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Potential for the effects of anabolic steroid abuse in the immune and neuroendocrine axis

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Abstract

Some of the effects that high-dose anabolic steroid abuse have and could have on the interactions between the immune and neuroendocrine systems are reviewed. Considering the past demonstrations on the actions of normal steroids on endocrine and immune responses, it is apparent that pharmacologically high doses of both normal and derivatized androgens (anabolic steroids) could have a significant effect. Indeed, some of the pathologies attributed to anabolic steroid abuse point to disturbances in the intimate connection between neuroendocrine and immune function and interaction. We attempt to review both the direct and indirect effects of this abuse, not only on this interaction but also on certain immune functions in particular. © 1998 Elsevier Science B.V.

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1. Discussion

The anabolic androgenic steroids are derivatives of testosterone (Murad and Haynes, 1980). Conventionally, they have been used in treating bone marrow failure, hypogonadal states, hereditary angioneurotic edema, renal disease anemia and the late stages of breast cancer (Wilson and Griffin, 1982; Goldman et al., 1984). Anabolic steroids have recently been placed on the Food and Drug Administration's list of controlled substances primarily due to the adverse effects seen in athletes taking high doses in attempts to enhance performance (Wilson, 1988). Over 40 anabolic steroids are available in both oral and injectable forms (Goldman et al., 1984). Some of the most often used forms include methandrostenolone and methyltestosterone, while the most used injectables include nandrolone and oxymethenelone (Goldman et al., 1984). The side effects of high dose anabolic steroid use can include sterility, testicular atrophy, gynecomastia, folliculitis, acne, enhanced erythropoiesis and increased risk of cardiovascular disease. Hepatic problems have also been associated with abuse including carcinoma, Wilm's tumor, hepatic angiosarcoma and peliosis hepatitis (Friedl, 1989; Yesalis and Bahrke, 1995; Zimmerman, 1978; Ishak, 1979). As a byproduct of abuse, human immunodeficiency virus (HIV) and hepatitis infections have also been reported in persons who have shared needles when injecting anabolic steroids (Yesalis et al., 1989). At present, it is not known if the side effects associated with anabolic steroid abuse result in a greater sensitivity to these infections. There have been multiple recent reviews written about anabolic steroid abuse (Clancy and Yates, 1992; Fehrenchick, 1991; Franklin, 1994; Fuller, 1993; Kennedy, 1992; Kleiner, 1991; Lane and Connor, 1994; Likas, 1993; Milhorn, 1991; Strauss and Yesalis, 1991; Yesalis et al., 1993; Wadler, 1994); but little has been published on the impact of anabolic steroids on the actual incidence and prevalence of disease in users (Yesalis and Bahrke, 1995).

Psychological profiles show behavioral changes associated with anabolic steroid abuse. Investigators have reported major depression and psychosis, increased aggressiveness and irritability, plus the potential for physical and psychological dependence have been reported. While a direct, toxic effect on neurons would be the simplest mechanism, the behavioral changes associated with anabolic steroids could have several causes (Bahrke and Yesalis, 1994; Clark and Barber, 1994; Masonis and McCarthy, 1995). For example, neurological effects have been associated with biological response modifiers such as cytokines (Opp et al., 1995; Plata-Salaman and French-Mul-

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len, 1994; Selmaj et al., 1991); particularly those cytokines we have found to be elevated by anabolic steroids. Cytokines such as IL-1 have been shown to enhance slow wave sleep (Opp and Krueger, 1991), induce sickness behavior (Bluthe et al., 1994) and affect eating behavior (Kent et al., 1992). In addition, intracerebroventricular administration of IFN-α induces a catatonic behavior (Blalock and Smith, 1981) and has been shown to cause malaise, lethargy and even confusion (Stringfellow, 1986). Thus, it is possible to expect that the reported anabolic steroid-associated behavioral changes (Bahrke and Yesalis, 1994; Clark and Barber, 1994; Masonis and McCarthy, 1995) may be influenced by cytokines. Additionally, cytokine expression in schizophrenics suggests one putative mechanism that might be relative to the anabolic steroid psychosis. Interleukin-2 production is decreased in stimulated lymphocytes from untreated schizophrenics (Bessler et al., 1995). Furthermore, in depressed individuals, numerous studies suggest that there are corticotrophin-releasing hormone (CRH) and other hypothalamic–pituitary–adrenal (HPA) axis abnormalities as well as immune alterations (Nemeroff, 1988).

