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Research report

The effect of sub-chronic nandrolone decanoate treatment on dopaminergic and serotonergic neuronal systems in the brains of rats

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Abstract

Anabolic–androgenic steroids (AASs) are widely abused by adolescents, although persistent AAS use can cause several adverse physical and mental effects, including drug dependence. The first aim of the present study was to study the action of nandrolone decanoate on dopaminergic and serotonergic activities in the brains of rats. In order to evaluate the anabolic or toxic effects of the dosing regimens used, selected peripheral effects were monitored as well. Male Wistar rats were treated for 2 weeks. Injections containing nandrolone (5 and 20 mg/kg, i.m.) or vehicle were given once daily, 5 days a week. The levels of dopamine (DA), 5-hydroxytryptamine (5-HT) and their metabolites were assayed from dissected brain regions 3 days after the last injection. Blood was collected for chemical assays before, after 1 week treatment and at decapitation. Both doses of nandrolone significantly increased the levels of 3,4-dihydroxyphenylacetic acid (DOPAC), a metabolite of DA in the cerebral cortex, and the higher dose of nandrolone increased the concentrations of 5-HT in the cerebral cortex compared with the vehicle. In addition, after nandrolone treatment, the levels of hemoglobin and erythrocytes increased, and reticulocyte levels decreased. The results suggest that nandrolone at supraphysiological doses, high enough to induce erythropoiesis, induces changes in the dopaminergic and serotonergic neuronal system in the brains of rats. These phenomena may account to some of the observed central stimulatory properties that have been reported following AAS abuse.
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Theme: Neural basis of behavior
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1. Introduction

Misuse of anabolic–androgenic steroids (AASs) is no longer limited to professional power training athletes and body builders (see review [69]). A large number of young adolescent abuse AASs to improve their physical fitness and appearance [19,29]. Even this type of use of doping agents probably involves more than a desire to enhance the users appearance or sports performance and appears to have much in common with the use of alcohol and tobacco [5,30]. The use of AAS is often associated with the use of psychotropic drugs such as cocaine, amphetamine and heroin [18,31], a phenomenon that may contribute to aggressive behavior [42]. Changes in mood, euphoria, delusions, depression and violent behavior are reported to be associated with the prolonged use of AAS [5,11,12,14,23,48–50]. On the basis of animal studies, it has been suggested that AAS abuse may constitute a risk factor in aggressive behavior, partly by affecting the serotonergic system in the brain [41,43]. The question whether AASs create dependency or not is contended. Several studies have shown that chronic AAS use may cause dependency [8,9,13,26,61]. The underlying biochemical mechanisms of AASs are still poorly understood. The mesocorticolimbic dopaminergic pathway is considered to play an important role in the reinforcement

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circuitry of the brain (see review [16,35,64]), and a connection between AASs and central dopaminergic activity has been reported in animal studies [32,63,66]. Moreover, it is suggested that the serotonergic as well as the dopaminergic systems are involved in the rewarding effects of various drugs (see review [38]). The purpose of the present study was to investigate the effects of the AAS nandrolone decanoate at supraphysiological doses on dopaminergic and serotonergic activities in the brains of rat. In order to evaluate anabolic and toxic effects of nandrolone at the dosing regimes used, we monitored the weight of the animals, plasma creatine concentration, levels of hepatic aminotransferases, as well as selected blood parameters. Measurement of these peripheral parameters also served as a proof of biological activity of nandrolone at the dosing regimens used.

2. Material and methods

2.1. Animals

Adult male Wistar rats, weighing 290–360 g, were delivered from Harlan Netherlands B.V., (Netherlands) at least 1 week prior to the experiments. The animals were housed individually in Macrolon III-type cages (20 × 36.5 × 18.5 = 730 cm^3) under controlled temperature (22 ± 1 °C) and humidity conditions with a 12 h light–dark cycle. The lights were on from 06:00 a.m. to 06:00 p.m., and all the experiments were conducted during this time. Standard laboratory breeding chow (Altromin Nr. 1314; Chr. Petersen A/S, Ringsted, Denmark) and tap water were freely available. The local institutional committee for animal care and use and the chief veterinary surgeon of the county administrative board approved the animal experiments, and they were conducted according to the guideline laid down in the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes.

2.2. Drug treatment

The animals were randomly divided into three groups (n = 12 per group). Each group received one of the following treatments: (I) vehicle (arachinoid oil and benzylalcohol; University Pharmacy, Finland), (II) 5 mg/kg nandrolone decanoate (Deca-Durabolin®, N.V. Organon, the Netherlands) or (III) 20 mg/kg nandrolone decanoate. The animals received one intramuscular (i.m.) injection daily, 5 days per week during a 2-week period (10 injections per animal). The doses of nandrolone decanoate were selected since 5 mg/kg and 15 mg/kg are found to affect behaviors [20,40] and neurochemistry [34,37] in the rat. The injections were given in the left and right hind leg every other day, respectively, and the weight of the animals was monitored before each injection. A mixture of arachinoid oil and benzylalcohol, the vehicles of Deca-Durabolin® was used as a control compound.

2.3. Sample collection

At the beginning of the first (day 1) and the second (day 8) treatment weeks, the rats were anesthetized with 5% halothane gas (Trothane, I.S.C Chemicals, England) and a 0.5 ml blood sample was collected from *vena caudalis*. The blood was collected in a tube containing 25 μl of Na_2EDTA-UH-Q water solution (0.16 mM). The samples collected from 6 animals in each group were centrifuged at +4 °C (1800 × g) and plasma was stored at −20 °C. The samples collected from the other 6 animals in each group were kept as whole blood at room temperature and a blood count was performed within 24 h. The animals were killed with CO_2 and decapitated 3 days after the last injection (day 17) and trunk blood was collected and processed as described above. The brains were rapidly removed and the brain regions (olfactory bulb, prefrontal cortex, cerebral cortex, striatum, nucleus accumbens, hippocampus, hypothalamus, as well as pons and medulla) were dissected and immediately frozen and stored at −70 °C until assayed.

2.4. Chemical and biochemical assays

The concentration of dopamine (DA), 5-hydroxytryptamine (5-HT; serotonin) and their metabolites 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA) in brain tissues were determined using high performance liquid chromatography (HPLC) with electrochemical detection and an Insertil ODS-3V 5 μm (250 mm × 4.6 mm ID) reverse-phase column (GL-Sciences, Tokyo Japan) as described earlier [27], with necessary modifications for processing brain tissue samples. The frozen samples were weighed and placed in Eppendorf vials and homogenized in 21-fold quantity of anti-oxidative solution (1.0 mM oxalic acid, 3.0 mM L-cysteine and 0.1 M acetic acid), using a Vibra-Cell VC 600 high intensity ultrasonic processor (Sonics and Materials, Danbury, CT, USA) equipped with a tapered microtip. The processing time was 1.5 s and the amplitude was set at 40% of the maximum value. After a 10-min centrifugation (5500 × g) at +4 °C, the supernatants were filtered through 0.45 μm Bulk Acrodisc LC 13 mm filter (Pall Gelman Laboratory, USA). The samples were injected in a volume of 10 μl and the flow rate was 1.2 ml/min.

The blood count was performed with an automated system composed of Sysmex F-800 (Toa Medical Electronics, Japan) and Sysmex Auto Diluter AD-260 (Toa Electronics, German). The following assays were carried: hemoglobin, red blood cells, hematocrit, white blood cells, MCV (mean corpuscular volume), MCH (mean corpus hemoglobin) and MCHC (mean corpus hemoglobin concentration). Reticulocytes were counted manually from a

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