Behavioral Alterations of Supraphysiological Doses of Androgenic Anabolic Steroids – A mini review

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Literature data offers evidence that AASs abuse is accompanied with psychiatric manifestations, as well as with different behavioral alterations from mild type, which are social acceptable, to uncontrolled and impulsive behavior with expression of aggression, anxiety, hypomania, and also manic episodes. Numerous investigations were performed on animal experimental models in order to make an insight to mechanisms underlying mechanisms for AASs impact on behavioral alterations. The absolute majority of literature sources declared the anxiogenic effect of AASs when applied in supraphysiological doses. The increased anxiety levels following AASs treatment seems to be a consequence of changes in various neuroregulatory systems (gabaergic, dopaminergic, etc.), as well as alterations in sex hormones receptors in specific brain regions, including hippocampus. Supraphysiological doses of AASs also affect mood by means of increased depressiveness. The prodepressant action of AASs is usually accompanied with significant reduction of growth factors (NGF, BDNF) release with consequent effects on neuromodulatory systems (gabaergic, dopaminergic) in rat prefrontal cortex and hippocampus. When applied in supraphysiological dose AAS significantly affected the quality of cognitive abilities, manifested as significant decline in spatial learning and memory. The negative impact of AASs on cognitive functions was attributed to significant alterations in acetylcholine, dopamine, norepinephrine, glutamate and serotonin levels in specific brain regions, responsible for regulation of learning and memory.

Anabolic androgenic steroids (AASs) are synthetic derivatives of the male hormone testosterone. AASs are compounds that have a great role in treatment of many chronic diseases [1]. They can exert strong effects on the human body that may be beneficial for athletic performance [2]. The abuse of AASs among adolescents [3] represents a public-health concern. AASs administration of supraphysiologival doses induces behavioral alterations such as violence and aggression [4]. Also, AASs abusers are characterized by anxious behavior and irritability with frequently mood swings [5].

BEHAVIORAL EFFECTS OF AASs

AASs abuse is accompanied with psychiatric manifestations, as well as with different behavioral alterations from mild type, which are social acceptable, to uncontrolled and impulsive behavior with expression of aggression, anxiety, hypomania, and also manic episodes [6]. Incidence of those effects depends on applied dose, duration, user personality structure, as well as on environment. Many users express paranoid jealous, extreme irritability, reduced power of judgment induced by feeling of invincibility. Also, acute psychosis, confused states, the appearance or exacerbation of tics may occur. Long term AASs users often manifest narcissism and hysteric behavior. Supraphysiologival doses of AASs can induce manic symptoms, frequently mood swings, which can be accompanied with violence and aggression [6, 7]. The term “roid rage” describes expression of angry and aggression of AASs abusers, and represents suddenly and very aggressive behavior provoked by minimal stimuli [8]. Many men who abuse AASs only in order to improve their appearance usually have accompanied muscle dysmorphia (pathologic state in which muscularity is the main preoccupation). That type of people is inclined to suicide attempts, with low life quality, and susceptible to abuse other substances [9].

Based on investigations performed on animal models, as well as in humans, relation between male sex hormones and psychologically functions and/or behavior was confirmed. The relationship between testosterone concentration and aggressive behavior was confirmed in several studies performed on animal experimental models, while different results were obtained in humans [10]. A lot of clinical trials showed that endogenous testosterone level does not directly related to aggressive behavior [11, 12]. AASs use can be associated with schizophrenia [13], dependence on steroids [14], affective and psychotic symp-
toms [6], murders and attempts of murder [15]. Literature data described alterations of mental health and behavior during AASs abuse such as hypomanic episodes [16], violent murders [17], abuse of children [16, 18] and spouses [18].

**BEHAVIORAL CHANGES RELATED TO AASs ABUSE**

Neuropsychiatric and behavioral effects induced by AASs abuse are well known and described in literature. Long term use of certain AASs in rodents induces behavioral and neurochemical alterations which is equivalent to similar behavioral modifications in humans after AASs abuse. It is confirmed that medical unjustified use of AASs leads to neurodegenerative alterations [19].

