Side Effects of Anabolic Androgenic Steroids: Pathological Findings and Structure–Activity Relationships

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Contents

Abstract Side effects of anabolic steroids with relevance in forensic medicine are mainly due to life-threatening health risks with potential fatal outcome and cases of uncertain limitations of criminal liability after steroid administration. Both problems are typically associated with long-term abuse and excessive overdose of anabolic steroids. Side effects may be due to direct genomic or nongenomic activities (myotrophic, hepatotoxic), can result from down-regulation of endogenous biosynthesis (antiandrogenic) or be indirect consequence of steroid biotransformation (estrogenic).

Logically, there are no systematic clinical studies available and the number of causally determined fatalities is fairly limited. The following compilation reviews typical abundant observations in cases where nonnatural deaths (mostly liver failure

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and sudden cardiac death) were concurrent with steroid abuse. Moreover, frequent associations between structural characteristics and typical side effects are summarized.

Keywords Side effects • Heart • Liver • Arteriosclerosis • Psychiatry

1 Methodological Limitations

The evaluation of side effects of anabolic androgenic steroid (AAS) abuse contains several methodological problems. Firstly, the exorbitant dosages, which are up to 40 times higher than typical medical applications, prohibit any ethically justified clinical studies. Observations of side effects of therapeutic applications are only partially valid due to their comparatively low dosages. Moreover, the therapeutic relevance of steroids is reduced to a few testosterone analogs for treatment of, e.g., male hypogonadism, renal failure associated with anemia, cancer associated protein wasting diseases, burns, AIDS and hereditary angioedema.

Reliable empirical data from bodybuilding are virtually unavailable, because self-reports of administered dosages and corresponding side effects are certainly biased.

Finally, observations of pathological findings in autopsy cases are less frequent and therefore not statistically significant. Moreover, the causality between steroid abuses, the cluster of pathological findings and a presumptive cause of death needs to be challenged, because steroid effects (including side effects, health risks and hazards) do not coincide with their analytical identification at the time of death. Therefore, these observations do reflect a general steroid-associated elevation of health risks in the bodybuilder cohort but typically cannot clarify the individual situation.

2 Mechanisms of Action and Substance Specificity

Genomic steroid action consists of direct regulation of gene transcription by ligand–receptor interaction or indirect modulation of coactivators. Biochemical effects (including side effects) of steroids may be categorized according to the various receptor types, i.e., androgen (hAR), estrogen, glucocorticoid (hGR), progesterone (hPR) and mineralcorticoid receptors. In addition, nongenomic effects of steroids are well described, e.g. the direct activation of ionotropic $GABA_A$ receptors by neurosteroids.

Both mechanisms are characterized by a high specificity of receptor–ligand binding, requiring structural congruence of steroids and corresponding receptors.

Different steroid receptor types are structurally related; the sequence homology of the ligand binding domains of hAR is relatively high (e.g. 55% with hPR, 51% with hGR; Gao et al. 2005) which suggests the potential of cross-reaction in particular after administration of high doses of steroids. Extra to this high homology of relevant

receptors, the steroidal ligands are characterized by a considerable structural similarity and may often be biotransformed into each other. Therefore, a strict differentiation of steroids into functional subgroups is neither expected nor observed.

All relevant endogenous steroid hormones are synthesized and biotransformed within the biochemical pathway shown in Fig. 1 (compare Kicman 2009). Consequently, biological phenomena can result from direct substance supplementation (e.g. abuse of anabolic steroids) or indirect effects associated with inhibition (suppression of gonadotropic hormones) or induction (formation of estrogens from testosterone) of endogenous biosynthesis. The availability of steroidogenic enzymes in target tissues (e.g. 5α-steroid-reductase in prostate or skin) is hence of primary importance for the regio-specificity of steroidal effects.

Regulation of steroid biochemistry is a complex process and subject to positive enzymatic amplification and negative feedback mechanisms. Any administration of a steroid – especially in amounts far beyond endogenous levels – will compromise the balance of its endogenous synthesis. The administration of testosterone leads to a rapid down-regulation of gonadotropic hormones (e.g. luteinising hormone), followed by termination of endogenous production of steroids and atrophy of steroidogenic organs (testis). This may result in a suppression of other endogenous steroids (e.g. glucocorticoids or neurosteroids) produced within the same biochemical pathway.

Specific correlations between steroid structure and corresponding side effects are based on exemplary animal or clinical studies in therapeutic dose ranges and remain vague.

With respect to endogenous steroids, androgenic side effects may clearly be attributed to reduction of a 4-double bond to 5α-dihydrotestosterone (DHT) by 5α-steroid-reductase and estrogenic effects are due to aromatisation of the steroid A-ring by steroid-aromatase (CYP19). However, a simplified extension of these principles to synthetic steroids is not generally valid.

Steroid side effects may either result from direct receptor agonism (whether or not in combination with metabolic activation) or may be due to a suppression of steroid biosynthesis. Factors determining the efficiency of steroid action are therefore the structural specificity as well as the availability of activating enzymes in the respective target cells (e.g. skin, brain region).

As a simplified review, main side effects may be associated with compounds frequently abused in sports and bodybuilding and typical structural characteristics, i.e.:

- Anabolic side effects of testosterone and analogs
- Enhanced androgenic effects, often associated with 5α-dihydrogenation of steroids
- Estrogenic side effects, depending on susceptibility to A-ring aromatisation
- Antiandrogenic effects based on a suppression of the hypothalamus–pituitary–adrenal/gonadal (HPA/HPG) axes, without clear structural determination
- Hepatotoxicity, clearly correlated with 17α-alkylation and the related inhibition of metabolic deactivation of steroids by oxidation of the 17β-hydroxy group.

