



Review article

Steroid metabolism in the brain: From bird watching to molecular biology, a personal journey



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ABSTRACT

Since Arnold Adolph Berthold established in 1849 the critical role of the testes in the activation of male sexual behavior, intensive research has identified many sophisticated neurochemical and molecular mechanisms mediating this action. Studies in Japanese quail demonstrated the critical role of testosterone action and of testosterone aromatization in the sexually dimorphic medial preoptic nucleus in the activation of male copulatory behavior. The development of an immunohistochemical visualization of brain aromatase in quail then allowed further refinement in the localization of the sites of neuroestrogens production. Testosterone aromatization is required for the activation of both appetitive and consummatory aspects of male sexual behavior. Brain aromatase activity is modulated by steroid-induced changes in the transcription of the corresponding gene but also more rapidly by phosphorylation processes. Sexual interactions with a female also rapidly regulate brain aromatase activity in an anatomically specific manner presumably via the release and action of endogenous glutamate. These rapid changes in estrogen production modulate sexual behavior and in particular its motivational component with latencies ranging between 15 and 30 min. Brain estrogens seem to act in a manner akin to a neurotransmitter or at least a neuromodulator. More recently, assays of brain estradiol concentrations in micropunched samples or in dialysis samples obtained from behaviorally active males suggested that aromatase activity measured *ex vivo* might not be an accurate proxy to the rapid changes in local neuroestrogens production and concentrations. Studies of brain testosterone metabolism are thus not over and will keep scientists busy for a little longer.

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“For such a large number of problems there will be some animal of choice or a few such animals on which it can be most conveniently studied (August Krogh, 1929).”

For me, it was the Japanese quail!

1. Introduction

My interest for birds started during my early childhood when I was trapping birds with my father during their autumn migration, an activity that was at the time very widespread in Belgium but became illegal (for good reasons) in the 1970's. I had at that time started studies in biology (then called zoology) and my interest for birds naturally transformed into a passion for bird watching and photography. At the end of my college years, I started a PhD project and quite naturally this research focused on birds. I was initially assigned a project attempting to determine the role of olfactory communication in the control of social behavior in ducks and I actually managed to collect experimental data suggesting the existence of pheromonal communication in ducks (Balthazart and Schoffeniels, 1979; Jacob et al., 1979) but this topic became recognized and matured only several decades later (e.g., (Hagelin et al., 2003; Bonadonna and Nevitt, 2004; Hagelin, 2007; Balthazart and Taziaux, 2009)). During my first year of PhD, I faced however a problem that I had not anticipated, even if it was obvious: ducks are seasonal breeders and testing the contribution of pheromones to the control of sexual behavior was only feasible during a few months each year which left me unoccupied for long periods of time. When the reproductive season ended, I therefore decided to try injecting testosterone to my male ducks to test whether this would activate sexual activity and thus allow me to analyze the effects of female odors on male behaviors. This experiment turned out to be very successful (Balthazart, 1974; Balthazart and Stevens, 1975) and over the years the endocrine controls of behavior occupied an increasing part of my scientific activity. Briefly summarized, this is how I became a behavioral endocrinologist...! even though this discipline was not represented in Belgium and only very scarcely in Europe.

Radioimmunoassays (RIA) for steroids were at that time beginning to generalize in biomedical laboratories and I took advantage of this new technology to analyze with a previously unmatched refinement the relationships between changes in plasma testosterone concentration and reproductive behaviors in captive male Rouen ducks (*Anas platyrhynchos*) (Balthazart, 1976; Balthazart and Hendrick, 1976; Balthazart et al., 1977a). In collaboration with Dr. Jean Claude Hendrick (University of Liege) we also established at that time the first RIA for follicle-stimulating hormone (FSH) based on a heterologous antibody (Croix et al., 1974) and combining this assay with the luteinizing hormone (LH) RIA developed a few years before by Brian Follett, Colin Scanes and Frank Cunningham (Follett et al., 1972) we became capable for the first time to monitor in a longitudinal manner the changes in activity of the pituitary-gonadal axis across the annual or daily cycles and correlate them with behavior (Balthazart and Hendrick, 1976; Balthazart et al., 1977a; Balthazart et al., 1977b). Significant correlations between changes in time of hormones and behavior were identified (Balthazart and Hendrick, 1976; Balthazart et al., 1977b) but to my surprise, I discovered on this occasion that individual differences in hormones, and in particular testosterone, concentrations did not relate to individual differences in behavior (Dessi-Fulgheri et al., 1976; Balthazart et al., 1977a; Ramenofsky, 1984) (Fig. 1).