There have been many studies on the effects of normal androgens on immune responses (Grossman, 1984, 1985, 1989; Grossman et al., 1979; Grossman and Roselle, 1986; Ansar et al., 1985; Coulson et al., 1982; Sasson and Mayer, 1981; Sthoeger et al., 1988;). However, the effects of high doses of anabolic steroids resulting from prolonged/chronic abuse on immune system responses have been largely undetermined. One early report suggested that anabolic steroids enhanced antibody responses and resistance to infection (Calabrese et al., 1989). In contrast, it was also suggested that anabolic steroid abuse reduced humoral and cell-mediated responses in both animals and humans (Mendenhall et al., 1990). In spite of these studies, the overall modulation of the immune system by anabolic steroid abuse remains to be fully elucidated. However, considering the previously described side-effects of high-dose abuse, it would appear that the immune and/or the neuroendocrine systems could be substantially involved. As an example, during high-dose use, feedback mechanisms that affect the hypothalamus and anterior pituitary gland could virtually abolish hormones such as ACTH (corticotrophin), luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the circulation (Rogol and Yesalis, 1992). In addition, anabolic steroids could possibly block or reverse the catabolic effects of glucocorticoids by competitive binding to the glucocorticoid receptor. Glucocorticoids are potent anti-inflammatory substances and generally downregulate the immune system (Munck et al., 1984). In light of this, two recent publications have demonstrated that glucocorticoids affect immune function by inhibiting the transcription factor, NF-κB, which normally functions to enhance the transcription and synthesis of many cytokines (Auphan et al., 1995; Schneinman et al., 1995). As mentioned previously, studies have shown that certain levels of anabolic steroids may be immunoenhancing (Mendenhall et al., 1990). Our recent studies indicate that anabolic steroids can upregulate NF-κB (Smith, E.M., Hughes, T.K., manuscript in preparation). Considering these new and other contrasting findings, the effects of long-term use of high levels of anabolic steroids on the immune and neuroendocrine systems remain to be fully elucidated. Overall, however, there appears to be a mechanism by which anabolic steroids may modulate the extra hypothalamic–pituitary production and action of hormones, such as those produced by the immune system (Blalock, 1985, 1989; Blalock and Smith, 1985; Weigent and Blalock, 1987) and those of the adrenal glands (Norman and Litwack, 1987; Temple and Liddle, 1970), and the production or action of cytokines.

Along these lines, a large amount of data suggests that a linkage exists between the immune and neuroendocrine systems (Blalock, 1985, 1989; Blalock and Smith, 1985; Smith, 1992; Smith et al., 1987; Weigent and Blalock, 1987). Many reports demonstrate that these systems communicate with each other by producing and responding to similar signal molecules, i.e., cytokines and neuropeptides. Not only do these molecules contribute to inter-communication, they also play a role in autoregulatory intra-communication processes within each system. More specifically, neuropeptides have been shown to affect immune responses through their influence on cytokine production and action. Conversely, cytokines are known to induce or influence the induction of hormonal messenger substances such as the pituitary hormone, ACTH and CRH (Hughes and Chin, 1994; Smith, 1992).

In the immune and neuroendocrine axis, ACTH has been the best characterized inter- and intra-'communicator' (Blalock, 1989). ACTH is derived from pro-opiomelanocortin (POMC) and was originally thought to be only produced by the anterior pituitary gland (Norman and Litwack, 1987); data now indicates that it is produced and is active in lymphocytes (Blalock, 1989). In the neuroendocrine system, its primary role is to play a central role in stress responses by acting on the adrenal glands to induce the production of corticosteroids (Norman and Litwack, 1987; Temple and Liddle, 1970) and dehydroepiandrosterone (DHEA) (Rosenfeld et al., 1971). Corticosteroids are well known immunosuppressive factors (Munck et al., 1984) and DHEA has recently been shown to modulate immune responses as well (Blauer et al., 1991; Lucas et al., 1985).