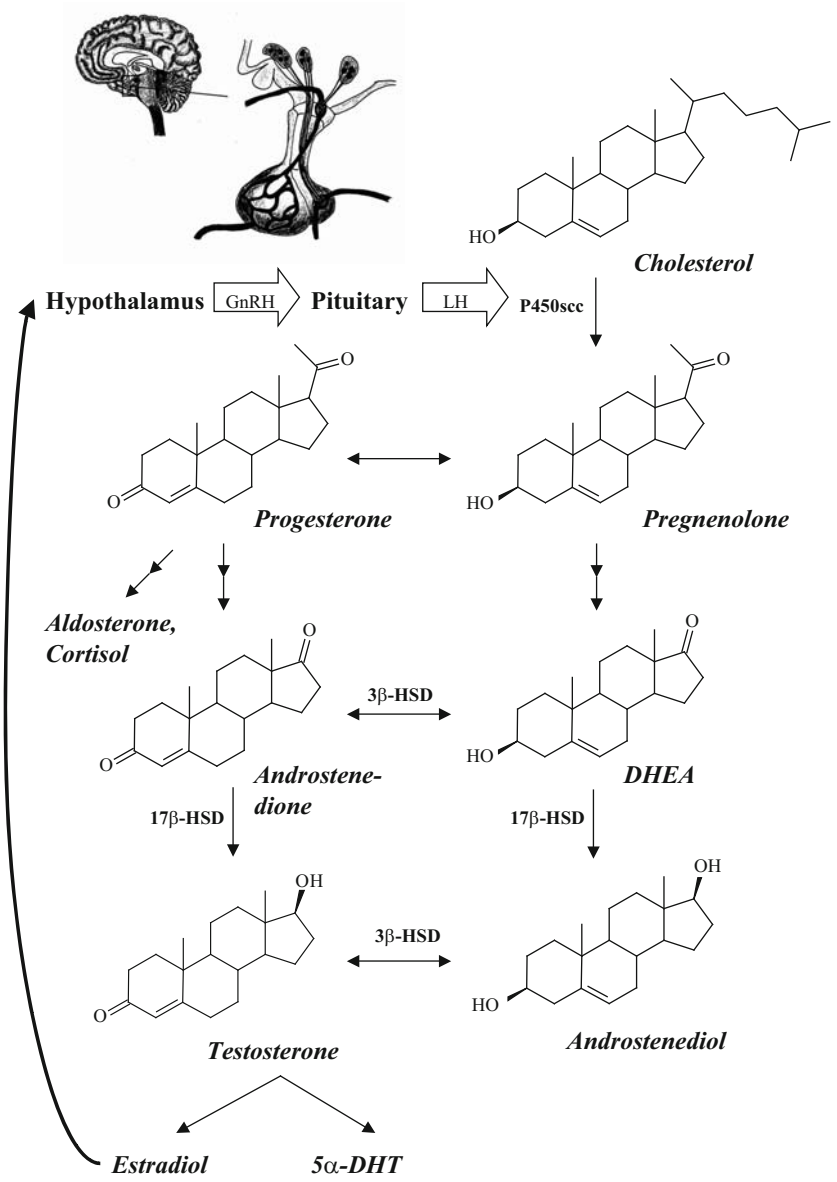

Fig. 1 Biochemical synthesis and metabolism of steroids

- Psychiatric effects of neurosteroids (characterized by 3α-hydroxylation and 5α-conformation of the A-ring) synthesized locally in the brain. The availability, induction or blocking of steroidogenic enzymes in relevant brain regions seems to be more relevant than peripheral steroid levels.

3 Anabolic Effects

3.1 Correlation of Steroid Structure and Anabolic Effects

The inactive intracellular receptor proteins are located in the cytosol. After formation of a receptor–ligand complex with suitable steroids and dimerisation, the receptor–ligand complex migrates into the cell nucleus and binds to a specific sequence of the DNA, leading to transcriptional activation of protein synthesis. Moreover, anticatabolic effects based on glucocorticoid receptor inhibition may contribute to anabolic effects.

The process is controlled by the specificity of ligand binding and DNA binding domain of the steroid receptors. Owing to the high similarity of the ligand binding domains of all receptors, steroid ligands cross-react with different receptors.

17β-Hydroxylation and an A-ring carrying a 3-keto or equivalent substitutions are thought to be the essential structural characteristics of anabolic effects and therefore affected by its biotransformation (Fig. 2). The time-limiting metabolic reaction of testosterone degradation is an A-ring reduction by 5α/β-hydrogenation. Further metabolic degradation leading to (partial) deactivation of anabolic steroids are oxidation of 3- and 17α/β-hydroxysteroids by various hydroxysteroid dehydrogenase (HSD) isoforms. Moreover, anabolic steroids are partially deactivated by aromatisation of the A-ring to yield estrogens.

Therefore, a protection of the respective groups contributes to the efficacy of anabolic effects and modifies the spectrum of potential side effects. The most potent measure to prolong its activity consists of alkylation in position 17α protecting the 17β-hydroxy group and enhances bioavailability and anabolic effects in particular after oral administration.

Typical modifications to prevent aromatisation and/or saturation of the A-ring are alkylation in positions 1 or 2, chlorination in position 4, insertion of the 2-oxa group (oxandrolone), introduction of a 1–2 double bond, reduction of the 4–5 double bond to yield 5α-dihydrosteroids and removal of the C19-methyl group.

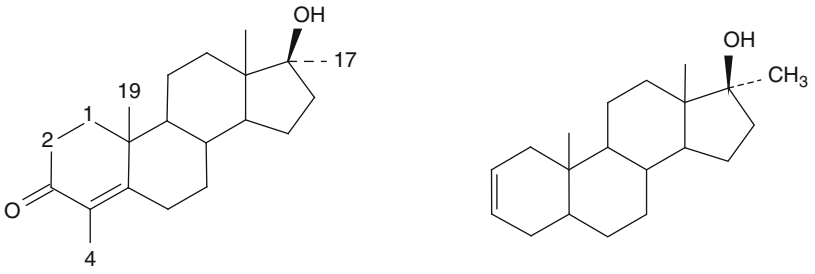

Fig. 2 Modifications of biological effects of steroids and their bioavailability may be achieved by structural modifications, particularly at positions 1, 2, 4 and 17 or removal of the angular C19. The β-conformation of the 17-hydroxy-group is essential for anabolic effects of steroids while 3-keto groups are considered to be supportive but not essential and may be replaced by a 2–3 double bond (e.g., desoxymethyltestosterone)

Generally, androgenic anabolic efficacy of steroids is governed by their receptor binding and susceptibility to biotransformation. DHT, metandienone and oxymetholone are supposed to be strong anabolic agents. Remarkably, the anabolic effects of desoxymethyltestosterone (1.6 times superior to testosterone), stanozolol or furazabol are significant in spite of lacking 3-keto groups.

3.2 Pathological Findings

The use of AAS in athletes is widespread, both for performance improvement and for augmenting muscular development and strength. However, AAS use is not limited to elite athletes and seems to be more extensive among recreational and amateur athletes (Catlin and Hatton 1991; Hartgens and Kuipers 2004). Strength athletes mainly use AAS to increase muscle mass and strength. Weightlifters and power-lifters strive primarily for strength, whereas bodybuilders train for muscle mass and body dimensions (Fig. 3).

The long-term side effects are related to structure of steroids, dosage, frequency of use, age at initiation and concurrent illicit drug use and have not been fully elucidated (Yesalis and Bahrke 1995). Nevertheless, there is a broad spectrum of possible adverse effects caused by supraphysiological AAS levels which are summarized in Table 1 (Catlin and Hatton 1991; Eklöf et al. 2003; Evans 2004; Graham and Kennedy 1990; Hartgens and Kuipers 2004; Haupt and Rovere 1984; Hickson et al. 1989; Karila 2003; LaBree 1991; Maravelias et al. 2005; Melnik et al. 2007; Modlinski et al. 2006; Narducci et al. 1990; Yesalis and Bahrke 1995). Of these, some are reversible and often constitute cosmetic problems only. However, others are irreversible and may lead to serious harm. Of these, the best documented effects are those on the cardiovascular system, serum lipids, liver and the reproductive system.

