ISSN: 2573-9514

Research Article

Journal of Addiction Research

Biological Mechanisms of Increasing the Resistance, Physiology of Progredient Adaptation and Validation of the Organism's Dependence on Psychoactive Substances

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Submitted: 25 July 2018; **Accepted**: 30 July 2018; **Published**: 13 Aug 2018

Summary

The article shows that the current level of physiology does not explain the biological mechanisms of the organism transition from one adaptation range to a higher one, with an increase in the strength of the regular stimulus above the sub-extreme level. A new trend in the physiology of adaptation - proqredient adaptation - explains the mechanism of increasing the resistance of the organism with dependence on psychoactive substances (PAS). It is scientifically proved, that dependence of the organism on PAS is not the disease, but the state of proqredient adaptation.

Keywords: Hypertrophy of The Neuroendocrine System, Proqredient Adaptation.

Urgency of the issue

It is known, that at the peak of dependence on any psychoactive substances (PAS), a person, for example, an opium (heroin) addict, uses doses, which are multiple times, almost 10 times, higher than the lethal dose for an ordinary person [3, p.23].

The fact that the drug user does not die is explained by the increase in the body's resistance in response to the increase in the dose of PAS [3, p.25].

But urgent issues of medicine are not only disclosure of the mechanisms of increasing resistance, but also validation of the physiological process occurring under the influence of increasing doses of psychoactive substance and the responsive increase in the body resistance in PAS dependence.

Purpose and objectives of the study:

Adaptive responses of the organism under regular exposure to a sub-extreme stimulus. Lack of adaptive responses of the body already known in physiology to explain the adaptation mechanisms in response to a further increase in the regular stimulus strength above the sub-extreme level in PAS dependent patients.

The pronounced responses by the vegetative nervous system (VNS) in PAS dependent patients indicate the vegetotrophy of most of these substances. Power of their influence is closest to the sub-extreme level. Responsive adaptive reactions of the organism under regular influence of the external factor of the average to sub-extreme strength were studied by L. Kh. Garkavi and co-authors [4, p.77]: Under the influence of sub-extreme stimuli, an activation reaction with the stages of primary and persistent activation is produced, indicating a higher activity of protective systems. The stage of persistent activation is true active resistance, which is stable and long enough - up to six months - in contrast to the training reaction and in the absence of constant exposure [4, p.79].

But in PAS dependence, the process does not result in the reaction of persistent activation; the dose to which the adaptation has been produced is habitual and results in no euphorizing effect.
To achieve neurophysiological shift sufficient for euphoria, a large dose is required.

But increase in the dose of PAS after the activation reaction is stressful for the organism. Stress in its development has three stages.

The first stage is the "anxiety reaction", the second one is the stage of resistance, when hypertrophy of the adrenal cortex with a steady increase in the formation and secretion of corticosteroids develops. They increase the amount of circulating blood and blood pressure, have an antihistamine effect, enhance gluconeogenesis, normalize physiological response, etc. The resistance of the organism to the stimulus increases. Prolonged exposure to the stimulus results in the stage of exhaustion, and death may occur. Doses of PAS above the stress level are lethal [1].

L.Kh.Garkavi and co-authors showed that: "the reactivity of the organism is represented by a number of floors (ranges), which does not exceed ten. In each floor: a weak stimulus causes the training reaction, an average sub-extreme stimulus - the activation reaction, a strong stimulus – the stress. The ranges are separated by the zone of non-reactivity, when increasing the stimulus level above the stress one or decreasing below the training one causes no reaction. Transition to the next range shows again the same order of reactivity: the reactions of training, activation, and stress [4, p.77].

But L.Kh.Garkavi and co-authors could not explain the mechanisms providing non-fatal transition of the organism from one floor (range) of adaptation to a higher one, after the reaction of primary and persistent activation and further enhancement of the effect above the sub-extreme, stress and higher levels.

Indeed, according to pathophysiology, without such adaptation mechanisms increasing the resistance, the body must die from "exhaustion", from failure of adaptation mechanisms, when the organism transits from the first adaptation range to the second. But this is not observed in a PAS dependent people. This indicates failure of the current level of physiology to explain the mechanisms providing the body transition from one adaptation range to a higher one.

In the history of narcology, attempts were made to explain the increase in resistance and the accelerated disintegration of PAS in the addict's organism by different causes. They are the occurrence of the state of chronic stress, activation of other states inactive in normal conditions or activation of systems that fulfill other functions, but with an increase in a PAS dose are forcedly involved in detoxification, etc. But all those assumptions have not been scientifically confirmed.

