Hormones and Behavior 99 (2018) 1–8

Contents lists available at ScienceDirect

Hormones and Behavior

journal homepage: www.elsevier.com/locate/yhbeh

Review article

Steroids and the brain: 50 years of research, conceptual shifts and the ascent of non-classical and membrane-initiated actions

Jacques Balthazart[a,*], Elena Choleris[b], Luke Remage-Healey[c]

[a] GIGA Neurosciences, University of Liege, B-4000 Liège, Belgium
[b] Department of Psychology and Neuroscience Program, University of Guelph, Guelph, Ontario N1G 2W1, Canada
[c] Center for Neuroendocrine Studies, University of Massachusetts Amherst, Amherst, MA 01003, USA

ARTICLE INFO

Keywords:
Neurosteroids
History of endocrinology
Genomic effects of steroids
Aromatase
Behavioral neuroendocrinology

ABSTRACT

This brief commentary reviews key steps in the history of steroid endocrinology that have resulted in important conceptual shifts. Our understanding of the "Fast Effects of Steroids" now reflect substantial progress, including the major concept that steroids act rapidly on a variety of physiological and behavioral responses, via mechanisms that are too fast to be fully accounted for by classical receptor-dependent regulation of gene transcription. Several so-called 'non-classical' mechanisms have been identified and include binding to membrane receptors and regulating non genomic signaling cascades. We survey the discovery of steroids, the initial characterization of their intracellular receptors, key progress in the understanding of the genomic effects of steroids and then the progressive discovery of the rapid non-classical and membrane-initiated actions of steroids. Foundational discoveries about brain steroid synthesis in neural processes and terminals has converged with emerging evidence for the rapid actions of steroids on brain and behavior. Had the rapid effects of steroids in the central nervous system been discovered first, these molecules would likely now be considered as a class of neurotransmitter.

1. Introduction

The notion that a diffusible message can control male sexual attributes including sexual behavior is classically associated with the experimental work of Arnold Adolf Berthold. He showed that the male characteristics disappear following castration but are reinstated by the graft of a testis, independently of where this testis is placed (Berthold, 1849). Later in the 19th century, Charles-Edouart Brown-Séquard injected himself with aqueous extracts of dogs and guinea pig testes and claimed that this had restored his vigor and feeling of well-being (Brown-Sequard, 1889) but effects were transient, and in retrospect presumably represented a placebo effect since testosterone is only very poorly soluble in water.

It took however nearly a century after Berthold to identify the chemical message responsible for these actions. In 1927, 20 mg of the sex steroid testosterone was isolated from about 20 kg of bulls testes and were shown to masculinize phenotypic traits in roosters, rats and pig (Gallagher and Koch, 1929). Procedures to isolate the steroid from animal tissues were then designed in the following decade by the European pharmaceutical companies Schering (Germany), Organon (The Netherlands) and Ciba (Switzerland). Organon was the first to isolate and identify the hormone and named it testosterone (David et al., 1935). Its structure was identified by Butenandt and its synthesis from cholesterol was achieved almost simultaneously by Butenandt and Hanisch and by Zubicka (Butenandt and Hanisch, 1935; Ruzicka and Wettstein, 1935) which earned them the 1939 Nobel prize in chemistry (Freeman et al., 2001).

Physiological effects of compounds from ovarian origin, to be later called estrogens, were identified by Allen and Doisy at about the same time in 1923 (Allen and Doisy, 1923). Estrone was independently isolated and purified by Allen and Doisy and by Butenandt in 1929 and estriol followed in 1930 (Parl, 2000). The most potent and best-studied estrogen, estradiol-17β was the last to be identified in 1933 (Lauritzen and Studd, 2005). It was then synthesized, chemically purified and its structure was determined by Doisy in 1935 (MacCorquodale et al., 1935). A partial synthesis from cholesterol was developed in 1940 and a full synthesis in 1948 (Lauritzen and Studd, 2005).