Although life-threatening side effects seem to be rare, nearly 100% of persons using AAS experience subjective side effects as a result of AAS use (Evans 2004; Parkinson and Evans 2006). However, there are numerous case studies and reports which reported serious adverse effects and deaths. Obviously, even many well designed studies do not reflect the AAS problem in real life. Many studies lack a control group and do not account for individual, exercise and environmental

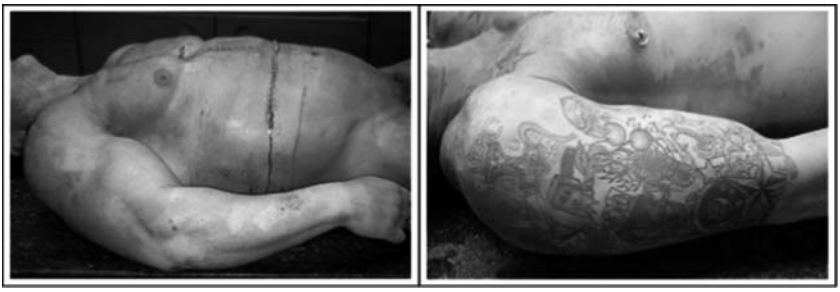

Fig. 3 External aspect of a professional bodybuilder (*left*) and of a recreational AAS user

Table 1 Possible adverse effects of AAS abuse

Cardiovascular system	*Psychic/behavioral disturbances*
Disturbed lipid metabolism	Mood swings
Elevated blood pressure, hypertension	Aggressiveness
Cardiac arrhythmias	Depressive symptoms
Myocardial hypertrophy	Manic symptoms
Cardiomyopathy	Sleep disturbances
Thrombosis	Withdrawal, dependence
Early myocardial infarction	Psychosis
Sudden cardiac death	
Endocrine/reproductive system	*Kidney*
Decrease of libido	Pollakisuria
Decrease of fertility	Increase of serum creatinine
Decreased LH and FSH	Kidney stones
Altered glucose metabolism	
Male-specific side effects	*Skin*
Testicular atrophy	Acne
Erectile dysfunction, impotence	Urticaria
Subfertility	Striae
Prostatic hypertrophy	Alopecia
Impaired spermatogenesis	
Gynecomastia	
Female-specific side effects	*Gastrointestinal tract*
Hirsutism, virilization	Queasiness
Voice deepening	Emesis
Menstrual irregularities	Diarrhoe
Clitoral enlargement	Hematemesis
Reduced breast size	
Liver	*Musculoskeletal*
Cholestasis, jaundice	Tendon damage
Peliosis hepatis	Bone pain
Neoplasia	Premature epiphyseal closure (adolescents)
Gall bladder stones	
Injection-related	*Various*
Hematoma	Edema
Infection	Fever, shivers
Fibrosis	Anaphylactic shock
Neuro-vascular injury	
Hepatitis B or C and HIV infection	

variables. Furthermore, the covert nature of their misuse may explain the limited and conflicting data concerning their side effects. Therefore, adverse effects might be much more severe than reported in the literature.

In a prospective study, a Finnish cohort of former elite power-lifters with presumed, but not verified, earlier use of AAS exhibited a 4.6-fold higher mortality compared to a control population, with myocardial infarction (Fig. 4) as the main cause of death (Pärssinen et al. 2000). A Swedish study suggested that AAS abuse is associated with an increased risk of premature death, especially among persons with additional substance abuse and/or psychiatric disease (Petersson et al. 2006a).

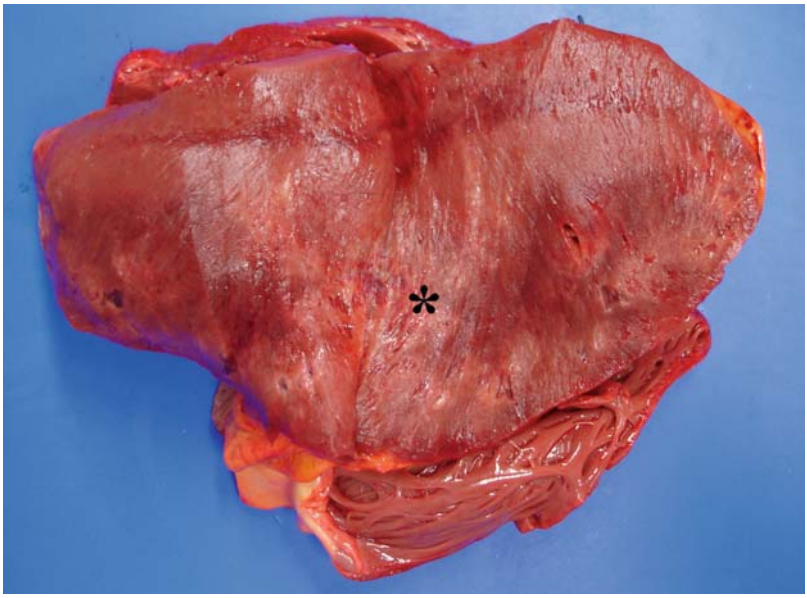

Fig. 4 Old myocardial infarction in a 30-year old AAS abuser

After long-term AAS abuse (sudden) cardiac death is the most common manifestation of AAS toxicity (Di Paolo et al. 2007; Dickerman et al. 1995; Fineschi et al. 2007; Hausmann et al. 1998; Luke et al. 1990; own observation).

Upon autopsy as well as in living persons, a dose-dependent left-ventricular hypertrophy has been observed (De Piccoli et al. 1991; Dickerman et al. 1997; Karila 2003; Karila et al. 2003; Krieg et al. 2007; McKillop et al. 1986; Nottin et al. 2006; Sachtleben et al. 1993; Sader et al. 2001; Thiblin et al. 2000; Urhausen et al. 2004; Yeater et al. 1996; own observation). Similar findings have been described for the cardiac ventricular septum (Sader et al. 2001). According to an echocardiographic study this concentric left-ventricular myocardial hypertrophy can still be demonstrated a long time after cessation of AAS abuse (Urhausen et al. 2004).

Other cardiac complications of AAS abuse include myocardial fibroses and myocardial necroses (Halvorsen et al. 2004; Luke et al. 1990; Sullivan et al. 1998; own observation), as well as early coronary sclerosis (Santora et al. 2006; own observation, Fig. 5).

As the cause of these alterations, coronary spasm, increased atherogenesis, impairment of coagulation and fibrinolyis as well as direct cardiotoxic (arrhythmogenic) effects of AAS have been proposed.

