrated that after eleutherococcus intake the muscle work is attended with less losses of glycogen, creatine phosphate and protein nitrogen. At the same time mobilization of lipids is accelerated (Dardymov, 1976). All these data suggest that regulation of energy and plastic supply underlies the biological action of eleutherococcus drugs.

It is known that any functional activity requires high expenditure of energy and plastic resources therefore the ability of eleutherococcus to regulate the most important processes forms the scientific basis of its wide biological action range. It has been shown, in particular, that the muscle load (swimming for 15 min) provokes inhibition of the RNA-polymerase reaction and 50%-decrease of the biosynthesis of messenger and ribosomal RNA in the rat liver. This is accounted for by the competition for energy between biosynthetic processes and functional muscle activity. Pretreatment with eleutherococcus speeds up twice as much recovery of normal biosynthesis of nucleic acids.

## **2. EFFECT OF ELEUTHEROCOCCUS ON THE BASIC ADAPTATION REACTION**

Since the action of eleutherococcus on the body is non-specific, the sites of application of its glycosides should be investigated in the non-specific reactions. The basic adaptation reaction (BAR) of Selye is the most convenient model for studying the adaptogenic action of eleutherococcus. The stress reaction is readily graded, the functional changes in its different phases are studied well, and, what is more important, any disease passes to a certain degree, through one or another stage of the BAR.

It has been demonstrated that 15 min after administering eleutherococcus drugs to fasting rats blood glycemia increases with a subsequent decrease in liver glycogen; the concentration of

lactic and pyruvic acids in muscles, and oxygen consumption by intact rats also increase (Dardymov, 1976). These facts show that eleutherococcus drugs activate glycolysis and are apparently accounted for by the adrenal-glucagon effect of eleutherococcus glycosides to stimulate calcium transport to mitochondria. It should be noted that in experiments on intact animals the adrenal-glucagon reaction to eleutherococcus drugs are not so marked and rapidly disappear. This effect is more substantial and stable in the initial period of activation of the adrenal-glucagon reactions with the aid of additional exposures. In particular, within the first 30 min after injection of adrenaline (20ug/kg) to rats pretreated with eleutherococcus, there is the more rapid and more significant increase in blood sugar than in the control group.

The adrenal-glucagon action of eleutherococcus has also been demonstrated in the other version of experiment. One hour after insulin was administered to rats (1 unit/kg) blood sugar reduced by 90%. When insulin was combined with eleutherococcus, the level of glycemia reduced by only 50%, i.e. eleutherococcus exerted a permissive action relative to adrenaline.

In the initial period of the stress reaction hyperglycemia is linked with both the adrenal-glucagon reaction and activation of the hypothalamus-pituitary-adrenal system. In suspension of rats (30 min) blood sugar increased by 9%, whereas that in animals given eleutherococcus extract (1ml/kg) by 27%. At the same time eleutherococcus activated mobilization of liver glycogen.

The poststressor action of eleutherococcus was also discovered in direct experiments. It was demonstrated that in suspension of rats by the skin fold on the neck (30 min) the concentration of 11-hydroxycorticosteroids in the peripheral blood increased 4-fold. In eleutherococcus pretreated rats exposed to this type of stress, the concentration of 11-hydroxycorticosteroids increased 5-fold.

The data presented indicate that in intact animals, eleutherococcus extract provokes a moderate adrenal-glucagon action which is potentiated at the very beginning of the alarm reaction and is apparently linked with its permissive action with regards to the peripheral effects of adrenaline and adrenocorticotrophic hormone.

The data are available that the adrenal-glucagon effect of eleutherococcus may also be realized by

activating the adenylate cyclase system (Bezdetk et al., 1980).

At the height of adrenaline-induced hyperglycemia or in the pronounced alarm reaction, eleutherococcus produces an opposite effect. Under adrenaline-induced hyperglycemia or hyperglycemia induced by stress (at the 60<sup>th</sup> min of suspension), eleutherococcus reduces blood sugar and somewhat prevents glycogen losses by the liver. Upon suspension of the animals (15 h) the concentration of blood 11-hydroxycorticosteroids increased 3-fold, whereas under stress preceded by eleutherococcus intake the concentration of corticosteroids increased only 2-fold, i.e. one could see an unusual antialarm action in eleutherococcus.