A colossal amount of progress has been made since these seminal discoveries of steroids. The study of hormone action has become an entire field of fundamental and applied research called Endocrinology (covering of course also actions of non-steroid hormones that are not covered here). This research has at several points reached a stage when

* Corresponding author at: GIGA Neurosciences, University of Liege, 15 Avenue Hippocrate, B-4000 Liège, Belgium.
E-mail address: jbalthazart@uliege.be (J. Balthazart).

https://doi.org/10.1016/j.yhbeh.2018.01.002
Received 27 December 2017; Received in revised form 30 December 2017; Accepted 2 January 2018
0018-506X/ © 2018 Elsevier Inc. All rights reserved.

most people could believe that all major questions had been solved and only details remained to be worked out. However new discoveries have repeatedly produced large magnitude shifts that challenge this belief and have led to major revisions of established concepts. One of the new concepts that started to emerge in the 1970's but whose real importance was only realized about two decades ago concerns the rapid, non-classical and membrane-initiated effects of steroids on brain and behavior. A special issue of *Hormones and Behavior* (Fast Effects of Steroids) is currently in preparation and will provide an overview of the current knowledge in this field. Here, we briefly summarize the major conceptual shifts that have taken place in Endocrinology during the last 50 years to provide context for our current understanding of this new mode of rapid steroid action. It is of course impossible to list here all discoveries that were made during this period but we will highlight a few significant findings that surrounded and prepared what we consider as the major recent rethinking of steroid signaling.

2. The foundations of the endocrinology of steroid hormones

From the time when steroid hormones became available for experimentation, their synthesis pathways and mode of action were the subject of active research. Progress in the available biochemical methods was however needed and it is only in the 1960's that the steroid synthesis pathways (see for review: (Feder, 1981)) and their intracellular binding sites began being uncovered in peripheral steroid-sensitive structures such as the uterus or the chicken oviduct (Jensen, 1962; Jensen and Jacobsen, 1962; Jensen et al., 1968; O'Malley et al., 1969). The detailed mechanism of action remained however unclear until more recently (see (Tsai and O'Malley, 1994)). In 1967–68, i.e., 50 years ago, a basic knowledge about steroid action was beginning to emerge. The chemical structure of steroids and a substantial part of their synthesis pathways had been identified, biochemical studies had discovered and characterized steroid receptors in peripheral steroid-sensitive structures and their presence was suspected in the central nervous system even if it remained impossible to fully characterize them due to their lower abundance.

By the end of the 1960's, the bases of endocrinology were established and this scientific enquiry had progressed enough that it became conceivable to attack the more difficult question of the role of steroid hormones in brain functioning. Soon thereafter, a number of prominent endocrinologists interested in brain function created the International Neuroendocrine Society under the presidency of Joseph Meites (Ramirez, 2017). One could believe that only details remained to be discovered but nothing was further away from the truth and many surprises were still in store. Entire new research areas were still to be identified and explored. We briefly discuss in this review the most significant of these fundamental discoveries, focusing to a large extent on steroid action in the brain, although it is impossible to cover all of them even superficially given the diversity and large number of topics.

3. Genomic action of steroids: The last 50 years

As already mentioned, in the 1960's the detail of the interaction of sex steroids with their intracellular receptors and how the activated receptors mediate changes in transcription (enhancement or silencing) was still to be uncovered (Tsai and O'Malley, 1994) and progress is in fact still ongoing. The anatomical distribution of these receptors was first characterized by binding assays on (micro-) dissected tissue samples and subsequently by techniques providing more anatomical resolution, which allowed substantial progress especially for understanding steroid action in the brain. At approximately the same time in the late 1960's, two laboratories developed the dry mount *in vivo* autoradiographic technique that allowed the visualization of steroid binding sites in the brain. This opened the route to the identification of the steroid-sensitive circuitry that mediates the activation of reproductive behaviors (Morrell et al., 1975; Pfaff and Keiner, 1973; Pfaff, 1968; Sar and Stumpf, 1972; Stumpf, 1968; Stumpf, 1970; Stumpf and Sar, 1976).

