Norethindrone Acetate and Testosterone Interactions in Mammary Gland, Uterus and Seminal Vesicles of Mice

J. ŠKARDA

Institute of Animal Physiology and Genetics, Academy of Sciences, Prague 10-Uhříněves, Czech Republic

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Abstract

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Young intact (18 days of age) and adult gonadectomized C3H/Di mice were used to study the biological effects of norethindrone acetate (NA) and utilization of NA stimulated/inhibited mammary, uterine, seminal vesicles and spleen growth as a test system for identification of androgenic activities. Females were treated for 10 days, males for 15 days. Mammary glands of NA-treated animals showed a progressive lengthening and branching of ducts and appearance of alveolar buds and interductal lobuloalveolar structures from the dose 3.125 in females and 12.5 $\mu g \cdot d^{-1}$ in males. NA from the dose of 12.5 $\mu g \cdot d^{-1}$ increased uterine weights and decreased seminal vesicle weights in young intact animals. NA had no androgenic effect on seminal vesicle weights in castrated males. NA mimicked the effect of a combination of estradiol plus progesterone in all organs studied. Testosterone alone had no effect on mammary growth in both sexes, however uterine and seminal vesicle weights were increased. Uterine weight was increased by testosterone at considerably higher (3000fold in young intact, 500fold in ovariectomized animals) doses than by estradiol. Mammary growth stimulated by moderate doses of NA (125 and 25 $\mu g \cdot d^{-1}$ in females; 25 and 50 $\mu g \cdot d^{-1}$ in males) was inhibited by testosterone. In uterus, however, testosterone acted cooperatively with moderate doses of NA to produce a higher uterine growth than that observed in animals injected with testosterone or NA alone. In young intact males, NA caused reduction in seminal vesicle weights was abolished by simultaneous application of testosterone.

Bioassay, steroid hormones, agonist, antagonist

All the derivatives of 19-nor-testosterone exhibit estrogenic/antiestrogenic and progestantional activities in addition to their androgenic effects. Norethindrone acetate (17α-ethynyl-19-nortestosterone acetate; NA) has been widely used as contraceptive agent (Van Look 1988) and as an agent treating adverse effects of menopause, e.g. Kliogest (Novo Nordisk A/S). It has been demonstrated that NA is bioconverted into several metabolites in target tissues. These metabolites not only retain hormonal activities similar to those exhibited by the parent compound but may also acquire new hormone agonistic, antagonistic or synergistic capabilities (Pérez-Palacios et al. 1981). The A ring of NA may be enzymatically reduced to 5α-dihydro NA that exerts very little, if any, progesterone-like effects as assessed by the induction of rat uterine uteroglobin and 5β, 5α-tetrahydro NA that displays a potent estrogenic-like effects. Both compounds possess antiprogestantional properties (Pasapera et al. 1995). Neumann et al. (1974a) have demonstrated that NA exerted different biological effect in different species; it was a gestagen in the rabbit, whereas in rats its predominant influence was estrogenic.

There is considerable concern about the increasing incidence of endocrine-related cancer and deteriorating reproductive health in humans, farm animals and wildlife. It is apparent that a large number of natural and man-made chemicals have the ability to mimic the action of the endogenous steroid hormones by binding to and activating/inhibiting their receptor functions (Payne et al. 2000). Because there is some overlap in biological activities between different steroid hormones and their analogues (the presence of multihormonal/

Address for correspondence:
Doc. MVDr. Josef Škarda, DrSc.
Ústav živočišné fyziologie a genetiky AV ČR
Přátelství 560, 104 00 Praha 10 - Uhříněves
Czech Republic

Phone: +420 2 677 009 614, 6771 1730-1
Fax: +420 2 677 710 803
e-mail: skarda@iapg.cas.cz
http://www.vfu.cz/acta-vet/actavet.htm