ACTH has been shown to be produced by lymphocytes in response to various inducers such as CRH and also following viral infection (Blalock, 1989). Specific ACTH receptors have been described on lymphocytes (Smith et al., 1987; Weigent and Blalock, 1987) as well as specific cytosolic receptors for DHEA (Meikle et al., 1992). The ACTH produced by lymphocytes has been shown to play a role in stress responses by our demonstration in hypophysectomized animals that ACTH production in lymphocytes

is paralleled by an increase in corticosteroid levels during and following the stress response (Smith et al., 1982). Furthermore, ACTH has been shown to directly influence immune responses such as antibody production (Johnson et al., 1982). Our recent finding that lymphocyte produced ACTH is processed to melanocyte-stimulating hormone (MSH) by neutral endopeptidase (CD10) on the lymphocyte surface further supports this contention. We found that the MSH product was an even more potent inhibitor of lymphocyte activation than its ACTH precursor (Smith et al., 1992). Once again, little is known about the effects of anabolic steroids on these activities.

Other hormones and neuropeptides have also been shown to be produced by lymphocytes. Examples include thyroid stimulating hormone (TSH), the endorphins, enkephalins, prolactin, arginine vasopressin/oxytocin, vasoactive intestinal peptide, luteinizing hormone and substance P (Blalock, 1989). Examples of cytokines that have been shown to be induced and/or interact with the above neuropeptides include interleukin (IL)-1, -2, -6, -10 and interferons-α, -β, and -γ plus tumor necrosis factor-α. Others also exist (Hughes and Chin, 1994; Smith, 1992). It should be noted that these cytokines represent both Th1 and Th2 T-lymphocyte products. Alterations of Th1 and Th2 cytokine profiles have been associated with progression of certain diseases such as AIDS (Clerici and Shearer, 1993; Maggi et al., 1994).

In addition to the peptide hormones and cytokines, it is possible that anabolic steroids might also inhibit the immunomodulatory and antiviral activities of endogenous androgens such as DHEA. This adrenal androgen has been shown to have numerous immunomodulatory activities (Blauer et al., 1991; Daynes et al., 1990; Lucas et al., 1985; Merrill et al., 1989; Schwartz, 1985; Weindruch et al., 1984) including enhancement of IL-2 production, prevention of autoantibody production, and inhibition of virus infection and cancer. The proposed mechanism for DHEA's antagonism has been attributed to its ability to reverse the immunosuppressive effects of glucocorticoids, especially cortisol (Blauer et al., 1991). The molecular mechanism(s) of this effect is presently unknown; however, DHEA and cortisol do not compete for a similar cytosolic receptor (Blauer et al., 1991; Kalimi and Regelson, 1988). In contrast, anabolic steroids and cortisol do compete for receptors (Snochowski et al., 1981). However, both DHEA and androgens such as anabolic steroids could modulate the immunosuppressive effects of cortisol, suggesting that interactions between DHEA and anabolic steroids and their immunoregulatory activities are possible.

Thus, the spectrum of the hormones and cytokines that are released by lymphocytes and the HPA axis indicate the potential for anabolic steroids to disrupt normal interactions within and between the immune and neuroendocrine systems. Furthermore, there are a significant number of cytokines that influence and/or induce hormones in neuroendocrine tissue (Hughes and Chin, 1994). Overall, given the known effects of anabolic steroid abuse, it is reasonable to think that they could play a major role in disrupting the immune and neuroendocrine network that we have described.

Given this, in recent studies, anabolic steroids have been implicated for activation of the hemostatic system in athletes resulting in abnormalities in coagulation (Fehrenchick et al., 1995). While this may not directly impact an immune or neuroendocrine response, the indirect effects of the abnormalities could ultimately do so. In addition, testosterone (and perhaps, other androgens such as anabolic steroids) will increase thromboxane A2 receptors resulting in an increase of the platelet aggregation response (Ajayi et al., 1995). Ultimately, these alterations could also lead to altered immune reaction and an increase in the cardiovascular disease in humans (Halushka et al., 1993; Huie, 1994) and experimental animals (Tseng et al., 1994). These abnormalities may be enhanced by interactions with other illicit drugs such as cocaine (Tseng et al., 1994; Welder and Melchert, 1993) that also have immune modulating functions (Stefano, 1989). In addition, human growth hormone has been used in combination with anabolic steroids (Haupt, 1993) that have been shown to effect certain immune responses (Smith, 1992).