The effects of AAS on blood pressure are still discussed controversially (Hartgens and Kuipers 2004; Sullivan et al. 1998). In some studies the development of hypertension could not be demonstrated after the chronic intake of AAS (Hartgens et al. 2003; Karila et al. 2003; Kuipers et al. 1991). In contrast, other studies

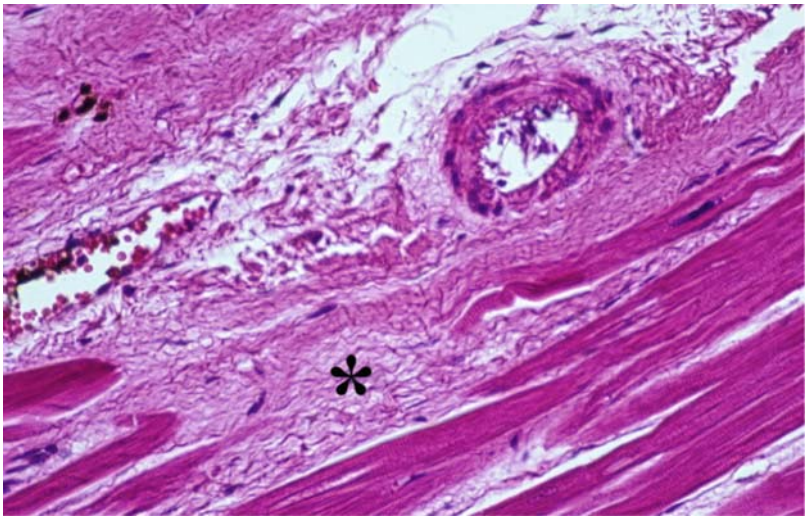

Fig. 5 Microphotograph of myocardial fibrosis in an AAS abuser

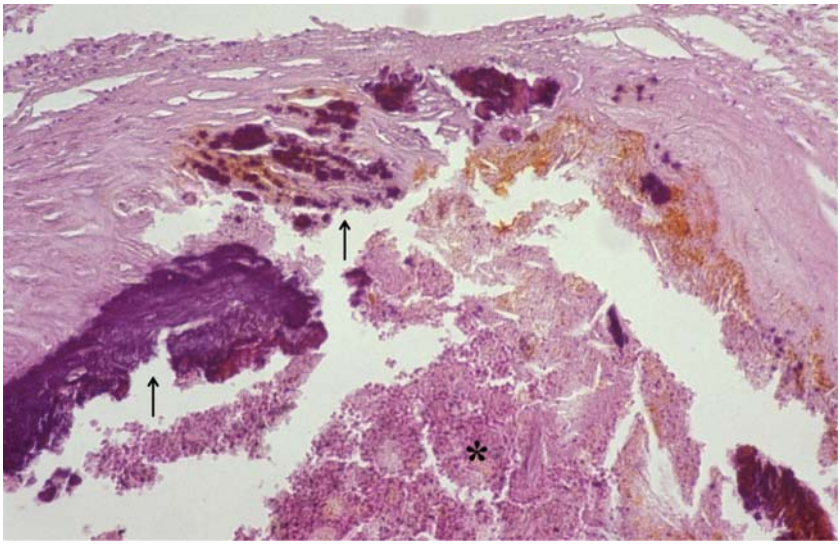

Fig. 6 Marked coronary artery sclerosis

observed the occurrence of hypertension after long-term AAS abuse (Grace et al. 2003; Rockhold 1993).

Besides morphological alterations, functional changes of the vascular system have been described after AAS abuse. These consisted of an increased aortic stiffness (Kasikcioglu et al. 2007) and an impaired vascular reactivity (D'Ascenzo et al. 2007; Ebenbichler et al. 2001; Lane et al. 2006). Although the alterations of

impaired vascular reactivity seem to be partially reversible after abstinence, consumers are at risk for vasospasm with subsequent myocardial infarction (Fig. 4). In an own autopsy case (Fig. 6), a 41-year old man died due to sudden cardiac death. The heart weighted 482 g and showed a severe coronary artery sclerosis. Toxicological analyses revealed high levels of metandienone.

4 Bioconversion of Steroids to Characteristic Androgens and Estrogens

4.1 Conversion to Androgens

Although androgenic and anabolic effects are mediated through the same receptor (hAR), the balance between both effects of steroids varies significantly and seems to be associated with certain structural characteristics. DHT in particular exhibits a hAR binding which is 2–10 times superior to testosterone. Therefore, conversion of T to DHT in androgen-responsive tissues (prostate) amplifies the androgenic effects considerably.

Since 5α-DHT is a potent androgenic substance, 5α-reduction of steroid A-rings is supposed to be a characteristic structural feature of androgens. Similarly, synthetic steroids with original 5α structure, e.g. mesterolone or methenolone, are potent androgenic compounds. Steroids with A-ring modifications stabilizing the A-ring conformation, e.g. stanozolol, oxandrolone or oxabolone, appear to be comparatively less androgenic. Another promising approach to partial separation of androgenic and anabolic effects is the removal of 19-methyl to yield 19-norsteroids. Nandrolone (19-nortestosterone) exhibits reduced androgenic effects but retains anabolic activity comparable to testosterone (Gao et al. 2005).

The ratio of anabolic (myotrophic) to androgenic effects of nandrolone is significantly higher than the corresponding index of testosterone, although both steroids are biotransformed by analog enzymes and pathways (Fig. 7). This is assumed to be due to the fact that 5α-dehydro-19-nortestosterone (relative to nortestosterone) binds with weaker affinity to the hAR, opposite to DHT which exhibits a higher affinity than testosterone.

Consequently, adrenergic effects of steroids are inconsistent and depend on the particular chemical structure. The administration of metandienone, nandrolone decanoate or testosterone cypionate stimulated male sexual behavior after gonadectomy, while stanozolol, oxymetholone or methyltestosterone showed no effect (Clark and Harrold 1997; Clark et al. 1997).

In females the administration of AAS will induce masculinization. Acne, reduction of libido and voice deepening was reported in the first weeks of abuse. After long-term AAS abuse menstrual irregularities, enlargement of the clitoris and reduction of breast size usually develops (Evans 2004; Hartgens and Kuipers 2004; Wu 1997). In contrast to males, some changes, e.g. voice deepening, are not fully reversible (Maravelias et al. 2005).

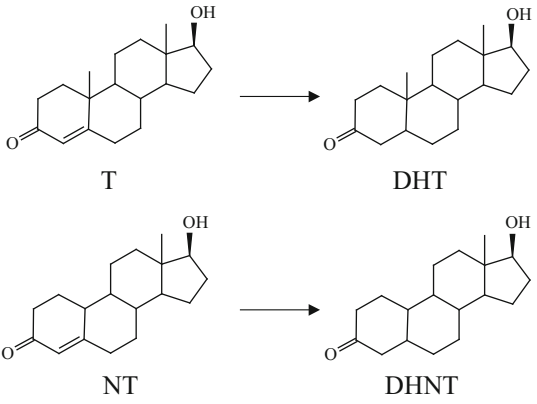

Fig. 7 Partial dissociation of myotrophic and androgenic effects by biotransformation of testosterone (T) and nandrolone (NT) to corresponding 5α-dehydro metabolites result in opposite effects. This is due to the fact that DHT has 2–10-fold androgen-receptor affinity (compared to T) while receptor binding of DHNT is weaker than NT. Therefore, bioconversion in androgen-responsive tissues may alter its activity in both directions

4.2 Conversion to Estrogens

Endogenic estrogens are biosynthesized by aromatisation of suitable steroid precursors, e.g. testosterone to estradiol. Similarly to AAS, the biological effects of estrogens are mainly governed by stereospecificity, i.e. 17β-estradiol is the most potent estrogen. Hence the estrogenic side effects are dependent on susceptibility of steroid A-rings to aromatisation (i.e. 19-hydroxylation, followed by cleavage of the C19 and subsequent enolisation of the 3-keto group; see Kicmann 2009). Structural modifications like reduction of 4–5 double bond (mesterolone or methenolone), A-ring condensation (e.g. stanozolol, Fig. 8), methylene substitution in position 2 (e.g. oxymetholone) or additional double bonds in the A-ring (trenbolone or tetrahydrogestrinone) significantly impede the conversion to estrogens and corresponding side effects.