**AASs and anxiety**

The most of literature data describe relationship between high level of anxiety and/or aggressiveness with alterations of limbic system. Studies performed on male rats showed that prolonged use of supraphysiological doses of AASs induce anxiety, whereby that effect was diminished by using of (intracerebroventricular injection) antagonist of CRH receptor type (antalarmin), [20]. Described anxiogenic effect was significantly altered by picrotoxin, antagonist of GABA, receptor type. Increasing of CRH mRNA was, also, detected in amygdala after chronic use of AASs. It is assumed that the sequence of events which induce high level of anxiety due to AASs use is: AASs increase presynaptic release of GABA mediated by CRH receptor type from central amygdale on surrounding structures which induce unbalance that lead to increment of anxiety [21]. Although there are 16 different genes for subunits of GABA receptors, the strongest alterations of gabaergic function, which can be cause of increase anxiety, performed via GABA, receptors with α2 subunit [22].

Behavioral alterations, such as high level of aggressiveness, are mostly connected for (latero-anterior) area of hypothalamus, which is confirmed by increased of molecular expression of estrogen receptor α or β, after AASs use, in mentioned part of brain which is responsible for control of expression of estrogen receptor α or β, after AASs use, in hypothalamus, which is confirmed by increased of molecular receptors with α2 subunit [22].

AASs use induces phosphorylation of NMDA (N-methyl D-aspartate) receptors which resulted in increasing of aggressiveness and impulsivity in rats of different age [31], with prominent effect on sigma-1 receptors [32]. Aggressiveness induced by AASs use is, also, related to changes in dopaminergic receptors in latero-anterior region of hypothalamus [33, 24]. That kind of aggressiveness is direct related to activity of dopaminergic D2 receptors (and on indirect way of dopaminergic D5 receptors) in that region. Alterations of dopaminergic receptors, as well as their influence on behavior, act indirectly – via changes in gabaergic neurons function [34, 35, 36].

Supraphysiological doses of AASs usually results in more dramatic consequences when administered to adolescents, compared to adults. Such potentiation of anxiogenic and reaction to stress has been explained by the fact that AAS application affects certain brain regions responsible for mood regulation that are still developing, expressing high hormone-neuromodulatory sensitivity [37]. It has been postulated that anxiogenic effect of AASs is mediated via negative impact on gabaergic system, which includes decline in the number of gabaergic neurons in specific brain regions involved in behavioral control, such as hippocampus [38].

Our results also confirmed clear anxiogenic effect following chronic treatment with AASs (nandrolone-decanoate and testosterone-enanthate) in adolescent rats [38, 39, 40]. As shown in Table 1, the increased anxiety level induced by AASs was accompanied with increased serum sex hormones (testosterone, dihydrotestosterone and estradiol)

<table>
<thead>
<tr>
<th>AAS Behavioral alteration</th>
<th>Postulated mechanism</th>
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<tbody>
<tr>
<td>Nandrolone-decanoate</td>
<td>Anxiety ↑↑↑, Depression ↑↑, Cognitive function ↓</td>
</tr>
<tr>
<td></td>
<td>Serum testosterone ↑↑, Serum dihydrotestosterone ↑↑, Serum estradiol ↓</td>
</tr>
<tr>
<td></td>
<td>Androgen receptors (hippocampus) ↑↑↑</td>
</tr>
<tr>
<td></td>
<td>Number of gabaergic neurons (hippocampus) ↓↓</td>
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<tr>
<td>Testosterone-enanthate</td>
<td>Anxiety ↑↑↑↑↑, Depression ↑↑↑↑↑, Cognitive function ↓</td>
</tr>
<tr>
<td></td>
<td>Serum testosterone ↑↑↑↑↑, Serum dihydrotestosterone ↑↑↑↑↑, Serum estradiol ↑↑↑↑↑</td>
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</tbody>
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Table 1. An overview of behavioral alterations observed following chronic treatment (20 mg/kg/week, s.c., for six weeks) with AASs (nandrolone-decanoate and testosterone-enanthate) with postulated mechanisms of action based on biochemical and immunohistochemical data [38, 39, 40, 46, 47].
levels. Supraphysiological doses also induced increase in androgen receptors expression (unpublished data), as well as decline in gabaergic neurons number [38] in hippocampus.