Anabolic steroids have also been shown to upregulate androgen receptor immunoreactivity in the brain (Menard and Harlan, 1993). Our recent findings describing the inhibition of ACTH production from lymphocytes by anabolic steroids indicate that a complex regulation of the pituitary–adrenal axis could be occurring during anabolic steroid abuse, which could be influenced both centrally in the CNS and peripherally by the immune system (Hughes et al., 1995). The CNS manifestations of anabolic steroid abuse are also manifested in behavioral changes as evidenced by multiple recent psychological profile studies (Choi and Pope, 1994; Isaacson and Bergman, 1993; Malone et al., 1995; Su et al., 1993). It would be interesting to correlate the degree by which the alterations in CNS structures such as brain androgen receptors and peripheral hormone production (Hughes et al., 1995; Menard and Harlan, 1993) mentioned above play a role in the behavioral abnormalities.

We have recently performed studies to further determine the potential for anabolic steroids to affect the immune and neuroendocrine axis (Hughes et al., 1995). In particular, we determined the effects of anabolic steroids on certain immune responses and their subsequent effects on extrapituitary production of corticotrophin by lymphocytes. Both 17-β and 17-α esterified anabolic steroids, nandrolone decanoate and oxymethenelone, respectively, were used. For these studies, we developed a murine abuse model in which mice were treated chronically with steroids approximating those levels seen in athletes during abuse (i.e., in humans $\pm$200 mg/day; adjusted for the mouse). In our studies, we found that the steroids significantly inhibited production of antibody to sheep red blood cells

(SRBCs); in some cases, the effect was dramatic. In contrast, the control androgens testosterone and DHEA or sesame seed oil vehicle had no effect. This finding is in contrast to some but agree with other previous studies (Calabrese et al., 1989; Mendenhall et al., 1990). An unexpected effect of the steroids was that they could directly induce the production of the inflammatory cytokines IL-1β and TNF-α from human peripheral blood lymphocytes. There was no effect on IL-2 or IL-10 (again, the control androgens testosterone and DHEA had no effect on any of the cytokines). In contrast to the above cytokines, we found that interferon production was significantly inhibited in certain cells. Considering the direct cytokine-inducing capacity of the anabolic steroids and their apparent association with behavioral changes as described previously, these data suggest at least one mechanism by which anabolic steroids might contribute to the CNS alterations. In our studies, we further found that the anabolic steroids significantly inhibited the production of corticotrophin in human peripheral blood lymphocytes following viral infection. Other studies of ours have indicated that this lymphocyte-derived ACTH can have significant effects on immune responses in the localized area of production (Smith et al., 1992).

2. Conclusion

These recent studies, taken in context with the others described previously, indicate that anabolic steroids have the potential to significantly affect processes associated with the immune, CNS and neuroendocrine systems. In doing so, it is apparent that abuse of anabolic steroids would further have a significant impact on the interactions that occur between these systems. We feel that all of these data provide an important impetus and rationale for further study into what is a relatively under-studied area in the arena of human drug abuse. It becomes even more important, since the abuse of these substances primarily occurs in the younger population in which long-term effects could become manifest during the aging process.

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References

Ajayi, A.A., Mathur, R., Malushka, P.V., 1995. Testosterone increases human platelet thromboxane A2 receptor density and aggregation responses. Circulation 91, 2694–2698.

Ansar, A.S., Dauphinee, M.J., Talal, N., 1985. Effects of short-term administration of sex hormones on normal and autoimmune mice. J. Immunol. 134, 204–210.

Auphan, N., DiDonato, J.A., Rosette, A., Helmberg, A., Karin, M., 1995. Immunosuppression by glucocorticoids: Inhibition of NF-kB activity through induction of IkB synthesis. Science 270, 286–290.

Bahrke, M.S., Yesalis, C.E. III, 1994. Weight training: A potential confounding factor in examining the psychological and behavioral effects of anabolic steroids. Sports Med. 18, 309–318.

Bessler, H., Levental, Z., Karp, L., Modai, I., Djaldetti, M., Weizman, A., 1995. Cytokine production in drug-free and neuroleptic-treated schizophrenic patients. Biol. Psychol. 38, 297–302.