In spite of lacking aromatisation, certain steroids (oxymetholone) exhibit significant estrogenic side effects, which are thought to be due to the cross-reaction of respective substances at high dosages with estrogen or progesterone receptors.

On the other hand, estrogenic effects of synthetic anabolic steroids may be increased with respect to testosterone, e.g. by 17α-alkylation. Aiming at a stabilization of the 17β-hydroxy group to prolong the anabolic effect, the 17α-alkyl group prevents a deactivation of 17β-estradiol to the (less potent) 17-keto or 17α-OH compounds (Fig. 8). Therefore, 17α- alkylated steroids – insofar as not A-ring protected – often cause comparatively stronger estrogenic effects (e.g. methyltestosterone, metandienone).

At supratherapeutic doses of AAS, the peripheral conversion of androgens to estrogens results in gynecomastia. Besides the pain and cosmetic implications of gynecomastia, surgical correction may be necessary (Hartgens and Kuipers 2004).

Estrogenic side effects may be reduced by administration of antiestrogens, which either suppress the aromatisation of steroids or selectively block the estrogen receptor. Due to the high potency of estrogenic side effects, these so-called antiestrogens are frequently abused amongst bodybuilders and are prohibited in sports.

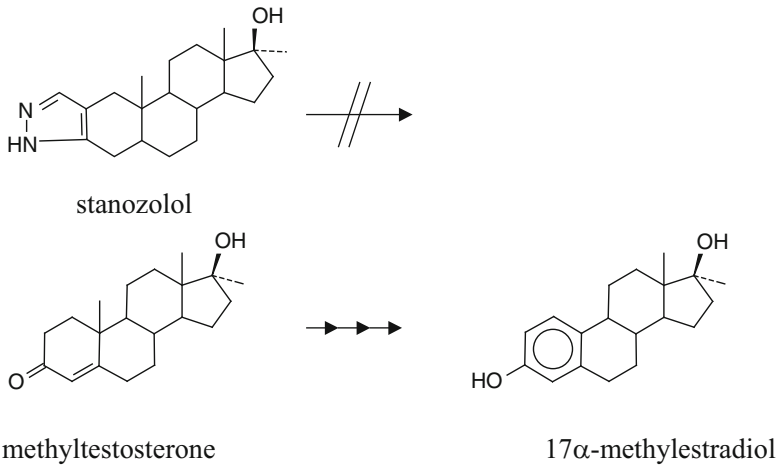

Fig. 8 Synthetic modification of steroids may suppress aromatisation and resulting side effects by A-ring stabilization (e.g., stanozolol, top). Alternatively, the presence of a 17α-methyl group prevents the deactivation of 17α-methylestradiol by oxidation of the 17β-hydroxy group, resulting in comparatively elevated estrogenic effects of methyltestosterone

For the prevention of gynecomastia, the self-administration of estrogen-receptor blocking substances such as tamoxifen is widespread (Hartgens and Kuipers 2004).

4.3 Suppression of Endogenous Steroid Biosynthesis and Pathological Effects on the Endocrine and Reproductive System

The negative feedback of elevated concentrations of testosterone, DHT or estrogens to the hypothalamus and pituitary leads to a suppression of endogenous production of gonadotropic hormones and endogenous steroids (Fig. 1), associated with morphological effects on endocrine systems (testis), psyche and sexual behavior.

According to animal experiments dealing with the influence of steroids on male sexual behavior (Clark and Harrold 1997; Clark et al. 1997), there was a significant suppression after high-dose administration of 17α-alkylated steroids (stanozolol, oxymetholone or methyltestosterone), whereas the application of metandienone, nandrolone decanoate or testosterone cypionate had little influence on expression of mounts, intromissions or ejaculations of intact male rats.

According to self reports of bodybuilders, boldenone, trenbolone and nanrolone were considered as the most unpleasant steroids due to their suppression of libido (Bachmann and Sinner 2007).

AAS suppress the HPG axis. As a consequence the exogenous intake of AAS will decrease the endogenous production of testosterone and gonadotropins

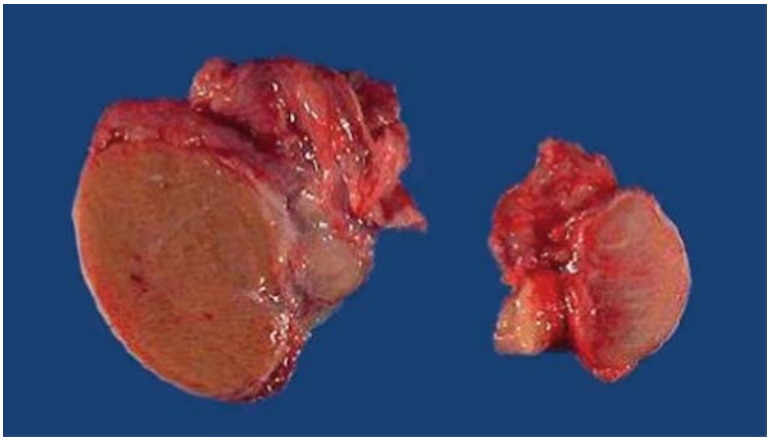

Fig. 9 Testicular atrophy in a 30-year old AAS abuser (*right*) compared to normal size (*left*)

(luteinising hormone – LH and follicle-stimulating hormone – FSH). The resulting side effects are gender-specific (Evans 2004; Hartgens and Kuipers 2004; Wu 1997; own observation). In males this suppression leads to a testicular atrophy (Fig. 9), a decreased spermatogenesis with a reduction of sperm count and motility, erectile dysfunction, impotence and a decrease of libido. These side effects are dose- and time-dependent and fully reversible months after abstinence (Hartgens and Kuipers 2004; Yesalis and Bahrke 1995). For erectile dysfunction the coadministration of sildenafil, tadalafil or vardenafil which might increase the risk of sudden cardiac death (own observation) is regularly reported.

The effects of AAS on the blood glucose level may include peripheral insulin resistance, hyperinsulism, hyperglycemia, and a reduced reaction to glucagons (Cohen and Hickman 1987; Graham and Kennedy 1990).

A reduction of thyroid hormones has also been observed after AAS use (Shahidi 2001).

4.4 Metabolic Suppression and Hepatotoxic Effects

There is sufficient evidence that hepatotoxic effects of steroids are associated with 17α-alkylation of the molecules (Applebaum-Bowden et al. 1987; Pey et al. 2003; Socas et al. 2005; Stimac et al. 2002). Both biochemical malfunctions such as effects on lipid profiles (increase of alkaline phosphatase, lactate dehydrogenase, conjugated bilirubin (Hall and Hall 2005)), high density lipoprotein (HDL)-C reduction or pathological increase of serum transaminases as well as morphological indicators of hepatocellular and intrahepatic cholestasis, adenomas, hepatic failure, hepatocellular hyperplasia, and general hepatic damage are significantly associated with 17α-alkylation of steroids. Interestingly, there seems to be a characteristic structural correlation to hepatotoxicity, extra to the obvious fact that 17α-steroids

are mainly taken orally at relatively high dosages, which potentially damage liver cells due to the high steroid load (first pass effects). However, other substances applied orally at high concentrations are not characteristically hepatotoxic (e.g. methenolone acetate). On the other hand, stanozolol is reported to cause liver damage regardless of its application pathway (intramuscular or oral).

