EFFECTS ON RAT BRAIN DOPAMINE AND DOPAC LEVELS AFTER SUB-CHRONIC NANDROLONE ADMINISTRATION FOLLOWED BY AN AMPHETAMINE CHALLENGE

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Summary

Anabolic androgenic steroids (AAS) are taken not only as performance-enhancing drugs in sports and exercise but also for reasons like intoxication and increased self-esteem. Besides the risk of unwanted physical effects, these abusers may suffer psychological side effects such as aggression, disinhibition and violent behaviour. It has also been suggested that AAS may induce drug dependence and serve as a gateway to abuse of other drugs. In this study, adult male Sprague-Dawley rats recieved i.m. injections with nandrolone decanoate (15 mg/kg) once daily for 14 days followed by an amphetamine challenge (5 mg/kg) on day 15. Brain tissue concentrations of dopamine and the metabolite 3,4-dihydroxyphenylacetic acid (DOPAC) were measured with high-performance liquid chromatography and electrochemical detection. Nandrolone decanoate abolished the effect of amphetamine on the DOPAC level in the hypothalamus and on the DOPAC/dopamine ratio in the hypothalamus and the hippocampus. These results support the hypothesis of AAS ability to affect neurotransmission in systems of the brain involved in development of drug dependence and aggression.

Keywords: anabolic androgenic steroids, nandrolone decanoate, dopamine, DOPAC, amphetamine, drug dependence

Introduction

Anabolic androgenic steroids (AAS) have been used as performance enhancing drugs by elite and amateur athletes for the last fifty years. Today an increasing number of adolescents administer AAS to improve physical appearance but also for reasons such as intoxication and increased self-esteem (1, 2). The abuse of AAS is associated with increased aggressive behaviour and loss of impulse control and it has been suggested that these substances are addictive (3) and may induce a susceptibility for engaging in abuse of other drugs (4, 5). In survey studies among adolescents, abuse of psychostimulants, alcohol and other drugs of intoxication are more frequent among AAS abusers than non-abusers (6) and these observations are confirmed in case studies of adult AAS abusers (7). According to a number of forensic studies, criminal violence, death at a young age and abuse of psychotropic substances are factors associated with lethal outcome of AAS abuse (8).

Animal models investigating behaviour have shown that the social aggression and dominance in rats is increased by AAS treatment, especially when combined with other drugs such as alcohol and amphetamine (9, 10). Recently, reports on self-administration of a number of AAS by hamsters have been published (11, 12) and rats present conditioned place preference when exposed to testosterone (13, 14). Further, AAS treated rats increase their voluntary intake of other drugs and seem to respond differently compared to control animals not pre-treated with AAS (10, 15-18).

There are several studies performed on rodents focusing on the neurochemical effects of AAS. The dopaminergic mesocorticolimbic system is reported to be important for the regulation of reward mechanisms such as reinforcement (19), reward related associative learning (20), reward prediction (21) and incentive salience (22). Dopamine receptors have been suggested to be involved in the acquisition of testosterone conditioned place preference (14). An autoradiographic study revealed down-regulated densities of the dopamine D_1-receptor in the caudate putamen and nucleus accumbens core and shell after two weeks of AAS administration. In contrast, the dopamine D_2-receptor density was up-regulated in the caudate putamen, nucleus accumbens core and ventral tegmental area but down-regulated in the nucleus accumbens shell (23). These results have been confirmed when measuring the content of mRNA for the same receptors (24) The presynaptically located dopamine transporter, which largely recycles dopamine, has also been reported to be up-regulated in the caudate putamen following two weeks of daily AAS injections (25). A weakness of the current literature is that only a few studies have included measurements of the levels of dopamine and its metabolites after AAS treatment and the findings are contradictory, most likely due to different dose regimens (10, 26, 27).

In view of the current literature, where AAS treatment causes opposing effects on dopamine D_1- and D_2-receptors and induce behavioural changes in animal models, both alone and in combination with other drugs of abuse, we hypothesize that the tissue content of dopamine and its metabolite DOPAC would be altered in the mesocorticolimbic, nigrostriatal and tuberoinfundibular dopamine pathways in the male rat brain, following sub-chronic AAS administration. In addition to this, there is a need for a sub-chronic study including a combination treatment with both nandrolone decanoate and amphetamine since amphetamine is a drug often used by AAS abusers and pre-

treatment with nandrolone decanoate affects amphetamine-induced behaviour in animal models.