No matter how full modern scientific research explain qualitative changes at the cellular and molecular level that lead to an increase in resistance in PAS dependent patients, it is clear that these changes can only be of adaptive, not pathological and damaging nature, otherwise they would lead not to an increase in resistance, but rather to a decrease in it, and the body would die since transition from the first floor of adaptation to the second [2]. Also, according to the dialectical principle of the mutual transition of qualitative changes to quantitative ones, accumulation of these changes should lead to qualitative and quantitative changes in the neuroendocrine system (VNS, internal secretion glands) which is responsible for the adaptation of the whole organism.

I would like to quote L.Kh. Garkavi, E.B. Kvakina, M.A.Ukolova - "it is possible to investigate separately the changes in any one system or at any one level, for example, molecular. But this is only a part of the changes in the overall complex reaction of the body. " Also I would like to quote I.N. Pyatnitskaya.

"Integral functional reactions to the intoxication of physiological systems are known to be no less important in maintaining homeostasis than biochemical protection" [5, p.58]. Consequently, we can speak about change of the body's response to a drug. "

Object and methods of investigation:

Features of the response of the neuroendocrine system to any external stimulus. Capacity of the neuroendocrine system for positive trophic changes. Hypertrophy and hyperfunction of the neuroendocrine system are histological and biochemical evidence.

The response of the body to any change in the internal environment depends primarily on the functional state of the VNS.

Thus, the reason of the altered reactivity of the organism and a steady increase in the overall resistance of the organism, should be sought in the central mechanisms of adaptation - in the neuroendocrine system.

The increase in resistance of the PAS dependent organism can be explained by the functional tension of the VNS and by the reaction of persistent activation only within one adaptation range. It is good health, physical activity, increased protective capacities of the body to various hazards - hypothermia, etc., which are clinically observed in the prodroma and possibly in the initial stage of alcohol dependence.

But VNS tension and the reaction of persistent activation fail to explain the transition from a lower to a higher adaptation range under PAS exposure above sub-extreme level and its further increase! After all, in such a situation, the body must experience stress with exhaustion and death! This can only be explained by the transcendental functioning of the neuroendocrine system, which can be possible only due to its adaptive hypertrophy, in response to the regular exposure to the external factor [3]. But is it possible? According to the theory of physiology of the development of interrelations between the structure and the function, in the course of ontogenesis (individual's development), functional activity is of particular importance and it is stimulated by the flow of stimuli affecting the organism as a result of changes in living conditions. Functional activity is the leading factor causing adaptive reactions in the body up to the development of morphological changes. Morphological changes occur in organs or systems stimulated by a flow of stimuli more regularly.

Even in the early 1800s, J. Lamarck suggested that "the work builds up the organs". P. Lesgaft's merit was the explanation of a specific morphological alteration of the organism during the exercise process. V.Ru showed that due to "trophic stimulation" in the working organ, the assimilation process begins to dominate over the dissimilation process, and morphological changes occur at the physiological level. The increase in energy reserves results in an increase in working efficiency.

It can be argued that the regular use of PAS - addressing the high response range - leads the entire body to the state of the activation reaction - hypermetabolic state, which does not contribute to the accumulation of reserves and the occurrence of positive trophic changes in the body. But one should remember that the hypermetabolic state develops in the "metabolic boiler" - at the level of tissue adaptation mechanisms [2, p.500]. Perhaps in the higher adaptation mechanisms - the neuroendocrine system-despite their tension, there are no hypermetabolization processes, which contributes to the accumulation of reserves leading to morphological changes in the neuroendocrine system in the form of hypertrophy, are there?

The observations of L.Kh. Garkavi and co-authors indirectly proves possible accumulation of reserves in the neuroendocrine system during the activation reaction; "Although the metabolism is highly active during the activation reaction, it is characterized by an equilibrium" [4, p.79], since to ensure "equilibrium" of constantly growing metabolic processes, a "powerful" neuroendocrine system is necessary.

But in PAS dependence, after the completion of the activation reaction and in further enhancement of the stimulus above the sub-extreme level and transition to the subsequent adaptation floor, the "equilibrium" of the metabolic processes takes place. But this is possible only when the functional adequacy of the vegetative

and endocrine systems grows in direct proportion to the strength of the external factor, which is possible only with hypertrophic neuroendocrine system and, as a consequence, its hyperproductivity.

Hypertrophy of VNS is evolutionally provided by the functional mechanism contributing to the accumulation of reserves - "advanced excitation" described in the 1930s by P.K. Anokhin: VNS responds to any stimulus with a somewhat excessive neurotransmitter ejection, as if in anticipation of possible future high consumption. VNS through neurotransmitters activates auxiliary and tissue adaptation mechanisms, and due to excesses of neurotransmitter ejection "takes a break" for its own recovery trophic processes [4]. Although the VNS regulates all the processes in the body, it has been established that there are biologically active substances produced by different cells of the organism that have a trophic effect on VNS itself. One of such substances is the nerve growth factor (NGF) - an insulin-like substance that stimulates the growth of sympathetic ganglia. NGF is produced in the salivary glands by the smooth muscle fibers of the walls of internal organs. Similarly, the adaptive-trophic effect on VNS is provided by neuropeptides: liberins, somatostatin, enkephalins, endorphins, bradykinin, neurotensin, cholecystokinin, ACTH fragments, oxytocin [5, p.251].