The significant association of hepatotoxicity and 17α-alkylation of steroids is likely due to its conjugation. D-ring glucuronides of estradiol and ethinylestradiol (Vore et al. 1983a,b) were found to cause dose-dependent reversible cholestasis (Vore et al. 1983a,b). Alternative injection of estradiols conjugated at position 3, [3-(β-D-glucuronide)] or position 17 [17β-(β-D-glucuronide)] to rats demonstrated that hepatotoxicity is clearly restricted to D-ring glucuronidation (Slikker et al. 1983; Vore et al. 1983a,b). Moreover, the development of cholestasis was observed after administration of glucuronides of testosterone or DHT, suggesting that A-ring modifications are less significant than conformation of the 17-glucuronide. A general decrease in toxicity was observed after A-ring saturation and reduction of 3-keto group to 3-hydroxy-steroids, but there is no correlation between liver toxicity and primary pharmacological (i.e. anabolic, estrogenic or progestational) effects (DeLorimier et al. 1965). 17β-Glucuronides were found to be specifically and strongly bound to a site in the canalicular membrane (Changchit et al. 1990). This structural and stereo specificity is thought to be due to the similarity of 17β-conjugates of steroids to bile acids, which are acidic 17β-substituted steroids. Steroid-induced cholestasis and hepatotoxicity may therefore initially be attributed to a competition between steroid-17β-(β-D-glucuronides) and bile acids for recognition at receptor sites or the decrease of permeability of hepatocytes (Vore et al. 1983b).

17α-Alkylation of steroids hugely diminishes the variety of metabolic pathways, because the formation of 17-keto metabolites or 17-epimers is blocked. In the case of testosterone, these metabolites represent the majority of urinary metabolites (see Fig. 9, Kicman 2009). After 17α-alkylation, the remaining portion of critical 17β-glucuronides is therefore potentially higher leading to an elevated risk of hepatotoxic effects. On the other hand, the formation of 17β-glucuronides maybe suppressed by alkylation.

4.4.1 Pathological Findings in the Liver

The alterations after AAS abuse are broad and include cholestatic jaundice (Chitturi and Farrell 2001; Ishak and Zimmerman 1987; own observations), peliosis hepatis (Ishak and Zimmerman 1987; Soe et al. 1992), focal nodular hyperplasia and adenoma (Ishak and Zimmerman 1987; Socas et al. 2005; Soe et al. 1992; own observation), as well as hepatocellular carcinoma (Ishak and Zimmerman 1987; Soe et al. 1992).

17α-Alkylated steroids as well as nonalkylated anabolic steroids are responsible for the development of hepatic adenoma (Fig. 10) and carcinoma (Socas et al. 2005;

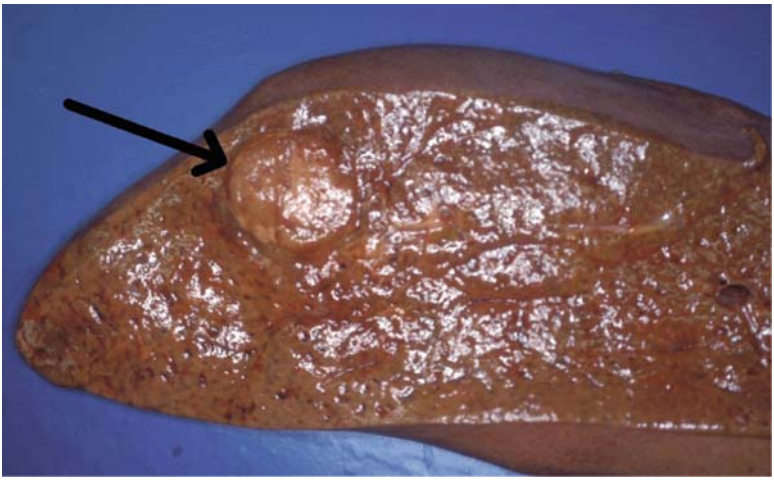

Fig. 10 Adenoma of the liver in an AAS abuser

Soe et al. 1992). Some authors recommend surgical removal of adenomas since those persons are at high risk for malignant progression and tumor hemorrhage with subsequent hepatic rupture (Socas et al. 2005). The risk of hepatic hemorrhage with hepatic failure is also high in peliosis hepatis characterized by the formation of multiple blood-filled cysts within the liver.

The mechanism of action is most likely from a direct toxic effect (Modlinski and Fields 2006). However, the incidence of the above mentioned changes after AAS abuse is still unclear.

4.4.2 Lipid Metabolism

Although many reports demonstrated premature arteriosclerosis after AAS abuse, there is so far no direct evidence for the causation of arteriosclerosis by AAS (Melchert and Welder 1995). However, the chronic abuse of AAS has been shown to induce profound alterations in serum lipid concentrations. There is a decrease of the vasoprotective HDL level (Ebenbichler et al. 2001; Fröhlich et al. 1989; Glazer 1991; Hartgens et al. 2004; Hislop et al. 2001; Karila 2003; Sader et al. 2001) and an elevation of the vasoaggressive low-density lipoprotein (LDL) (Fröhlich et al. 1989; Glazer 1991; Hurley et al. 1984; Webb et al. 1984), resulting in a decreased HDL/LDL ratio. These alterations of lipid parameters seem to be especially associated with stanozolol (Applebaum-Bowden et al. 1987; Sloane and Lee 2007) and oxymetholone (Pavlatos et al. 2001).

Other laboratory parameters of lipid metabolism that might be impaired are a decrease in lipoprotein (a) (Cohen et al. 1996; Fröhlich et al. 1989; Hartgens et al. 2004; Hislop et al. 2001; Lenders et al. 1988; Lippi et al. 1997; Zmuda et al. 1996)

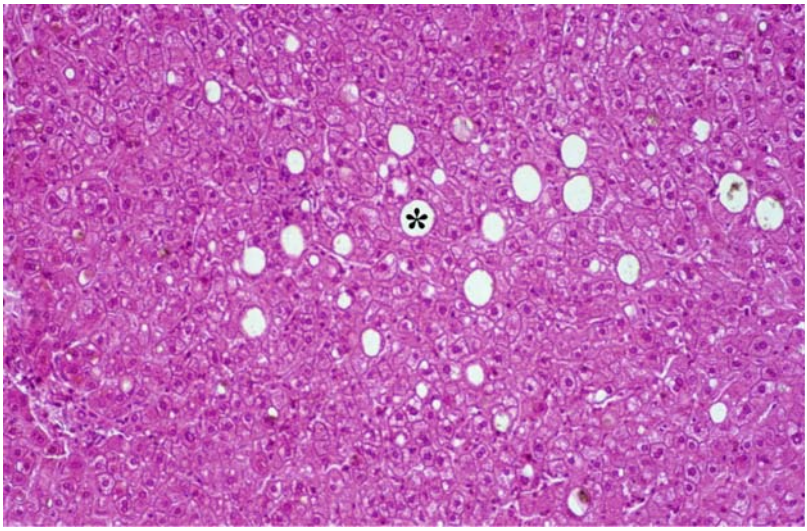

Fig. 11 Lipid droplets in the liver of an AAS abuser

and apolipoprotein A-I and A-II (Fröhlich et al. 1989; Zuliani et al. 1989) and an elevation of the apolipoprotein B level (Hartgens et al. 2004; Zuliani et al. 1989).

