Molecular and Cellular Endocrinology 371 (2013) 5–14

Contents lists available at SciVerse ScienceDirect

Molecular and Cellular Endocrinology

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

Review

A brief history of adrenal research
Steroidogenesis – The soul of the adrenal

Walter L. Miller

University of California, San Francisco, San Francisco, USA

ARTICLE INFO

Article history:
Available online 30 October 2012

Keywords:
Adrenal cortex
Adrenal history
Adrenal hyperplasia
Brown-Sequard
Steroid hormones
Steroidogenic enzymes

ABSTRACT

The adrenal is a small gland that escaped anatomic notice until the 16th century, and whose essential role in physiology was not established until the mid 19th century. Early studies were confounded by failure to distinguish the effects of the cortex from those of the medulla, but advances in steroid chemistry permitted the isolation, characterization and synthesis of many steroids by the mid 20th century. Knowledge of steroid structures, radiolabeled steroid conversions, and the identification of accumulated urinary steroids in diseases of steroidogenesis permitted a generally correct description of the steroidogenic pathways, but one confounded by the failure to distinguish species-specific differences. The advent of cloning technologies and molecular genetics rapidly corrected and clarified the understanding of steroidogenic processes. Our laboratory in San Francisco was one of several contributing to this effort, focusing on human steroidogenic enzymes, the genetic disorders in their biosynthesis and the transcriptional and post-translational mechanisms regulating enzyme activity.

Contents

1. Introduction to the Keith Parker Memorial Lecture

It was indeed an honor to give the second Keith Parker Memorial Lecture at the biennial Adrenal Cortex Conference. Keith was a friend and a creative, ground-breaking scientist who was taken from us far too soon. We all miss him deeply. Following his discovery of the transcription factor SF1 (steroidogenic factor 1), much of Keith's career concerned adrenal development in rodent systems, while mine has concerned human steroidogenesis, but we were both focussed on the adrenal. Below I shall recount some of the history of adrenal research, then mention some contributions from my lab and suggest some future directions.

2. Anatomists: discovery of the adrenal

Whereas it is self-evident that the adrenal has always been with us, early anatomists apparently failed to note its presence. In the context of describing animal sacrifices, Leviticus 3:4 and 4:9 both refer to "...the two kidneys, and the fat that is on them, which is by the flanks..." (King James translation) and in a different context Claudius Galen (ca. 130–201) only described 'loose flesh' atop the left kidney (Leoutsakos and Leoutsakos, 2008). Thus it seems that the ancients could not distinguish the adrenals from the peri-nephric fat, and anyone who has collected ungulate adrenals at an abattoir will confirm that the differentiation of the adrenal from adjacent fat and lymph nodes is not trivial. In 1563 Bartolomeo Eustachius (1520(?)–1574), who was Professor of Anatomy at the Collegio della Sapienza in Rome and a challenger