"When excited in neurons, metabolic processes are intensified, the amount of RNA increases, and the synthesis of proteins in neurons is enhanced. In neurons and glia cells surrounding them, these processes are multidirectional. RNA in nerve cells is increased due to the enhancement of its synthesis in a neuron and due to the transport of RNA from glial cells to neurons "[6, p.250].

Adaptation, positive, trophic changes lead to hypertrophy of the vegetative nervous system, which makes it hyperproductive and allows adequate response to the increasing influence of PAS by the increasing release of mediators.

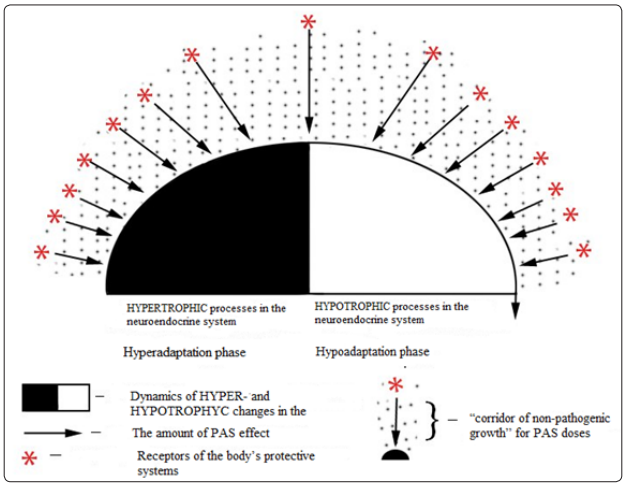
Histological evidence of VNS hypertrophy with regular exposure to a medium-strength stimulus is Selye's stress research: "adrenal glands bloom" (the adrenal medulla is a modified sympathetic ganglion) [2, p.525]. There is no doubt in the VNS hypertrophy and in the activation reaction, since the process of adrenal hypertrophy is not spasmodic. There is no doubt that due to the mechanism of "advanced excitation", the internal secretion glands "takes a break" for trophic recovery processes, which leads to their hypertrophy and hyperfunctionality.

As early as in 1930s, it was found that chronic morphinization causes hypertrophy of the cortical layer of the adrenal glands in rats, which produces the "adaptation hormones" - glucocorticoids (hydrocortisone, cortisone and corticosterone), increasing the resistance of the organism to intensive stimuli [3, p.260]. Evidences of adaptive hypertrophy of the endocrine system are L. Kh. Garkavi and co-authors' observations under conditions of training and activation reactions – enlargement of the thymus gland and adrenal cortex, a prolonged increase in the thyroid and reproductive gland functions [4, p.78].

Results of the study and their discussion

Thus, under the regular exposure to PAS as a sub-extreme stimulus, while hypermetabolic processes occur in the "metabolic boiler," accumulation of reserves takes place in the neuroendocrine system, as a result of "advanced excitation". This accumulation of reserves leads to adaptive hypertrophy and hyperfunction of the neuroendocrine system, which results in an increase in the general and specific resistance of the organism to a certain PAS.

That is why, a subsequent, increasing, potentially extreme dose of PAS has a sub-extreme non-pathogenic effect on the body. The condition persists for the further adaptation (see the figure below).



Thus, in PAS dependence, in each range and in the transition to a higher adaptation range, one should speak not of the reaction dyad: activation and persistent activation, but of the reaction tetrad: activation, persistent activation, then stress with "anxiety reaction", and the stage of resistance. And the hypertrophy of the neuroendocrine system that has developed to this moment, does not allow development of the final stage of stress - exhaustion. With an increase in the dose of PAS and transition to another range, everything comes around. It is more correct to call such a process a state of not chronic, but regular, unfinished stress. Stress without the exhaustion stage, no matter how regular it is, cannot be considered as a disease. That allows the body to transit to a higher range of adaptation without death. It becomes clear that increased resistance in persistent activation reaction responding to regular sub-extreme exposure to PAS and the resistance stage in stress responding to the further regular exposure to an increasing dose of PAS are functional manifestations of adaptive hypertrophic changes in VNS.

