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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 supraphysiological 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. Supraphysiological 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 use, antagonist of $GABA_A$ 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 $GABA_A$ 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 aggression [23]. It has been described that prolonged use of AASs lead to significant alteration of different systems (serotonergic, dopaminergic and glutamatergic), resulted in increased level of anxiety and aggressiveness [24, 25]. Literature data showed that decreased level of serotonin is associated with expression of impulsive aggression, both on animal models and humans [26]. Related to that fact, it is known that chronic administration of AASs can lead to decrease expression of 5-HT1A receptors, parallel with increase in activity of 5-HT2A receptors in mentioned region of hypothalamus [27, 28]. That alteration of ratio of these two types of serotonergic receptors is considered as the key event which resulted in aggressive behavior. Similar alterations of serotonergic system are also described in hippocampus, septum, amygdala, and neocortex. It is interesting to note that after AASs use in adolescent population, in the same region (latero-anterior area of hypotalamus), significant alterations in glutamatergic system are evident [29, 30]. AASs use induces phosphorilation 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 AAS was accompanied with increased serum sex hormones (testosterone, dihydrotestosterone and estradiol)

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].

AAS	Behavioral alteration	Postulated mechanism
Nandrolone-decanoate	Anxiety ↑↑ Depression ↑ Cognitive function ↓	Serum testosterone ↑ Serum dihydrotestosterone ↑ Serum estradiol ↑ * Androgen receptors (hippocampus) ↑↑↑ * Number of gabaergic neurons (hippocampus) ↓↓
Testosterone-enanthate	Anxiety ↑↑↑ Depression ↑↑↑ Cognitive function ↓	Serum testosterone ↑↑↑ Serum dihydrotestosterone ↑↑↑ Serum estradiol ↑↑↑ * Androgen receptors (hippocampus) ↑↑ * Number of gabaergic neurons (hippocampus) ↓↓

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 consequences 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 modification of hypothalamic-pituitary-adrenal (HPA) axis with decreased BDNF levels that correspond to current pathophysiological basis for depression [41]. This assumption was estimated by means of evaluation of biochemical alterations 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 concluded 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 testosterone-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 neuropeptide 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 numerous processes involved in control of learning and memory (spatial mapping and learning, working memory, investigation of a new space, recurrent learning, etc) in humans, as well as in animals. Although there are numerous behavioral tests for the estimation of cognitive functions, the huge majority of reliable data considering spatial learning and memory in animals has been acquired using standardized procedures [48, 49]. Although, when applied in single dose (slightly above physiological values) AASs did not significantly affect cognitive functions [50], repeated supraphysiological doses of exogenous testosterone (administered intracerebraly) induced dose-dependent decline of spatial memory [51].

It has been frequently reported that AAS significantly affected the quality of cognitive abilities. Namely, ND administration has been addressed to significant decline in spatial learning and memory [52]. At the same time, the diminishing of cognitive functions was observed following TE application [53]. The specific impact of AAS on cognitive functions that are determined in hippocampus was confirmed by the fact that the similar response to AAS treatment was reported after parenetral application [52] and direct administration into hippocampal tissue, and even in some specific hippocampal regions, such as CA1 region [53].

The clear relationship between the AAS levels and alterations in cognitive functions was also confirmed by the results obtained in studies performed using AAS antagonists [54]. The confirmation for proposed mechanism can be found in results of the study in which the blockade of androgenic receptors (with flutamide) prevented the decline in cognitive functions induced by AASs administration [51].

However, although the majority of literature data demonstrate the adverse effects of AAS on cognitive functions, it should be noticed that AAS treatment may improve cognitive functions under certain circumstances [55]. The observed discrepancies considering the overall impact of AAS on cognitive functions may appear as a consequence of the huge differences in the methodological approach that include the differences in: the applied AAS, doses administered, protocols duration, the age of experimental animals, and (the most frequently) simultaneous administration of different AASs (*„stacking"*).

Nevertheless, there is no disagreement considering the negative impact of AASs on cognitive functions when applied in supraphysiological doses. The results of previous investigations showed that sex hormones may affect memory processes by means of alterations in various neurotransmitters' systems. Therefore, it has been described that AASs treatment had significant impact on acetylcholine [56], dopamine [57], norepinephrine [57], glutamate [58] and serotonin [59] levels. Also, it has been confirmed that sex hormones rapidly alter neuronal activity by increased affinity for neurotransmitters' binding, or directly, by inducing the changes in cell membrane permeability for certain ions in some specific brain regions, including hippocampus [56, 60]. The previous studies showed that sex hormones significantly affected total cholinergic system in brain, affecting the memory processes at the same time [56, 61]. Their influence may involve increased hippocampal acetylcholine release [62], as well as alterations in acetylcholine transferase and esterase activity [63].

Also, it has been described that testosterone administration leads to decrease in serum gonadotropine levels

[64], as well as androgenic precursors, such as DHEA and DHEA-S [65]. DHEA-S activates alosteric site on gabaergic receptor that prevents the opening of chloride channels inducing, in that way, the increased neuronal excitability [66]. The administration of DHEA-S, negative alosteric receptors modulator of $GABA_A$ receptors, stimulates increased hippocampal acetylcholine release [62], which is involved in memory functions [67]. Furthermore, testosterone, acting as a nonselective antagonist of sigma receptors, may induce prolonged decline in sigma receptors' function and consequent attenuation in NMDA receptors function [68]. Exactly, the reduction in NMDA receptors function has been found to be the reason for decline in spatial memory [68, 69]. Beside, the AAS-induced down regulation of cognitive functions can also be connected to increased expression of prodynorphin mRNA in hippocampus [70]. The postulated mechanism that potentiates the adverse effect of AASs on cognitive functions is based on the fact that specific brain regions involved in control of cognitive functions (such as hippocampus) have been shown to express large number of androgen receptors [71].

The complexity of evaluation for AASs impact on cognitive functions is even more increased by the fact that AASs may be converted into estrogen (aromatization) in some brain regions, and therefore, their action can be followed via estrogen receptors afterwards. Interestingly, the increased estradiol levels are connected to improved cognitive functions [56, 72]. Considering the fact that the conversion of testosterone into estradiol has positive feedback itself, when analyzing the impact of supraphysiological doses of AASs on cognitive functions, it should be taken into consideration that final outcome of AASs induced alterations in cognition appears as the results of two completely opposite phenomenon – the negative effects of AAS and beneficial influence of estradiol on cognitive functions.

Unpublished data obtained in our lab also confirmed significant decline of cognitive functions following chronic treatment with AASs (nandrolone-decanoate and testosterone-enanthate) in adolescent rats. As shown in **Table 1**, the negative impact of AAS on cognitive functions was also accompanied with previously described biochemical and immunohistochemical data: serum sex hormones levels, androgen receptors expression, and number of gabaergic neurons in hippocampus.

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 prodepressant 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. 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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