Blalock, J.E., 1985. Proopiomelanocortin-derived peptides in the immune system. Clin. Endocrinol. 22, 823–827.

Blalock, J.E., 1989. A molecular basis for bidirectional communication between the immune and neuroendocrine systems. Physiol. Rev. 69, 1–32.

Blalock, J.E., Smith, E.M., 1981. Human leukocyte interferon (HuIFN-α): Potent endorphin-like opioid activity. Biochem. Biophys. Res. Commun. 101, 472–478.

Blalock, J.E., Smith, E.M., 1985. A complete regulatory loop between the immune and neuroendocrine systems. Fed. Proc. 44, 101–111.

Blauer, K.L., Poth, M., Rogers, W.M., Bernton, E.W., 1991. Dehydroepiandrosterone antagonizes the suppressive effects of dexamethasone on lymphocyte proliferation. Endocrinology 129, 3174–3174.

Bluthe, R.M., Pawlowski, M., Suarez, S., Parnet, P., Pittman, Q., Kelley, K.W., Dantzer, R., 1994. Synergy between tumor necrosis factor and interleukin-1 in the induction of sickness behavior in mice. Psychoneuroendocrinology 19, 197–207.

Calabrese, L., Kleiner, S., Barna, B., Skibinski, C., Kirkendall, D., 1989. The effects of anabolic steroids and strength training on the human immune response. Med. Sci. Sports Exerc. 214, 386–392.

Choi, P.Y., Pope, H.G., 1994. Violence toward women and illicit anabolic androgenic steroid abuse. Ann. Clin. Psychiatry 6, 21–25.

Clancy, G.P., Yates, W.R., 1992. Anabolic steroid use among substance abusers in treatment. J. Clin. Psychiatry 53, 97–100.

Clark, A.S., Barber, D.M., 1994. Anabolic–androgenic steroids and aggression in castrated male rats. Physiol. Behav. 56, 1107–1113.

Clerici, M., Shearer, G.M., 1993. A Th1–Th2 switch is a critical step in the etiology of HIV infection. Immunol. Today 14, 107–111.

Coulson, P.B., Thornwaite, T., Skafar, D.F., Seaver, S.S., 1982. Modulation for glucocorticoid hormone receptor levels in chicken lymphoid tissue following treatment with androgens in vivo. J. Steroid Biochem. 17, 1111–1119.

Daynes, R.A., Dudley, D.J., Araneo, B.A., 1990. Regulation of murine lymphokine production: II. Dehydroepiandrosterone is a natural enhancer of interleukin 2 synthesis by helper T cells. Eur. J. Immunol. 20, 793–802.

Fehrenchick, G.S., 1991. Anabolic/androgenic steroid abuse and thrombosis: Is there a connection?. Med. Hypotheses 35, 27–31.

Fehrenchick, G.S., Hirokawa, S., Mammen, E.F., Schwartz, K.A., 1995. Anabolic–androgenic steroid abuse in weight lifters: Evidence for activation of the hemostatic system. Am. J. Hematol. 49, 282–288.

Franklin, J.F., 1994. Addiction medicine. J. Am. Med. Assoc. 271, 1650–1651.

Friedl, K.E., 1989. Reappraisal of the health risks associated with the use of high doses of oral and injectable androgenic steroids. Proceedings of the Technical Review Meeting on Anabolic Steroid Abuse. National Institute on Drug Abuse, Rockville, MD.

Fuller, M.G., 1993. Anabolic–androgenic steroids: Use and abuse. Compr. Ther. 19, 69–72.

Goldman, B., Klatz, R., Bush, P., 1984. List of commonly used anabolic steroids with chemical structures and normal dosages. In: Goldman, B. (Ed.), Death in the Locker Room, Appendix 24. Icarus Press, South Bend, IN, pp. 299-301.

Grossman, C.J., 1984. The regulation of the immune system by sex steroids. Endocr. Rev. 5, 435–455.

Grossman, C.J., 1985. Gonadal steroids and the immune response. Science 227, 257–261.

Grossman, C.J., 1989. Possible underlying mechanisms of sexual dimorphism in the immune response, fact and hypothesis. J. Steroid Biochem. 34, 241–251.