This lipid profile has been demonstrated to persist up to five months after cessation of AAS abuse (Thiblin et al. 2000). However, based on the observations that AAS may induce an atherogenic lipid profile, they are considered as a potent cardiovascular risk factor (Ebenbichler et al. 2001; Glazer 1991). Therefore, the abuse of AAS is associated with the development of coronary artery disease and an increased risk of both acute vascular occlusion and arrhythmic sudden death (Thiblin et al. 2000).

In an own autopsy case, a 31-year-old male died due to metabolic failure (Fig. 11). The heart weighted 536 g. Toxicological analyses revealed high levels of steroid esters (testosterone, nandrolone, boldenone) as well as stanozolol, clenbuterol, and tetrahydrocannabinol.

5 Neurosteroids and Psychiatric Effects

5.1 Biosynthesis of Neurosteroids

The influence of steroids on mood, behavior and libido is undisputed and proven by a multitude of clinical observations. Typical changes in behavior and mood are significantly correlated to variations in steroid biochemistry (e.g. menstrual cycle, age-related steroid reduction). Biochemical malfunctions may cause typical

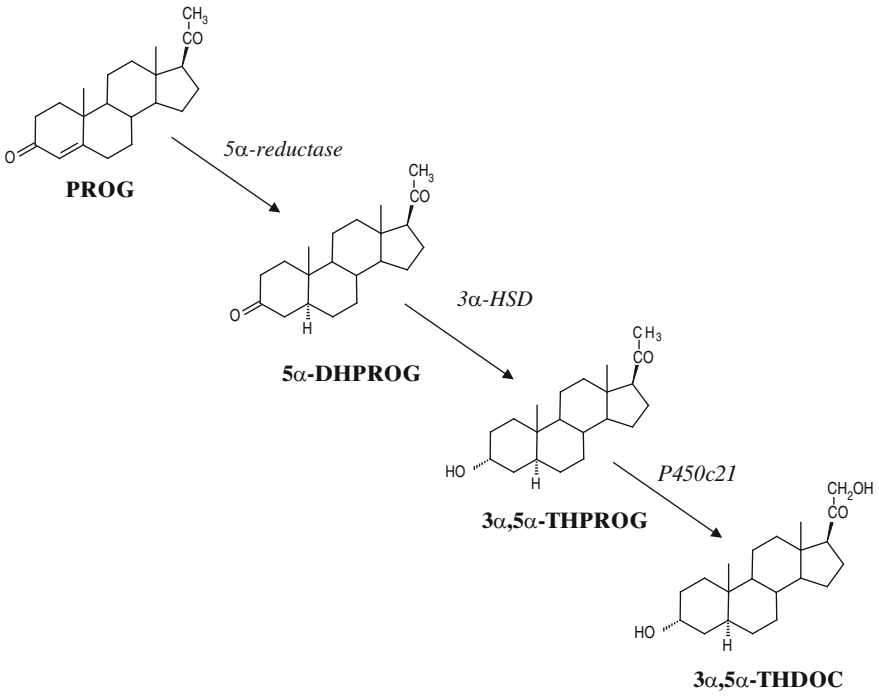

Fig. 12 Neuronal biosynthesis of neurosteroids, e.g., 3α,5α-tetrahydrodesoxycorticosterone (3α,5α-THDOC) from endogenous progesterone (PROG). The biochemical pathway is controlled by conventional enzymes of steroid biochmistry, i.e., 3α-hydroxysteroid dehydrogenase (3α-HSD) and 5α-reductase

psychiatric symptoms (adrenal hypoactivity associated with sleeplessness and inability to concentrate), and inhibition of steroid secretion and/or blocking of their effects proved to be an adequate measure for treatment of depressions (Dubrovsky 2005; Giammanco et al. 2005; Nelson and Chiavegatto 2001).

The best examined mechanism of steroid-related neuroactivity is the $GABA_A$ modulatory effect of neurosteroids (Belelli and Lambert 2005; Herd et al. 2007; Hosie et al. 2006). It consists of a positive modulation of the GABAergic effects at low dosages and GABA-mimetic activity at elevated concentrations, leading to a general suppression of excitatory neurotransmissions. This is consistent with a central inhibitory activity of these neurosteroids, which are known to express hypnotic, antidepressive or anxiolytic effects. The steroid ganaxolone 3α-methyl-progesterone, for instance, was approved as a hypnotic due to its GABA mimetic potential.

These GABA modulatory neurosteroids comprises certain metabolites of endogenous steroids which are mainly characterized by 3α-hydroxylation and the 5α-conformation of the saturated A-ring and often the presence of a 20-carbonyl group. The 3α orientation of the hydroxy group seems to be of particular importance for neuroactivity of steroids (Fig. 12). 3β-Alkylation significantly improves

the pharmacological effect of respective compounds (e.g. ganaxolone) by suppression of metabolic degradation (similar to 17α-alkylation of steroids to prolong their anabolic effects). Typical examples are 3α,5α-tetrahydroprogesterone (allopregnanolone) and 3α,5α-tetrahydrodesoxycortisosterone (THDOC).

These neuroactive steroids do not act as endocrine hormones. Steroids are definitely capable of easily passing the blood–brain barrier and may diffuse into the central nervous system after endogenous synthesis in the gonads or adrenal glands as well as after abuse of synthetic steroids. Nevertheless, there is evidence that neurosteroids act as paracrine receptor modulators and their specific neuronal response is mainly governed by biotransformation in the brain. The regio-selectivity of neuronal effects appears to be controlled by the availability of enzymes in the brain.

However, the main pharmacodynamic mode of neuroactivity action is central inhibition and hence not eligible to explain enhanced aggressiveness as a potential side effect of steroid abuse. Conclusive alternative pathways are

- Inhibition of the GABA mimetic effects of neurosteroids by antagonism,
- Suppression of biosynthesis of GABA mimetic steroids,
- Influence of glucocorticoid suppression as a consequence of steroid supplementation (e.g. trenbolone),
- Effects of high levels of estrogen biotransformation products from anabolic steroids,
- Indirect effects on serotonin or dopamine neurotransmission.