In other experiments, eleutherococcus extract was administered to rats prior to one-hour swimming, the temperature of water being 24°C. The animals were sacrificed shortly after swimming. The drug was shown to produce no substantial effect on the content of adenosine 3.5-cyclic monophosphate (cAMP) and guanosine 3.5-cyclic monophosphate (cGMP) in the liver, muscles and blood. However, one hour after swimming the content of cAMP in the liver and blood of rats given eleutherococcus exceeded control by more than two times, while that of cGMP in the muscle and liver by 2-2.5 times. It can be concluded that following severe stress eleutherococcus enhanced both catabolic and anabolic processes.

Eleutherococcus reduces the cAMP/cGMP ratio, thereby predetermining the body's response to stress according to the "cholinergic" type, with the predominance of anabolic process over catabolic ones.

Therefore, in the second phase of the functional load, when the adrenal-glucagon reactions and reactions on the part of the hypothalamus-pituitary-adrenal system exceed the optimal level, corresponding with the animals' status, eleutherococcus enhances insulin-like reactions.

The permissive action of eleutherococcus glycosides with regard to insulin is realized in the peripheral tissues at the expense of glucose transition via the cell membranes and its phosphorylation by hexokinase, one of the slowest components in glucose utilization chain.

It was demonstrated that at diverse stressful exposures, blood  $\beta$ -lipoproteins acquire the inhibitory properties relative to glucose metabolism. As is the case in diabetes mellitus.

Eleutherococcus glycosides prevent the inhibitory action of  $\beta$ -lipoproteins isolated from plasma of the stress-exposed animals on the isolated diaphragm of intact rats *in vitro* and yeast hexokinase.

In the stage of exhaustion during which animals demonstrate a catastrophic decrease in the energy and plastic resources and atrophy of the adrenals, eleutherococcus drugs still continue to maintain functioning of the hypothalamus-pituitary-adrenal system at the optimal level and prevent depletion of energy and plastic resources. In effect eleutherococcus prolongs the stage of resistance both at the expense of reduction of the alarm reaction and the stage of exhaustion. The action of eleutherococcus drugs on stress may be illustrated by the principal scheme.

The effect of eleutherococcus drugs on the BAR depends on the intensity and duration of a stressful exposure. In the initial alarm reaction marked by induction of catabolic reactions eleutherococcus enhances them. In full development of the alarm reaction, when anabolic and insulin-like reaction are induced, eleutherococcus also enhances these reactions. The presence of the crossing over points explains why different authors sometimes obtain contradictory results. If the effect of eleutherococcus on the BAR is not investigated over time and is fixed only within one to two time intervals, the probability is high that the researcher may discontinue experiments and sacrifice animals near points "a" or "b" thus failing to detect any influence of the adaptogen on the functions under study.

It should be mentioned that the zones adjacent to points "a" and "b" are fairly wide. In particular, during suspension of rats for varying times, zone "a" lasts minimum from two to six hours, whereas under other exposures for longer. For example, under 90-day hypokinesia, zone "b" lasts 10-15 days, i.e. the experimenter, working in this zone, will not see any effect of eleutherococcus, like in experiments on normal adult animals in the absence of any hormonal induction.

The discovery of an unusual antistressor action produced by eleutherococcus drugs in the alarm reaction frequently gives rise to the question whether

the drug reduces the body resistance, since the BAR is a protective reaction. It has been demonstrated in numerous experiments that eleutherococcus drugs increase the non-specific body's resistance, in particular, muscular working capacity of animals (Brehkman and Dardymov, 1966). In other experiments, rats were first exposed to stress (suspension for 24 h) and then were placed for 5 min into a thermostatically controlled box at air temperature of 70°C. The experimental rats received subcutaneous injections of total eleutherococcus (5 mg/kg) five times during the entire stressful exposure. It has been demonstrated that at high temperature all the animals (intact and exposed to stress) developed clonic seizures and only 43% of the animals given eleutherococcus.

A decrease of the level of the alarm reaction caused by eleutherococcus and

concurrent increase in the animals' resistance to additional damaging exposures are explained by the fact that eleutherococcus does not block stress reaction but improves energy metabolism of the working tissues primarily at the expense of the insulin-like action. The drug creates conditions under which the necessity of high activity of the hypothalamus-pituitary-adrenal system no longer arises and thus the stressful reaction decreases by itself, automatically, according to the feedback mechanism.

The capacity of eleutherococcus to regulate automatically the body's physiological functions depending on its requirements is a unique property of the adaptogens. This ability explains a wide range of the non-specific action of eleutherococcus, the normalizing effect pattern, and demonstrates the drug safety.

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