The aim of this study was to examine whether sub-chronic treatment with the AAS nandrolone decanoate affects the tissue content of dopamine and its metabolite DOPAC in areas of the male rat brain involved in aggression and the development of drug dependence, alone or in combination with amphetamine.

Materials and methods

Animals

Both studies were performed on male Sprague-Dawley rats, ten weeks of age (B&K, Sollentuna, Sweden). The animals were housed four in each cage at a temperature of 22°C and 60% humidity. The twelve-hour light/dark circle started at 6 a.m. and food and water were provided *ad libitum*. After being allowed to adapt to the new environment for 14 days, the rats were randomly divided into treatment groups, each consisting of eight animals. Two groups received a daily i.m. injection of nandrolone decanoate (15 mg/kg) for 14 days, whereas two groups was administered i.m. injections of vehicle once daily for 14 days. Injections were given in the hind leg, alternating between left and right (injection volume 0.1 ml). On day 15, one vehicle treated and one nandrolone treated group received a single i.p. injection of amphetamine (5 mg/kg). The two remaining groups received saline as vehicle. The animals were sacrificed by decapitaion one hour after the amphetamine injection. The brains were rapidly removed for dissection using a rat brain matrix (Activational Systems, Warren, MI, USA). The frontal cortex, medial prefrontal cortex, nucleus accumbens, amygdala, caudate putamen, hypothalamus, hippocampus, and the periaqeductal grey were collected, put on dry ice and kept in Eppendorf tubes at –80°C, until prepared for analysis. The Animal Care and Ethical Committee in Uppsala, Sweden approved the experimental procedure.

Extraction of monoamines

The brain tissues were homogenized by sonication in 500 μl of a chilled mixture of 0.1 M perchloric acid with 2 mg/ml ethylenedinirtilotetraacetic acid disodium salt dihydrate (EDTA). The tissues and homogenates were kept on ice. The homogenates were then centrifuged for 15 minutes at 12 000 rpm in 4°C. The supernatants were collected in new Eppendorf tubes and stored at –80°C until analyzed.

HPLC-EC

The levels of dopamine and DOPAC were measured using a reversed-phased high performance liquid chromatography (HPLC) system with isocratic eluation and electrochemical detection (EC) (ESA Inc. Chelmsford, MA, USA). The system consisted of a ReproSil-Pur C18-AQ, 150x3 mm, 5 μm column, a Rheodyne 7161 injector with a 150 μl loop, an ESA Analytical Cell Model 5011, a Guard Cell Model 5020 and an LKB 2150 HPLC pump (LKB Produkter AB, Bromma, Sweden). The monoamines were detected at an oxidation potential of 350 mV and the guard cell was set to 400 mV. The flow rate was 0.8 ml/min and the chromatograms were obtained with the AZUR chromatographic software (Datalys, France).

The following mobile phase was used: sodium acetate trihydrate (55 mM), 1-octansulphonic acid sodium salt (180 μM), EDTA (10 μM) and 10% methanol dissolved in

purified water (Milli-Q Plus 185, Millipore). pH was set to 4 by addition of 70% acetic acid and the buffer was then filtered (0.22 μm, Millipore) and degassed with helium (28).

The sample volume injected ranged from 20 to 40 μl and the amounts of the monoamines were determined using the external standard method. Calibration curves were created with pure dopamine and DOPAC dissolved and diluted in 0.1 M perchloric acid containing 2 mg/ml EDTA. The chemicals were obtained from Sigma-Aldrich Chemicals Sweden AB, and were all of analytical grade.

Statistics

The levels of dopamine, DOPAC and the ratios between these were statistically analyzed with one-way ANOVA followed Fisher's PLSD for post-hoc comparisons using StatView 5.0.1. The tests were considered significant when $p<0.05$.

Results

DOPAC/dopamine ratios are presented in Table 1 and the tissue levels of dopamine and DOPAC after i.m. injections once daily with nandrolone decanoate (15 mg/kg) for 14 days and a single i.p. injection of amphetamine (5 mg/kg) on day 15, in Figure 1.