**AASs and depression**

The principal surmises for neuropsychiatric consequenc- es that follow AAS administration are based on the results obtained in studies with rats treated with high doses of AASs. It has been shown that application of stanozolol induced decrease in BDNF (brain-derived neurotrophic factor) levels in hippocampus and prefrontal cortex. At the same time, the decrease in low-affinity glucocorticoide receptors expression was observed in hippocampus, as well as the elevation of morning plasma corticosterone levels [41]. Lowered production of BDNF is considered as an element of maladaptive response to stress, and was found to be accompanied with decreased volume of hippocampus and prefrontal cortex. Taken altogether, those conditions resemble the alterations usually observed in depression [42]. Chronic treatment with AAS in rats leads to modificat- ion of hypothalamic-pituitary-adrenal (HPA) axis with decreased BDNF levels that correspond to current patho- physiological basis for depression [41]. This assumption was estimated by means of evaluation of biochemical alter- ations in various brain regions in animals treated with stanozolol [43]. Unlike serotonin levels that were lowered in all investigated brain regions, stanozolol administration affected dopaminergic system in rats in prefrontal cortex and hippocampus, with no significant effect in striatum and nucleus accumbens. Therefore, it has been conclud- ed that described reduction of dopaminergic content in prefrontal cortex may resemble neurochemical ground of depression [43]. Some specific effects of high doses of AASs in certain brain regions were manifested as increased NGF (nerve growth factor) levels in hippocampus and septum [44], with reduction of NGF levels in basal forebrain [45]. Analyzing those literature data, it seems that disturbances in neurotrophic factors levels may me notably involved in pathogenesis of mood disorders, such as depression.

As shown in Table 1, results obtained by our research team also showed prodepressant effect following chronic treatment with AASs (nandrolone-decanoate and testoster- one-enanthate) in adolescent rats [46, 47]. Prodepressant effect of AAS was accompanied with increased serum sex hormones levels, and increase in androgen receptors expression (unpublished data). At the same time, the decline in gabaergic neurons number [46] was observed in hippocampus. Also, the prodepressant action of nandrolone-decanoate correlated with decreased serum levels of neuro- peptide Y, as well as decreased number of neuropeptide Y-positive interneurons in hippocampal regions [46].

**CEREBRAL MECHANISMS INVOLVED IN AAS-INDUCED ALTERATIONS OF COGNITIVE FUNCTIONS**

Hippocampus unequivocally plays the key role in numer- ous processes involved in control of learning and memory (spatial mapping and learning, working memory, investiga-
Further investigations should provide more detailed and subtle information related to mechanisms responsible for behavioral alterations accompanied with AASs abuse.

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Notes

The authors declare no competing financial interest.

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CONCLUSION

Androgenic anabolic steroids abuse, as one of the very actual health concern especially among adolescents, has numerous and serious adverse effects, including undesirable behavioral alterations. The variety of psychiatric manifestations, such as violence and aggression, observed following prolonged AASs administration in supraphysiological doses appear due to a plethora of neurophysiological and biochemical abnormalities. The anxiogenic and pro-depressant outcome of AASs abuse and/or decline in cognitive functions, according to the data obtained in animal experimental models, may include mechanisms that affect behavioral control at the level of sex hormones receptors and metabolism, as well as alterations in growth factors levels and functions, in various neuromodulatory systems (gabaergic, dopaminergic, etc.) in specific brain regions.

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