Available online at www.sciencedirect.com
ScienceDirect
Life Sciences 80 (2007) 2093–2107
Life Sciences
www.elsevier.com/locate/lifescie

Minireview

The digitalis-like steroid hormones: New mechanisms of action and biological significance

Maoz Nesher [a], Uri Shpolansky [a], Haim Rosen [b], David Lichtstein [a,*]

[a] Department of Physiology, The Hebrew University-Hadassah Medical School, Jerusalem, Israel
[b] The Kuvin Center for the Study of Infectious and Tropical Diseases, The Hebrew University-Hadassah Medical School, Jerusalem, Israel

Received 4 January 2007; accepted 14 March 2007

Abstract

Digitalis-like compounds (DLC) are a family of steroid hormones synthesized in and released from the adrenal gland. DLC, the structure of which resembles that of plant cardiac glycosides, bind to and inhibit the activity of the ubiquitous cell surface enzyme Na^+, K^+-ATPase. However, there is a large body of evidence suggesting that the regulation of ion transport by Na^+, K^+-ATPase is not the only physiological role of DLC. The binding of DLC to Na^+, K^+-ATPase induces the activation of various signal transduction cascades that activate changes in intracellular Ca^{++} homeostasis, and in specific gene expression. These, in turn, stimulate endocytosis and affect cell growth and proliferation. At the systemic level, DLC were shown to be involved in the regulation of major physiological parameters including water and salt homeostasis, cardiac contractility and rhythm, systemic blood pressure and behavior. Furthermore, the DLC system has been implicated in several pathological conditions, including cardiac arrhythmias, hypertension, cancer and depressive disorders. This review evaluates the evidence for the different aspects of DLC action and delineates open questions in the field.

Keywords: Digitalis; Ouabain; Na^+, K^+-ATPase; Natriuretic hormone; Steroids

Contents

* Corresponding author. Department of Physiology, The Hebrew University-Hadassah Medical School, Jerusalem, Israel. Tel.: +972 2 675 8522; fax: +972 2 643 9736.
E-mail address: davidli@ekmd.huji.ac.il (D. Lichtstein).

0024-3205/$ - see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.lfs.2007.03.013

Introduction

Digitalis is a general term for steroidal drugs prepared from the seeds and dried leaves of the genus *Digitalis*, which are used as a cardiac stimulant. More than a quarter of a century has elapsed since the first demonstrations, at the cellular and molecular levels, of the presence of digitalis-like compounds (DLC) in mammalian tissues. The hundreds of scientific reports that have appeared since then unequivocally support the notion that these compounds function as hormones in mammals: They are synthesized and released from the adrenal gland and by interacting with their receptor, Na^+, K^+-ATPase, they affect numerous cellular functions. It is the purpose of this review to provide a broad overview of the structure and biosynthesis of these hormones, with a detailed discussion of their mechanisms of action and biological significance, as well as to delineate the open questions in this field.

Historical perspective

The medical use of digitalis steroids (cardiac glycosides), for more than 200 years, stemmed from an herbal remedy rather than from laboratory chemistry. The English physician William Withering is credited with discovering in 1775 that the foxglove plant could help those suffering from abnormal fluid buildup, or dropsy, as it was called in those days (Peck and Wilkinson, 1950). In 1930, Sydney Smith of Burroughs Wellcome isolated the steroid glycoside digoxin from Digitalis lanata and this compound and other similar derivatives have been developed into drugs still used to treat heart failure and atrial fibrillation (Kelly and Smith, 1996). Structurally related steroids, the bufadienolides (see below), were identified in toad venom: Familiarity with the toxicity of toad venom goes back to ancient times. Physicians of antiquity mentioned medicines prepared from toads, and described their effect on the heart and respiration. In China and Japan, the dried venomous secretion of the Chinese toad, formed into round, smooth, dark brown discs and known as Cha'an Su or Senso, is still used today to treat conditions such as tonsillitis, sore throat, and palpitations. It is also used as a topical anesthetic and aphrodisiac. The structure of the different bufadienolides was studied in great detail (Meyer and Linde, 1971). The presence of endogenous DLC in mammalian tissues was postulated based on theoretical and physiological considerations. Already in 1885 the British physiologist Ringer suggested that an endogenous compound which stimulated cardiac contraction in a manner similar to digitalis glycosides may be present in the human circulation (Ringer, 1885). In 1953, Nobel laureate Szent-Gyorgyi

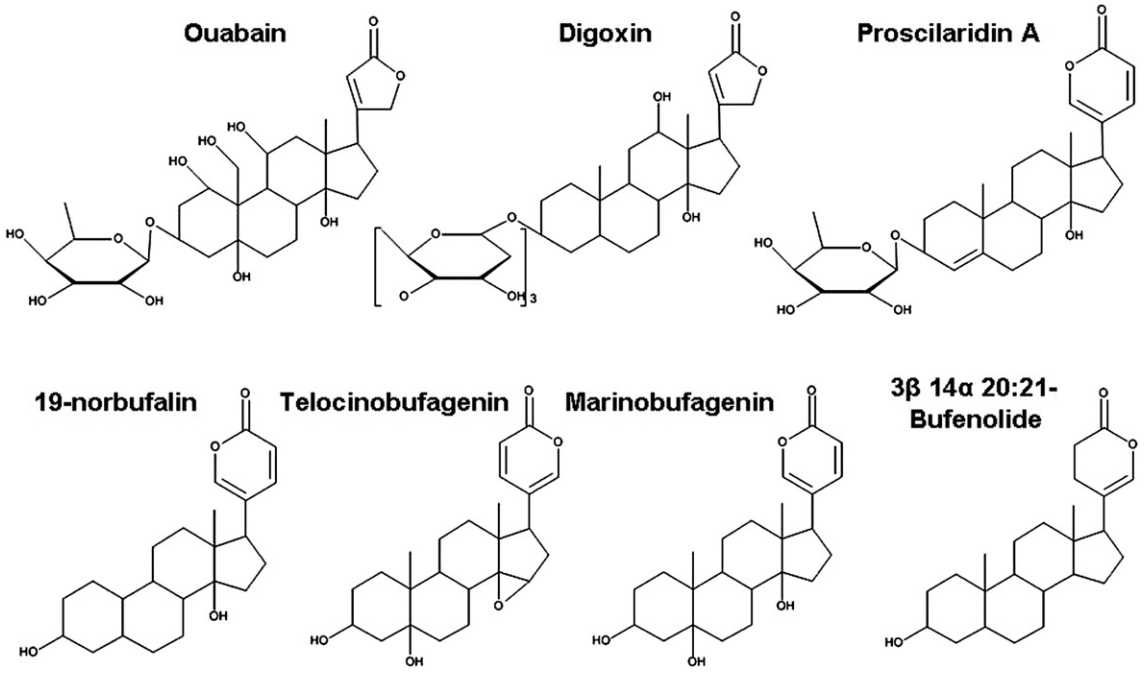

Fig. 1. Structure of digitalis-like compounds identified in human tissues. See text for details.