DOES 5α-REDUCTASE STIMULATION IMPROVE COGNITIVE FUNCTIONS, WHILE INHIBITION IMPROVE IMMUNITY?

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The two hypotheses presented here may seem too good to be true. And it may well be so. If not, these hypotheses have substantial utility. In any case, these simplified versions need to be reformulated as more research results are accumulated, or existing ones unbeknownst to the author are incorporated. These hypotheses have been generated by the author's empirical research of over 30 years. Those findings are summarized in two papers [1,2].

Steroid 5α-reductase (5αR) stimulates the conversion of steroids such as testosterone (T) and progesterone (P) to dihydrotestosterone (DHT) and dihydroprogesterone (DHP), respectively [11,13,23]. DHT and DHP are further reduced by 3α-hydroxysteroid dehydrogenase (3αHSD) to 3α-androstanediol (A-diol), and 3α,5α-tetrahydroprogesterone (THP/ "Allo") [11,13]. Such metabolic activities take place in central and peripheral nervous system sites as well [11,13].

Frye et al [12] demonstrated that "DHT has cognitive enhancing effects, independent of estradiol, which are attenuated by a [3αHSD] inhibitor, indomethacin [by inhibiting
A-diol formation from DHT]." In yet another animal model [5], T, but not non-aromatizable DHT, improved working memory, however. And Brinton et al [6] demonstrated that THP promoted "neurogenesis in vitro and in vivo in transgenic mouse model of Alzheimer's disease [AD]." And THP is decreased in the prefrontal cortex of AD patients; the "levels are inversely correlated with neuropathological disease stage" [21]. P has neuroprotective properties in experimental models of neurodegeneration [12,17,18]. "[P] increased the levels of DHP and THP in plasma and hippocampus and prevented kainic-acid-induced neuronal loss" [8]. By contrast, the synthetic progestin medroxyprogesterone acetate (Provera) failed to mimic P in this experiment [8]. 5αR inhibitor finasteride blocked the increase in DHP and THP in plasma and hippocampus, following P administration, and also abolished the neuroprotective effect of P [8]. Further, indomethacin blocked the neuroprotective effect of both DHP and THP [8]. Nevertheless, indomethacin, along with other non-steroidal antiinflammatory agents (NSAIAs), has been used in the treatment of AD [17], though many "long-term, placebo-controlled clinical trials ... produced negative results" [17]. A mechanism for the beneficial effects of NSAIDs against AD is thought to be "an allosteric modulation of gamma-secretase activity, the enzyme responsible for the formation of amyloid-beta" which is considered to be "independent from the anti-cyclooxygenase activity [of NSAIDs] and is related to the chemical structure of the compounds, with some NSAIDs being active (ibuprofen, sulindac, flurbiprofen, indomethacin, diclofenac) and others not (naproxen, aspirin, celecoxib)" [17].

It has been known that substantial differences exist in innate immune functions between the sexes [3,7]. These differences have been (largely) attributed to sex hormonal influences [3,7]. Though estrogens are believed to potentiate immune functions and androgens to suppress them, the influences of sex hormones on immune functions are more complex, as are on cognitive functions. A well-known example to psychiatrists is the beneficial effects of female gender, as well as of estradiol [19], in the course and severity of schizophrenia, whereas, the prevalence of excess anxiety is nearly twice as common in

women of menstruating age. And a single sublingual dose of T inhibits fear induced startle response in women [16].

Anabolic hormones have been used as immune enhancing agents. "Ghione [14] was the first to demonstrate an 'anti-infective' action of 4-chlorotestosterone in experimental infection by *Nocardia asteroids* in rabbits and mice, and in experimental staphylococcal infection of mice" [22]. Indeed, more recently, addition of an anabolic agent, in addition to good nutrition, has been advocated in wound healing [9]. This should follow that T, with its anabolic properties, should have immune enhancing properties. However, numerous studies have shown otherwise [3,7]. And yet, the same group [7] later identified, and confimed, DHT as the crucial immune depressing hormone after trauma-hemorrhage [7-see Fig. 3]. More specifically, DHT suppresses interleukin-4 and gamma-interferon [4]. And, the powerful immunosuppressant, cyclosporin A, stimulates 5αR [10]. Furthermore, Gilliver et al [15] demonstrated that "systemic [5αR inhibition mimicked] the effects of castration in a rat model of cutaneous wound healing" [15].

Thus it is reasonable to hypothesize that 5αR stimulation could enhance *certain* cognitive functions, and that 5αR inhibition could enhance *certain* immune functions.

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