E-mail address: wlmlab@ucsf.edu

0303-7207/$ - see front matter
http://dx.doi.org/10.1016/j.mce.2012.10.023

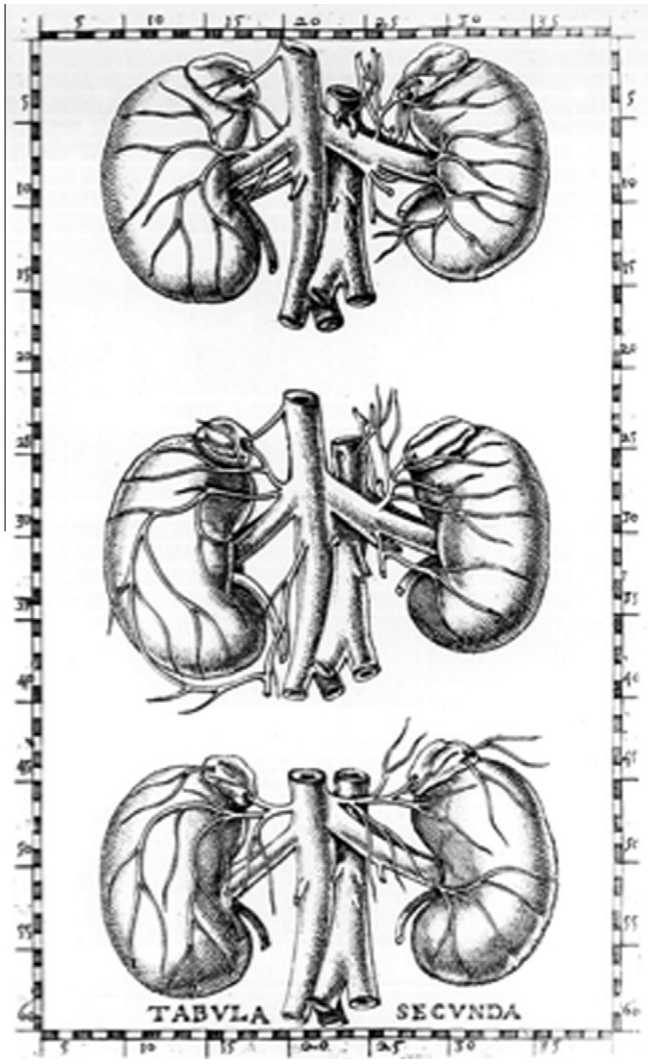

Fig. 1. Plate 47 from Eustacchio's 'Tabulae Anatomicae', as reproduced by GM Lancisi in 1714 as 'Tabulae Anatomicae'. Image captured on line.

of Galenic authority, published his tome 'Opuscola Anatomica'. This work, which correctly described the anatomy of the inner ear and the eustachian tube, referred to the adrenals as 'glandulae renibus incumbentes' in the description of the kidneys. However, because Eustacchio feared the Roman Catholic inquisition, most of the accompanying anatomic engravings (completed in 1552 by Pier Matteo Pini) were not published, but were sequestered in the Papal library until Clement XI gave them to GM Lancisi, who published them in 1714 as 'Tabulae Anatomicae' (Carmichael, 1989; Mezzogiorno and Mezzogiorno, 1999). Eustaccio's plate 47 shows the adrenal anatomy with remarkable accuracy (Fig. 1), but throughout the 150 years that the church hid Eustacchio's work, most anatomists questioned his claim to have discovered a suprarenal organ. In 1716, the Academy of Sciences in Bordeaux conducted an essay competition to determine the function of the adrenals, but none of the entries was deemed worthy of the prize, and the Academy then redirected its attention more productively to wine. The Danish anatomist Caspar Bartholin, better known for Bartholin's glands, described the adrenals as hollow organs filled with 'black bile', probably a poetic description of the adrenal medulla undergoing post-mortem autolysis. Finally, in 1805, Georges Cuvier (1769–1832) distinguished the cortex and medulla, but offered no functional insights (Cuvier, 1805).

3. Physiologists: adrenal function

The linkage of earlier anatomy with clinical observation in the mid 19th century began the modern era of adrenal research. Thomas Addison (1793–1860) first described tuberculosis of the adrenal in 1849 (Addison, 1849) and then wrote his famous, detailed monograph "On the Constitutional and Local Effects of Disease of the Suprarenal Capsule" in 1855 (Pearce, 2004). In studies of (autopsied) patients with anemia, he found bilateral adrenal pathological changes that appeared to be independent of the anemia (Fig. 2). His clinical description is classic: "The discoloration pervades the whole surface of the body, but is commonly most strongly manifested on the face, neck, superior extremities, penis, scrotom, and in the flexures of the axillae and around the navel ... The leading and characteristic features of the morbid state to which I would direct your attention are, anaemia, general languor and debility, remarkable feebleness of the heart's action, irritability of the stomach, and a peculiar change of the colour in the skin, occurring in connection with a diseased condition of the suprarenal capsules." Addison was a brilliant observer who also described the first cases of what we now know to be pernicious anemia (vitamin B12 deficiency) and adrenoleukodystrophy, which is more commonly associated with Paul Schilder (1886–1940). But Addison did not understand how adrenal disease led to the symptoms he described so clearly.

Addison's work influenced Charles-Edouard Brown-Sequard (1817–1894), arguably the most brilliant and intriguing character in 19th century medical science (Fig. 3A). Born to an American sea captain father and French mother on the (then British) island of Mauritius in the Indian Ocean, Brown-Sequard was educated in Paris and at various times practiced or held Professorships in London, Boston, New York, Philadelphia, Richmond, Glasgow, Dublin and Paris, was elected to the UK's Royal Society (1860), the US National Academy of Sciences (1868), and France's Academie des Sciences (1886), and published over 500 papers. He reportedly crossed the Atlantic Ocean 60 times, spending a total of 6 years at sea (Rengachary et al., 2008). He is best known today as one of the fathers of modern neurology, including discovery of the decussation of sensory fibers in the spinal cord and his description of spinal hemiparaplegia (Brown-Sequard Syndrome). Brown-Sequard was the first to go beyond mere observation and bring experimentation and quantitation to medical research. In 1856 he demonstrated that adrenalectomy (but not a sham operation) was lethal, and conjectured that the adrenals secreted the

Fig. 2. Reproduction of a figure of a (deceased) patient, from Thomas Addison's monograph "On the Constitutional and Local Effects of Disease of the Suprarenal Capsule". Image captured on line.