Another group of neuroactive steroids with potential GABA antagonistic effects includes estrogens or androgen sulfoconjugates (Gibbs et al. 2006; Schumacher et al. 2008). Typical examples of the latter group are sulfates of pregnenolone and dehydroepiandrosterone. Polar conjugates are no longer capable of migrating through the blood–brain barrier and are hence synthesized locally. Brain concentrations of steroid conjugates were found to be independent of blood levels and remained unchanged after adrenalectomy or gonadectomy. Generally, these compounds are considered to be GABA antagonists with opposite biological effects. Structural characteristics of these compounds are less significant.

5.2 Behavioral–Psychiatric Side Effects

The general development of aggressiveness after steroid abuse is epidemiologically not proven. The evaluation of this presumptive correlation in recent literature remains controversial. Cases of positive association of steroid abuse and aggressiveness (Daly et al. 2003; Kouri et al. 1995; Perry et al. 2003; Pope et al. 2000a,b; Su et al. 1993) are described as well as the absence of significant effects (Anderson et al. 1992; Yates et al. 1999), which may be due to the existence of opposed

pharmacodynamic mechanisms, involving similar steroids acting as either agonists or antagonists. Moreover, suppression of biosynthesis and biotransformation of steroids is of paramount importance for neuroactivity of AAS.

So far, there is no obvious structure–activity correlation to explain or predict the potential of anabolic steroids as candidates for elicitation of aggressive behavior.

The enzymatic biosynthesis of neurosteroids is a prerequisite for neuroactivity of steroids and may logically be affected by inhibition of enzymes. Application of enzyme blockers (e.g. finasteride to inhibit 5α-reductase) significantly reduces central nervous effects of neurosteroids (Reddy 2004).

Similarly, neuroactive effects are significantly reduced by competitive antagonism with structurally related compounds like 17-phenyl-5α-androst-16ene-3α-ol (Kelley et al. 2007; Mennerick et al. 2004).

Self reports of enhanced aggression connected with the abuse of anabolic steroids is often devoted to particular compounds like fluoxymesterone or trenbolone. According to animal studies, enhanced aggression was correlated with the administration of testosterone and methyltestosterone, while stanozolol was even found to inhibit aggression (Breuer et al. 2001; McGinnis et al. 2002).

Moreover, there are assumptions that the balance between estrogen and androgen receptor mediated signaling is essential for relevance of steroids in aggression enhancement (Clark and Henderson 2003).

However, there is clear evidence that changes of behavior and aggression enhancement do not necessarily develop coincidentally with steroid abuse. These effects seem to parallel the suppression of endogenous biosynthesis of steroids rather than levels of exogenous steroids. Administration of testosterone propionate was demonstrated to cause reduction of concentration of GABA inhibitory allopregnenolone in the brain of treated mice, corresponding to enhancement of aggression (Pinna et al. 2005). Elevated aggression amongst AAS abusers was correlated with attenuated concentrations of endogenous testosterone and behavioral effects of AAS were shown to be secondary to endogenous steroid levels (Thiblin and Petersson 2005; Daly et al. 2003).

Testosterone levels have been associated with aggressive behavior (Bahrke and Yesalis 2004; Brower 2002; Copeland et al. 2000; Trenton and Currier 2005; Uzych 1992). Moreover, violent behavior and concomitant criminality associated with AAS abuse has been reported in several cases (Choi et al. 1990; Eklöf et al. 2003; Hall et al. 2005; Klötz et al. 2006, 2007; Pope et al. 2000a,b; Pope and Katz 1994; Thiblin et al. 2000; Trenton and Currier 2005; Yesalis and Bahrke 1995). A confounding factor in those cases is that high risk behavior may also be the primary problem of those who abuse AAS (Middleman and DuRant 1996).

Other behavioral changes include irritability, depressive and manic symptoms as well as psychosis (Hall et al. 2005; Talih et al. 2007; Thiblin et al. 1999). In addition, it has been suggested that depressive symptoms during AAS use may convey an increased risk of suicide (Brower et al. 1989; Thiblin et al. 2000).

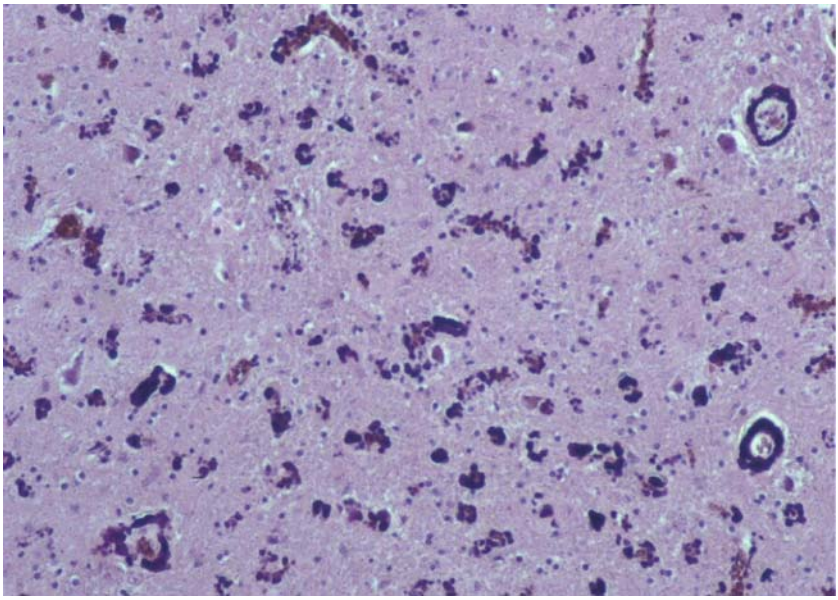

Fig. 13 Microphotograph of striato-pallido-dentate calcinosis (Fahr's disease) in an AAS abuser

Another emerging problem is the concomitant use of other drugs. Significant associations between the use of anabolic steroids and the use of cannabis, amphetamines, cocaine, cigarettes, and alcohol have been reported (Arvary and Pope 2000; DuRant et al. 1993; Kanayama et al. 2003; Petersson et al. 2006a,b; Simon et al. 2006; own observation). Especially in adolescents, the protocol of injecting steroids represents an increased level of commitment to illicit drug use, which often leads anabolic steroid users to engage in behavior similar to that of other drug abusers (DuRant et al. 1993). Furthermore it has been demonstrated that AAS have the potential for physical and psychic addiction, with the occurrence of withdrawal symptoms after cessation of AAS abuse (Arvary and Pope 2000; Bahrke and Yesalis 2004; Brower 2002; Copeland et al. 2000; Lukas 1996; Talih et al. 2007; Trenton and Currier 2005). Therefore, AAS may serve as "gateway" to other illicit drug abuse with substantial associated morbidity and even mortality (Arvary and Pope 2000; Kanayama et al. 2003).

Moreover, morphological alterations of the CNS are observed. Besides cardiovascular complications, AAS have been associated with the occurrence of stroke (Akhter et al. 1994; Chu et al. 2001; Frankle et al. 1988; Laroche 1990; Mochizuki and Richter 1988; Pálfi et al. 1997). Striato-pallido-dentate calcinosis (Fahr's disease) has been described in an AAS abuser which could be associated with AAS-induced hypercalcemia (Büttner et al. 2001; Sahraian et al. 2004) (Fig. 13).

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