Table 1

DOPAC/dopamine ratios after 14 days of nandrolone decanoate treatment and an amphetamine challenge

Tissue	Treatment			
	VEH+VEH	VEH+AMPH	ND+VEH	ND+AMPH
Hypothalamus	0.22 ± 0.02	0.13 ± 0.01 a)	0.17 ± 0.004 a)	0.22 ± 0.02 b)c)
Hippocampus	1.21 ± 0.10	0.64 ± 0.08 a)	1.13 ± 0.20 b)	1.07 ± 0.14 b)
Medial prefrontal cortex	0.19 ± 0.01	0.13 ± 0.01 a)	0.20 ± 0.02 b)	0.15 ± 0.02 a)c)
Frontal cortex	0.40 ± 0.03	0.60 ± 0.12	0.34 ± 0.06	0.70 ± 0.32
Caudate putamen	0.18 ± 0.01	0.04 ± 0.003 a)	0.15 ± 0.02 a)b)	0.05 ± 0.02 a)c)
Nucleus accumbens	0.23 ± 0.02	0.09 ± 0.01	0.20 ± 0.03	0.22 ± 0.09
Amygdala	0.46 ± 0.05	0.44 ± 0.11	0.38 ± 0.05	0.29 ± 0.04
Periaqeductal grey	0.11 ± 0.01	0.09 ± 0.01	0.10 ± 0.01	0.10 ± 0.01

Table 1. The ratios between DOPAC and DA, expressed as mean ± S.E.M., after a sub-chronic treatment with vehicle (VEH) or nandrolone decanoate (ND) including a challenge with amphetamine (AMPH) or VEH in the control groups (n = 7-8). Data were analysed with one-way ANOVA and Fisher's PLSD post-hoc analysis. Significant differences are presented as follows ($p<0.05$): a) vs VEH+VEH; b) vs VEH+AMPH; c) vs ND+VEH

Figure 1

Dopamine and DOPAC tissue levels after 14 days of nandrolone decanoate treatment and an amphetamine challenge