Grossman, C.J., Roselle, G.A., 1986. The control of immune response by endocrine factors and the clinical significance of such regulation. Prog. Clin. Biochem. Med. 4, 9.

Grossman, C.J., Nathan, P.M., Taylor, B.B., Sholiton, L.J., 1979. Rat thymic dihydrotestosterone receptors: Preparation, location and physiochemical properties. Steroids 34, 539–553.

Halushka, P.V., Masuda, A., Matsuda, K., 1993. The Gordon Wilson Lecture. Regulation of thromboxane A2 receptors by testosterone: Implications for steroid abuse and cardiovascular disease. Trans. Am. Clin. Climatol. Assoc. 105, 95–103.

Haupt, H.A., 1993. Anabolic steroids and growth hormone. Am. J. Sports Med. 337, 468–474.

Hughes, T.K., Chin, R., 1994. Interactions of neuropeptide and cytokines. In: Stefano, G.B., Scharrer, B. (Eds.), Neuropeptides and Immunoregulation. Springer-Verlag, pp. 101–119.

Hughes, T.K., Fulep, E., Juelich, T., Smith, E.M., Stanton, G.J., 1995. Modulation of immune responses by anabolic androgenic steroids. Int. J. Immunopharmacol. 17, 857–863.

Huie, M.J., 1994. An acute myocardial infarction occurring in an anabolic steroid abuser. Med. Sci. Sports Exerc. 26, 408–413.

Isaacson, G., Bergman, U., 1993. Can anabolic steroids cause personality changes?. Nordisk Med. 108, 180–181.

Ishak, K.G., 1979. Hepatic neoplasms associated with contraceptive and anabolic steroids. In: Lingeman, C.H. (Ed.), Carcinogenic Hormones. Springer-Verlag, NY, pp. 73–128.

Johnson, H.M., Smith, E.M., Torres, B.A., Blalock, J.E., 1982. Neuroendocrine hormone regulation of in vitro antibody production. Proc. Natl. Acad. Sci. U.S.A. 79, 4171–4174.

Kalimi, M., Regelson, W., 1988. Physiochemical characterization of [^{3}H] DHEA binding in rat liver. Biochem. Biophys. Res. Commun. 156, 22–29.

Kennedy, M.C., 1992. Anabolic steroid abuse and toxicology. Aust. New Zealand J. Med. 22, 374–381.

Kent, S., Bluthe, R.M., Dantzer, R., Hardwick, A.J., Kelley, K.W., Rothwell, N.J., Vannice, J.L., 1992. Different receptor mechanisms mediate the pyrogenic and behavioral effects of interleukin-1. Proc. Natl. Acad. Sci. U.S.A. 89, 9117–9120.

Kleiner, S.M., 1991. Performance-enhancing aids in sport: Health consequences and nutritional alternatives. J. Am. Coll. Nutr. 10, 163–176.

Lane, J.R., Connor, J.D., 1994. The influence of endogenous and exogenous sex hormones in adolescents with attention to oral contraceptives and anabolic steroids. J. Adolesc. Health 15, 630–634.

Likas, S.E., 1993. Current perspectives on anabolic–androgenic steroid abuse. Trends Pharmacol. Sci. 14, 61–68.

Lucas, J.A., Ahmed, S.A., Casey, M.L., MacDonald, P.C., 1985. Prevention of autoantibody formation and prolonged survival in New Zealand Black/New Zealand White F1 mice fed dehydroisoandrosterone. J. Clin. Invest. 75, 2091–2093.

Maggi, E., Mazetti, M., Ravina, A., Annunziato, F., De Carli, M., Pierre-Piccini, M., Manetti, R., Carbonari, N., Maria-Pesce, A., Del Prete, G., Romagnani, S., 1994. Ability of HIV to promote a Th1 to Th0 shift and to replicate preferentially in Th2 and Th0 cells. Science 265, 244–248.

Malone, D.A., Dimeff, R.J., Lombardo, J.A., Sample, R.H., 1995. Psychiatric effects and psychoactive substance use in anabolic–androgenic steroid users. Clin. J. Sports Med. 5, 25–31.

