SEX HORMONE INFLUENCES ON YAWNING BEHAVIOR

ACTA NEUROBIOL. EXP. 1980, 40: 515-519

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Young male albino rats yawn significantly more than females or castrated males when injected with physostigmine (0.10 mg/kg). Treatment with testosterone (100 µg daily) during seven days restores cholinomimetically induced yawning in castrated males, and increases yawning in normal and androgenized females. Treatment with estradiol (200 µg daily) during one week does not modify physostigmine induced yawning behavior in castrated males nor in androgenized fernales.

Although yawning is a simple behavioral item not obviously related to the sexual sphere, several reports have appeared pointing towards a curious association between yawning and some elements of sexual behavior. Injections of ACTH, MSH, or peptides possessing similar hormonal activity, into the cerebrospinal fluid or the brain, induce a peculiar stretching and yawning syndrome (SYS) in several animal species (6, 7). The same treatment also produces a display of sexual excitement, both in male (2, 3) and female rabbits (1). Associated yawning and penile erections have been observed during and between waves of cortical spreading depression in male rats (4). Jakobartl and Huston (16) have recently suggested that both the SYS and the penile erections observed after intracranial injections of ACTH (and other peptides) could be after-effects of spreading depression produced by these substances. With low doses of apomorphine and other dopaminergic agonists injected systemically, Mogilnicka and Klimek (18) have also observed associated yawning with penile erections in adult rats, observation which we have confirmed (unpublished results).

Even if little or no sex differences exist in the SYS induced by ACTH (1), the release of yawning behavior in monkeys in response to their mirror images seems to be sex-bound: Hall (10) mentioned that females in this experimental situation rarely "yawned". Cholinomimetically-induced yawning in adult rats also seems to be sex dependent: males injected with physostigmine yawn significantly more than females (21). In the present report we describe some experiments which suggest that cholinergic yawning is subject to distinct sex hormone influences.

Young male albino rats, 30-day-old, injected intraperitoneally with physostigmine salicylate (0.10 mg/kg, as base), and observed during one hour as formerly described (13, 22), yawn significantly more than female littermates, or males castrated when 11 day old. This age for testes ablation was selected so as not to interfere wiih the perinatal critical period of hormonal masculinizing effects on the CNS, and distant enough from the first test with physostigmine for the effects of castration to become evident. Castrated males treated with daily injections of testosterone (100 µg) from the 30th to the 37th day, are undistinguishable from intact males in their yawning response to the anticholinesterastic drug. Such restoration of yawning is not obtainable by treatment with estradiol benzoate (200 µg daily).

A single androgenizing (19) injection of testosterone (250 µg) to one-day-old female rats (n = 16) does not modify the physostigmineinduced yawning response tested on the 30th postnatal day, when compared to that of normal females (n = 16) (Fig. 2). A second test, performed on the 37th day, after one week treatment with testosterone (100 µg daily), demonstrated highly significantly increased yawning responses in both groups, in comparison to their responses in the

first test ($P < 0.001$, Mann-Whitney U Test) (20). The difference in yawning frequency between normal and androgenized females after this treatment is also statistically significant ($P < 0.01$), the average number of yawns of the latter group being more than 1000/o higher than in the former, during one hour after physostigmine injection.

It is unlikely that so important quantitative differences in cholinomimetically induced yawning between male and female rats are due to simple pharmacokinetic effects, as have been described for other drugs. These are generally interpreted as the result of sex hormone influences upon microsomal enzymes participating in drug metabolism, androgens stimulating, while estrogens and progesterone inhibit microsomal enzymes activity (5). Therefore, the greater yawn promoting effect of physostigmine in male rats, compared to females, in testosterone treated castrated males compared to the untreated castrates, and in testosterone treated females compared to normal females, could hardly be understood as due to pharmacokinetic effects of testosterone on the metabolism of physostigmine. These would rather tend to reduce than to increase the anticholinesterasic action of physostigmine.

The greater yawning-inducing effect in testosterone treated neonatally androgenized females is also consistent with the idea that the differences observed are the result of true androgenic hormonal effects exerted upon the central nervous system, both at an early (perinatal) period of development, and later on in life. In the particular effect analyzed by us, testosterone treatment of one-day-old females seems to have increased their sensitivity to testosterone administrated one month later. The level of the central nervous system at which testosterone might interact with the neural structures responsible for cholinomimetically induced yawning is unknown, and only broad hypothetical suggestions may be advanced. Because of the early ontogenetic maturation of cholinergic yawning (13, 21), it has been suggested that the neural circuitry responsible for yawning behavior seems to be localized at the lower brainstem region. The observation of yawning in Gamper's mesencephalic human being (17) also points in that direction. This does not necessarily mean that the influence of testosterone is exerted at such a caudal level, because it might also be mediated by descending pathways from higher placed nervous sites, i.e. in the limbic system, well known as steroid hormone targets.

Although the described effect of testosterone is upon a behavioral pattern including important cholinergic links, the hormonal action might as well take place in cholinergic or cholinosensitive neurons, or in neurons of some of the specific monoarnine pathways, which could exert some modulating influences on yawning. Such alternatives should be considered when reports have appeared describing yawning in adult rats evoked by dopaminergic agonists (18), and a strong facilitation of physostigmine-induced yawning by Lu 10-171 (22), a potent and selective serotonin uptake inhibitor (15). Sex differences and the effect of gonadal steroids on brain serotonin levels, 5-HT synthesis or turnover have been the subject of research by several groups in recent years (4, 8, 9, 11, 12) but the results remain controversial.

Even if the functional significance of the above described hormonal effects on yawning are obscure, they do confirm the possibility envisaged by Young et al (23) that "gonadal substances may affect behavior beyond that which is primarily sexual in the sense of being directed solely towards the attainment of sexual aims".

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