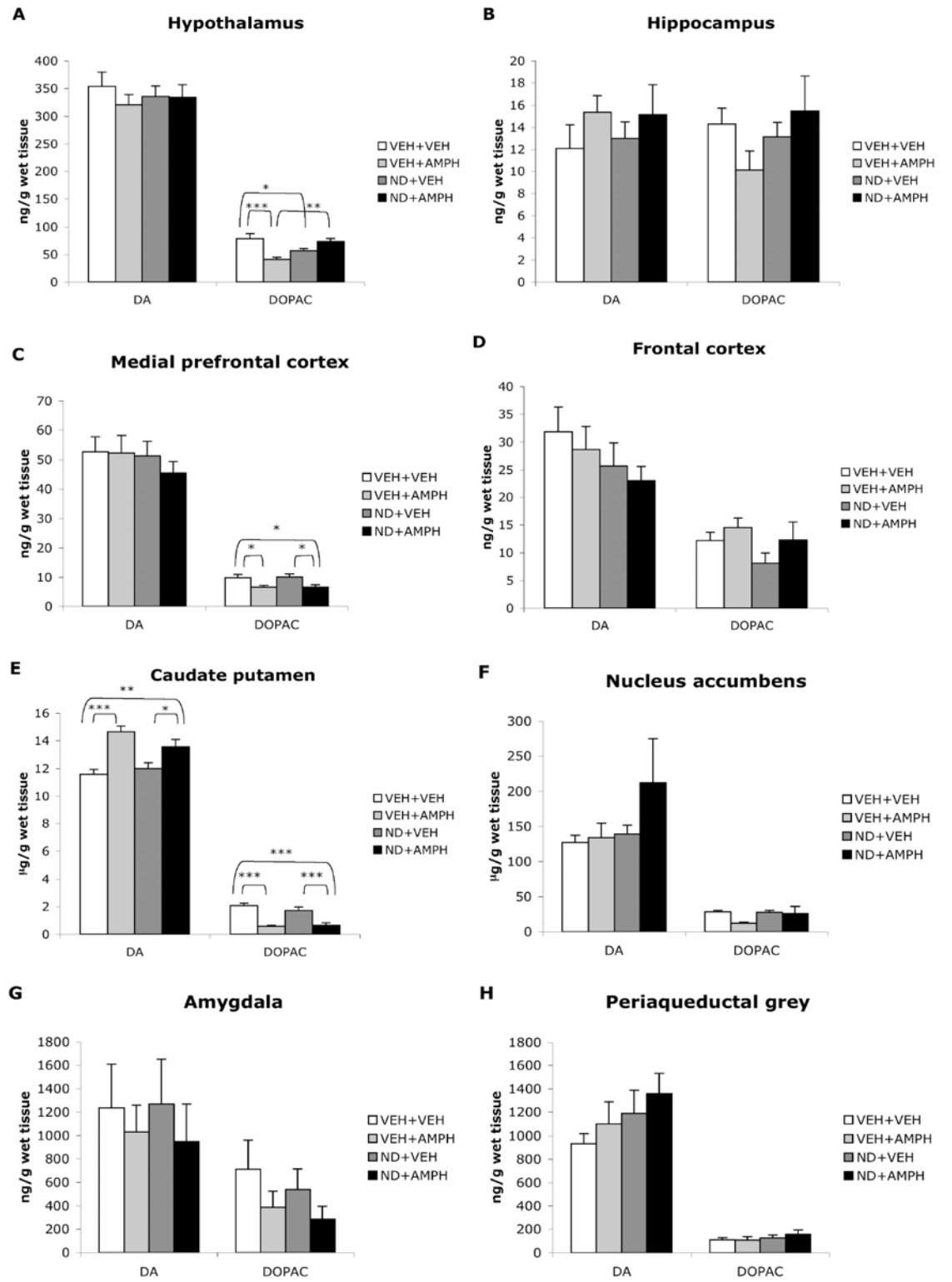

Figure 1. Dopamine (DA) and DOPAC concentrations in ng/g wet tissue expressed as mean ± S.E.M., after a sub-chronic treatment with vehicle (VEH) or nandrolone decanoate (ND) including a challenge with amphetamine (AMPH) or VEH in the control groups (n = 7-8). Data were analysed with one-way ANOVA and Fisher's PLSD post-hoc analysis. Significance levels: * p<0.05; ** p<0.01; *** p<0.001

Effects due to amphetamine alone
Amphetamine caused an increase in dopamine tissue content compared to controls in the caudate putamen ($p<0.0001$). The tissue content of DOPAC was decreased in the caudate putamen ($p<0.0001$), the hypothalamus ($p=0.001$) and the medial prefrontal cortex ($p=0.026$) by amphetamine compared to vehicle. The ratio between DOPAC and dopamine was decreased in the caudate putamen ($p<0.0001$), the hippocampus ($p=0.004$), the hypothalamus ($p=0.0003$), and the medial prefrontal cortex ($p=0.001$) compared to the control group.

Effects due to nandrolone decanoate alone
The DOPAC tissue content was decreased in the hypothalamus ($p=0.034$) compared to vehicle, as was the DOPAC/dopamine ratio ($p=0.030$).

Effects due to nandrolone pre-treatment and amphetamine challenge
The dopamine level was increased in the caudate putamen in the group which was subjected to both nandrolone pre-treatment and amphetamine challenge, compared to vehicle ($p=0.003$) and nandrolone alone ($p=0.016$). In the hypothalamus, the DOPAC tissue content was increased by the combination of nandrolone and amphetamine compared to amphetamine alone ($p=0.001$). In the caudate putamen ($p<0.0001$ and $p=0.0004$ respectively) and medial prefrontal cortex ($p=0.023$ and $p=0.015$ respectively), the tissue content of DOPAC was decreased after combined administration, compared to the control and nandrolone group. In the hippocampus, the DOPAC/dopamine ratio was increased compared to amphetamine alone ($p=0.027$). The DOPAC/dopamine ratio in the hypothalamus was increased after combined treatment, compared to both the amphetamine treatment ($p<0.0001$) and the nandrolone treatment ($p=0.013$). In the caudate putamen ($p<0.0001$ and $p=0.0002$ respectively) and the medial prefrontal cortex ($p=0.049$ and $p=0.020$ respectively), the DOPAC/dopamine ratios were decreased compared to vehicle and nandrolone alone.

No significant changes were observed in the amygdala, frontal cortex, nucleus accumbens or periaqeductal grey.

Discussion

The most important result of the present study is the ability of nandrolone decanoate pre-treatment to abolish the effect of amphetamine on the hippocampal DOPAC/dopamine ratio and the hypothalamic DOPAC level and DOPAC/dopamine ratio. These findings provide neurochemical support for the hypothesis that AAS abusers self-medicate with other drugs to compensate for AAS-induced dysregulations in e.g. the mesocorticolimbic system and that AAS thereby function as a gateway to abuse of other drugs (4, 5). Our findings are further supported by several recent animal behavioural studies, presenting attenuated conditioned place preference and enhanced abstinence reactions to morphine and cannabis in mice, increased self-administration of ethanol and also abolished ethanol-induced sedation in rats, when pre-treated with nandrolone (10, 15, 17, 18). In accordance with our study, Lindqvist found no effects on the dopaminergic system by nandrolone alone but presented changes in ethanol-induced behaviour after two weeks of nandrolone pre-treatment (10). Increased levels of DOPAC and DOPAC/dopamine ratios have been reported in the hypothalamus, cortex and striatum, but these studies applied

dose regimens different from ours and that of Lindqvist, and no challenge with other drugs were performed in those studies (26, 27).