When molecular biology techniques including DNA sequencing became routine, the first cDNA encoding the glucocorticoid receptor was cloned (Hollenberg et al., 1985; Weinberger et al., 1985) followed rapidly by cloning of the cDNA encoding other steroid receptors including the androgen (AR) (Chang et al., 1988; Lubahn et al., 1988) and the estrogen (ER) (Green et al., 1986) receptor. This was followed by the production of specific antibodies and *in situ* hybridization probes that allowed confirming distributions identified earlier by *in vivo* autoradiography (Simerly et al., 1990). Since immunohistochemistry and *in situ* hybridization are more sensitive and more specific, these techniques identified additional populations of brain cells that express low concentrations of these receptors that were later shown to have a clear functional significance (e.g. the low density of ER present in the telencephalon that modulate cognitive processes, (Gervais et al., 2017).

Detailed analysis of the sequence of cloned steroid receptors demonstrated that they all consist of six defined domains (labeled A through F) including domains that have a conserved sequence and function (Evans, 1988; Mangelsdorf et al., 1995). Purification of receptor proteins based on the affinity for their ligand or for DNA was incredibly challenging since these proteins are expressed at extremely low levels, especially in the brain. The identification of the conserved functional domains and the development of molecular biology tools greatly facilitated this work leading to the identification of new receptors in this family including orphan receptors that had no known ligand at the time they were identified (Rousseau, 2013). This resulted namely in the cloning of a second ER that was named ERβ to distinguish it from the previously identified receptor now renamed ERα (Kuiper et al., 1996; Mosselman et al., 1996; Tremblay et al., 1997).

Great progress was also made during the last 50 years in the understanding of how steroid receptors regulate gene expression and this work is still ongoing (Bain et al., 2014; Kumar and McEwan, 2012; Tsai and O'Malley, 1994). Early work indicated that nuclear steroid receptors require common cofactors that constitute a limiting factor when competition, or squelching, between different receptors takes place (Meyer et al., 1989). Confirmation of the existence of such cofactors was first obtained by Onate and colleagues in the O'Malley laboratory who cloned and sequenced an mRNA coding for the steroid receptor coactivator 1 (SRC-1), a protein closely associated with progestin receptors (Onate et al., 1995). This was the beginning of a new chapter in the endocrinology of steroid receptors: the identification of the steroid receptor coregulators, a class of proteins that either enhance (co-activators) or decrease (co-repressors) gene transcription mediated by steroid receptors. More than 300 members have now been identified in this family of proteins (see Nuclear Receptor Signaling Atlas at https://www.nursa.org/nursa/index.jsf) and their functional significance is still far from being elucidated (O'Malley et al., 2008; Wang et al., 2016).

Quite surprisingly it was also discovered that activation of steroid receptors could take place in the absence of steroids and play a significant functional role (Power et al., 1991). In particular, studies demonstrated that dopamine activates progestin receptors in the brain and in this way modulate female sexual receptivity (Mani et al., 1994; Mani and Blaustein, 2012). This mechanism is however not limited to the progestin receptor and, for example, also concerns ER (Schreihofer et al., 2001). Along the same lines, it became clear in the 1990's that conventional 'reproductive' hormones like estrogens and progestins could regulate distinctly non-reproductive neural endpoints, such as basal forebrain cholinergic pathways (Gibbs, 1997), and hippocampal plasticity (Woolley, 1998). Therefore, the complexity of steroid receptor signaling and neural targets became evident as non-steroid molecules regulated steroid receptors, and 'reproductive' steroid hormones shaped behavioral arousal and memory encoding.

In a remarkable convergence, the source of steroids acting in the brain has also been completely revised during these last 50 years. It was initially thought that the male brain was essentially exposed to

Download English Version:

https://daneshyari.com/en/article/6793900

Download Persian Version:

https://daneshyari.com/article/6793900

Daneshyari.com