This absence of relationship had actually been suggested in an indirect manner before the advent of sensitive assays for steroid hormones. In a classical study, Grunt and Young had shown that individual differences in sexual behavior of guinea pigs (*Cavia porcellus*) disappeared following castration (sexual behavior progressively vanished) but were

quickly re-established when castrated subjects were all treated with a standard dose of exogenous testosterone (Grunt and Young, 1953). This idea was confirmed in multiple subsequent studies and it was established that in general, individual concentrations of hormones correlate with the behavior of the subjects only during periods of rapid changes or social instability such as the beginning of the reproductive season or the establishment of a social hierarchy (see (Ramenofsky, 1984) for an early example in quail). At these times the individual correlations actually reflect different rates of adaptation to a new situation and are therefore indirectly correlations with changes across time.

This general existence of correlations in time but not across subjects between hormones and behavior caught my interest and actually turned out to be one of the topics that I investigated in different contexts during my entire career. I hypothesized that the lack of correlation reflected the existence of individual differences in sensitivity of the brain to steroid action. Two candidates were at that time (late seventies) the prime suspects as agents modulating this sensitivity: the concentration or affinity of steroid receptors and the activity of steroid metabolizing enzymes. I set out to test these ideas in avian models known for displaying a discrepancy between changes in behavior and in plasma concentrations of sex steroids.

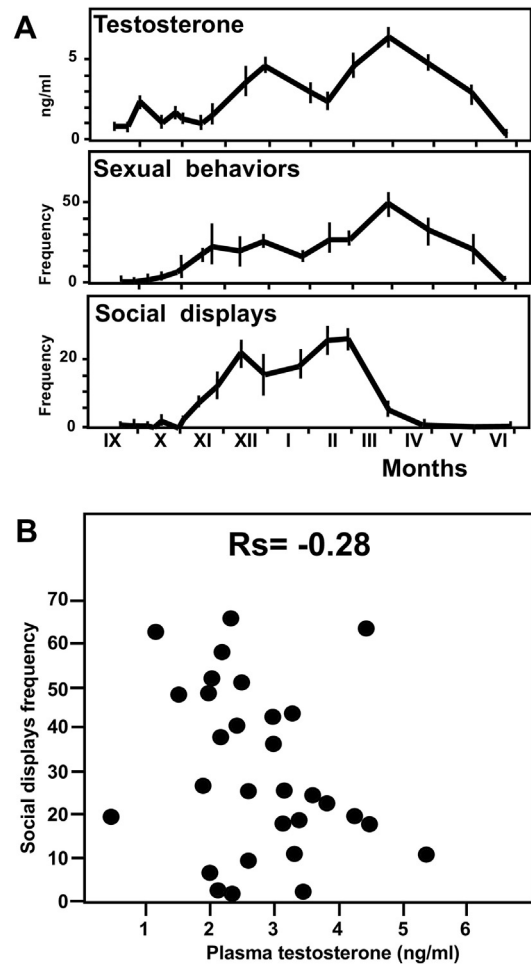


Fig. 1. Annual variations in plasma testosterone concentrations and frequencies of sexual behaviors or social displays (A) and correlations between individual frequencies of social displays and plasma testosterone concentrations at the peak of spring behavioral activity (B) in male domestic ducks. During the annual cycle, changes in plasma testosterone are clearly predictive of the changes in frequencies of the two types of behaviors but when the behavior is fully established in spring, the individual differences in behavior and testosterone are not related. The Spearman rank correlation between social displays and testosterone is only -0.28 (Not significant; see panel B for individual points) and is even smaller between sexual behaviors and testosterone ($R_s = 0.05$). Redrawn from data in Balthazart and Hendrick (1976) and Balthazart et al. (1977a).

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