Possible mechanisms by which nandrolone might affect the biochemical response to amphetamine are several. Amphetamine induces dopamine release by entering the pre-synaptic terminal via the dopamine transporter in exchange for cytosolic dopamine. It is also hypothesized that amphetamine has the ability to remove dopamine from the synaptic vesicles by reversal of the vesicular monoamine transporter situated in the vesicular membrane and to inhibit dopamine degradation by monoamine oxidase. The result is a decreased intracellular level of dopamine and DOPAC, the main intracellular metabolite. When the extracellular level of dopamine is increased to such an extent, it triggers negative feedback mechanisms such as activation of the pre-synaptic dopamine D_2-autoreceptor, which inhibit further dopamine synthesis and release (29).

Two weeks of nandrolone administration has indeed been shown to increase the levels of the dopamine D_2-receptor transcript and protein, together with decreased levels of the dopamine D_1-receptor transcript and protein, in the mesocorticolimbic and nigrostriatal systems, shown by *in situ*-hybridisation and autoradiography (23, 24). The same dose regimen of nandrolone also resulted in increased density of the dopamine transporter protein in the caudate putamen (25). These alterations resembles those following lesions of the nigrostriatal dopamine pathways (30) and interpreted as an AAS-induced dopaminergic dysregulation, it might contribute to explain the attenuated effects of amphetamine in the hippocampus and the hypothalamus after nandrolone pre-treatment.

So far, there are only sparse reports of the ability of nandrolone decanoate to affect dopamine synthesis or metabolism. Neither the mRNA contents of tyrosine hydroxylase (TH) and amino acid decarboxylase (AADC) in the substantia nigra and ventral tegmental area, nor the accumulation of L-dopa in the striatum have been shown to change in the rat brain after repeated nandrolone administration (24, 26). There are, to our knowledge, no studies of catechol-*O*-methyl transferase (COMT) and only one report on monoamine oxidase (MAO) activity, where only the hypothalamus was examined (26). No change in MAO activity was detected, but again, the dose regimen differed greatly from ours and makes the comparison difficult. It would also be interesting to examine whether AAS treatment affects the vesicular monoamine transporter and its ability to store dopamine in vesicles.

Amino acids like GABA and glutamate exert inhibitory and excitatory control of dopamine release, respectively. Repeated administration of supra-therapeutic doses of AAS increase the sensitivity of $GABA_A$ receptors (31) and the tissue level of glutamic acid decarboxylase-65 (GAD_{65}) in the hypothalamus among other regions (32) while down-regulated mRNA levels of certain NMDA receptor subunits have been presented in both the hypothalamus and hippocampus (33). It is still not clarified if nandrolone decanoate produces neuroactive metabolites but several endogenous steroids have been shown to allosterically modulate NMDA and GABA receptor function (34, 35).

The significant changes in dopamine level, DOPAC level and DOPAC/dopamine ratio presented in the caudate putamen, and in DOPAC level and DOPAC/dopamine ratio in the medial prefrontal cortex are due to the amphetamine treatment. No significant changes were observed in the amygdala, frontal cortex, nucleus accumbens or periaqeductal grey, although a trend towards an amphetamine effect is present in the

nucleus accumbens. The maximum effect of amphetamine on dopamine release is expected to take place 40 minutes after administration while behavioural effects are most prominent between 60 and 120 minutes after amphetamine administration. The time point of sacrificing the animals was chosen to 60 minutes after amphetamine injection and that might explain the absence of statistically significant dopaminergic changes by amphetamine in the nucleus accumbens and frontal cortex (36). Another difficulty with interpreting measurements of dopamine in tissue homogenates is that it cannot be discriminated between intracellular and extracellular levels, which means that the level of DOPAC and the ratio between DOPAC and dopamine provide more accurate information about the dopaminergic system in this kind of study.

In conclusion, the present study demonstrates novel findings of sub-chronic treatment of AAS upon dopamine pathways in areas of the male rat brain involved in reward properties and aggressive behaviour. Nandrolone decanoate abolished the effect of amphetamine on the hypothalamic DOPAC level and DOPAC/dopamine ratio and on the hippocampal DOPAC/dopamine ratio. These results might contribute to explain the behavioural changes observed during the different phases of AAS abuse in humans and support the hypothesis of AAS functioning as a gateway to abuse of other drugs.

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