Masonis, A.E.T., McCarthy, M.P., 1995. Direct effects of the anabolic/androgenic steroids, stanozolol and 17-α-methyltestosterone on benzodiazepine binding to the γ-aminobutyric acid receptor. Neurosci. Lett. 189, 35–38.

Meikle, A.W., Dorchuk, R.W., Araneo, B.A., Stringham, J.D., Evans, T.G., Spruance, S.L., Daynes, R.A., 1992. The presence of dehydroepiandrosterone-specific receptor binding complex in murine T-cells. J. Steroid Biochem. Mol. Biol. 42, 293–304.

Menard, C.S., Harlan, R.E., 1993. Up-regulation of androgen receptor immunoreactivity in the rat brain by androgenic–anabolic steroids. Brain Res. 622, 226–236.

Mendenhall, C.L., Grossman, C.J., Roselle, G.A., Hertelendy, Z., Ghosn, S.J., Lamping, K., Martin, K., 1990. Anabolic steroid effects on immune function: Differences between analogs. J. Steroid Biochem. Mol. Biol. 37, 71–76.

Merrill, C.R., Harrington, M.G., Sutherland, T., 1989. Plasma dehydroepiandrosterone levels in HIV infection. J. Am. Med. Assoc. 261, 1149.

Milhorn, H.T., 1991. Anabolic steroids: Another form of drug abuse. J. Mississippi State Med. Assoc. 32, 293–297.

Munck, A., Guyre, P.M., Holbrook, N.J., 1984. Physiological functions of glucocorticoids in stress and their relation to pharmacological action. Endocr. Rev. 5, 25–44.

Murad, F., Haynes Jr., R.C., 1980. Androgens and anabolic steroids. In: Gilman, A.G., Goodman, L.S., Gilman, A. (Eds.), The Pharmacological Basis of Therapeutics, 6th edn. Macmillan, New York.

Nemeroff, C.B., 1988. The role of corticotrophin-releasing factor in the pathogenesis of major depression. Pharmacopsychiatry 21, 76–82.

Norman, A.W., Litwack, G., 1987. Hormones. Academic Press, Orlando, FL.

Opp, M.R., Krueger, J.M., 1991. Interleukin-1 involvement in the regulation of sleep. In: Rothwell, N., Dantzer, R. (Eds.), Interleukin-1 in the Brain. Am. J. Physiol. 260, 995–999.

Opp, M.R., Smith, E.M., Hughes, T.K., 1995. Interleukin-10 (cytokine synthesis inhibitory factor) acts in the central nervous system of rats to reduce sleep. J. Neuroimmunol. 60, 165–168.

Plata-Salaman, C.R., French-Mullen, J.M.H., 1994. Interleukin-1 inhibits Ca^{2+} channel currents in hippocampal neurons through protein kinase C. Eur. J. Pharmacol. 226, 1–10.

Rogol, A.D., Yesalis, C.E., 1992. Anabolic–androgenic steroids and athletes: What are the issues?. J. Clin. Endocrinol. Metab. 74, 465–469.

Rosenfeld, R.S., Hellman, L., Roffwarg, H., Weitzman, E.D., Fukushima, D.K., Gallagher, T.F., 1971. Dehydroiso-androsterone is secreted episodically and synchronously with cortisol by normal men. J. Clin. Endocrinol. 33, 87–92.

Sasson, S., Mayer, M., 1981. Effect of androgenic steroids on rat thymus and thymocytes in suspension. J. Steroid Biochem. 14, 509–517.

Schneinman, R.I., Cogswell, P.C., Lofquist, A.K., Baldwin, A.S., 1995. Role of transcriptional activation of IkBa in mediation of suppression by glucocorticoids. Science 270, 283–286.

Schwartz, A., 1985. The effects of dehydroepiandrosterone on the rate of development of cancer and autoimmune processes in laboratory rodents. In: Woodhead, A.D. (Ed.), Molecular Biology of Aging. Basic Life Sciences 35. Plenum, New York, pp. 181–91.

Selmaj, K., Raine, C.S., Farooq, M., Norton, W.T., Brosnan, C.F., 1991. Cytokine cytotoxicity against oligodendrocytes. J. Immunol. 147, 1522–1529.