This process is called progredient (or progressive) adaptation. Beliefs about the unity of form and function, the stereotyped thinking that "if changes in the body are acquired and irreversible, therefore, they are pathological," have led to the erroneous judgment that the body's dependencies on PAS should be considered as diseases. There is the expression "any disease is an adaptation." But the opposite statement that "any adaptation is a disease" in relation to PAS dependencies is inadmissible. It is because neither failure, lack of adaptive capabilities, necessity of compensation for the adaptive capabilities of the body at the expense of any tissues or body systems is observed, nor the disease develops resulted from hypertrophy of the neuroendocrine system and its high adaptive sufficiency leading to an increase in general and specific resistance. Thus, the adaptive possibilities grow in direct proportion to the increase in the dose [5]. The role of the receptors of the body's protective systems indicating possible overdose of PAS is also important (- in the figure), as well as the experience of narcotization.

Due to the vegetotrophic nature of PAS, in PAS dependencies, the

mechanism of PAS action, in contrast to the disease, is also different. Common pathogenic factors – without pronounced vegetotrophy - cause damage at first, and only then a protective reaction of the organism develops. PAS, simultaneously or primarily, affect the receptors of VNS, which causes its timely or even advanced reaction to possible damage from the PAS effects. The increase in the exposure dose occurs through the "non-pathogenic corridor" - between the body's protective systems and the timely responding, hypertrophic neuroendocrine system (see Fig.2). That is why the acquired biological changes in PAS dependence are only of adaptive nature. One should talk about adaptively changed reactivity, about the adaptive attraction to PAS or, conversely, about the readaptation - deprivation syndrome, about adaptively changed behavior, and so on.

In the final stage of the dependence (see figure), depletion of the adaptive capabilities of the organism, due to the hypotrophy of the neuroendocrine system (the receptors of the protective systems indicate possible PAS overdose), leads to a parallel decrease in the dose of PAS that a person is able to adapt. The effect of PAS turns out to be sub-extreme again and pathology is not observed either.

Pathology in PAS dependence is an accompanying phenomenon.

The explanation of the increased resistance of the adaptive hypertrophy of the neuroendocrine system does not contradict the development of biochemical theories of the euphoria etiology, explains the internal mechanism of clinical manifestations in PAS dependence.

Under alcohol exposure, when to achieve euphoria and acquire dependence, abuse with adaptive, qualitative or quantitative changes in the mechanisms responsible for the euphoria is required, the accompanying increase in tolerance can be explained by the neuroendocrine system hypertrophy.

Hypertrophy and hyperproductivity of VNS in the first stage of alcohol dependence explain maintaining the body tone during the week intervals of sobriety, in the absence of alcohol stimulation.

Compensatory stress and hyperproduction of neurotransmitters or residual neurotransmitter excess, due to VNS hypertrophy, explains adrenergic tension and vegetative disorders in the alcohol withdrawal syndrome.

The hypertrophy and hyperproductivity of the sympathetic part of VNS against the background of the gradual exhaustion of the parasympathetic department (adrenergics ystem is more resistant even in ontogenesis) also explain the qualitative change (according to narcotism age) of the sedative PAS (hypnotics, alcohol, opiates) effect on the body, transformation of their initial sedative action into a stimulating one.

The hypertrophy of the neuroendocrine system due to prior narcotization explains the rapid development of alcohol dependence in former opium addicts in alcoholization: rapid increase of alcohol tolerance, the rapid formation of alcohol abstinence syndrome, the developement of binge drinking (to develop alcoholism in former drug addicts, it is sufficient to develop only a specific tissue adaptation to alcohol).

Stimulation of the hypertrophic neuroendocrine system and increase in the overall resistance of the organism explain the fact that many stimulants (caffeine), eliminating some effects of ethanol, however, do not change its pharmacokinetics, prolong its intoxicating effect.

Initially the psychomotor agitation in PAS-dependent people getting narcosis can be based on the excitement of the hypertrophic sympathetic department of VNS.

Hypertrophy and hyperfunctionality of the neuroendocrine system explains the tolerance of alcohol-dependent people (not only of the aliphatic group of alcohols) to xenobiotics - they can take medicines "with handfuls" [4, p.57]. As the PAS dependence develops, the adaptation hypertrophy and hyperfunctionality of the neuroendocrine system lead to the fact, that its role as a functional mechanism of protection and adaptation increases and becomes the leading one.

Conclusions

1. Under regular sub-extreme exposure of the organism to psychoactive substance, physiological adaptation processes develop and lead to the hypertrophy of the neuroendocrine system.
2. Under regular sub-extreme exposure to psychoactive substance, progredient adaptive hypertrophic changes in the neuroendocrine system lead to an increase in the resistance of the organism.
3. In psychoactive substances dependence, due to the adaptive hypertrophy of the neuroendocrine system and the increased resistance, potentially extreme doses have a nonpathogenic sub-extreme effect on the organism.
4. Dependence of the body on psychoactive substances due to the increased resistance of the organism and the transformation of the effect of potentially extreme doses into the sub-extreme effect is the adaptation process.

Recommendations

It is necessary to validate the dependence of the body on psychoactive substances not as a disease, but as a state of proqredient adaptation.

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