Smith, E.M., 1992. Hormonal activities of cytokines. Chem. Immunol. 52, 154–172.

Smith, E.M., Brosnan, P., Meyer, W.J. III, Blalock, J.E., 1987. An ACTH receptor on human mononuclear leukocytes: Relation to adrenal ACTH receptor activity. New Engl. J. Med. 317, 1266–1269.

Smith, E.M., Meyer, W.J., Blalock, J.E., 1982. Virus-induced corticosterone: A possible lymphoid adrenal axis. Science 218, 1311–1313.

Smith, E.M., Hughes, T.K., Hashemi, F.B., Stefano, G.B., 1992. Immunosuppressive effects of corticotrophin, melanocortin and their possible significance in human immunodeficiency virus infection. Proc. Natl. Acad. Sci. U.S.A. 89, 782–786.

Snochowski, M., Saartok, T., Dahlberg, E., Erikson, E., Gustafson, J.A., 1981. Androgen and glucocorticoid receptors in human skeletal muscle cytosol. J. Steroid Biochem. 14, 65–71.

Stefano, G.B., 1989. Role of opioid neuropeptides in immunoregulation. Prog. Neurobiol. 33, 149–159.

Sthoeger, Z.M., Chiorazzi, N., Lahita, R.G., 1988. Regulation of the

immune response by sex hormones: I. In vivo effects of estradiol and testosterone on pokeweed mitogen-induced human B-cell differentiation. J. Immunol. 141, 91–98.

Strauss, R.H., Yesalis, C.E., 1991. Anabolic steroids and the athlete. Annu. Rev. Med. 199, 449–457.

Stringfellow, D.A., 1996. Clinical application of interferons and their inducers. In: Stringfellow, D.A. (Ed.), Clinical Pharmacology, Vol. 3. Marcel Dekker, New York, pp. 111–114.

Su, T.P., Pagliaro, M., Schmid, P.J., Pickar, D., Wolkowitz, O., Rubinow, D.R., 1993. Neuropsychiatric effects of anabolic steroids in male normal volunteers. J. Am. Med. Assoc. 269, 2760–2764.

Temple, T.E., Liddle, G.W., 1970. Inhibitors of adrenal steroids biosynthesis. Ann. Rev. Pharmacol. 10, 199–218.

Tseng, Y.T., Rockhold, R.W., Hoskins, B., Ho, I.K., 1994. Cardiovascular toxicities of nandrolone and cocaine in spontaneously hypertensive rats. Fundam. Appl. Toxicol. 22, 113–121.

Wadler, G.I., 1994. Drug use update. Med. Clin. North Am. 78, 439–455.

Weigent, D.A., Blalock, J.E., 1987. Interactions between the neuroendocrine and immune systems: Common hormones and receptors. Immunol. Rev. 100, 79–108.

Weindruch, R., McFeeters, G., Walford, R.L., 1984. Food intake reduction and immunologic alterations in mice fed dehydroepiandrosterone. Exp. Gerontol. 19, 297–394.

Welder, A.A., Melchert, R.B., 1993. Cardiotoxic effects of cocaine and anabolic steroids in the athlete. J. Pharmacol. Toxicol. Methods 29, 58–61.

Wilson, J.D., 1988. Androgen abuse by athletes. Endocr. Rev. 9, 181–199.

Wilson, J.D., Griffin, J.E., 1982. The use and misuse of androgens. Metabolism 29, 1278–1295.

Yesalis, C.E., Bahrke, M.S., 1995. Anabolic–androgenic steroids. Curr. Iss. Sports Med. 19, 326–340.

Yesalis, C., Wright, J., Lombardo, J., 1989. Anabolic–androgenic steroids: A synthesis of existing data and recommendations for future research. Clin. Sports Med. 1, 109–134.

Yesalis, C.E., Kennedy, N.J., Kopstein, A.N., Bahrke, M.S., 1993. Anabolic–androgenic steroid use in the United States. J. Am. Med. Assoc. 270, 1217–1221.

Zimmerman, H.J, 1978. Hormonal derivatives and other drugs used to treat endocrine diseases. In: Zimmerman, H.J. (Ed.), Hepatotoxicity, The Adverse Effects of Drugs and Other Chemicals on the Liver Experimental Procedures.