Natural Toxins

Editors: D Eaker and T Wadström

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Editors

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Natural Toxins

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Preface

Poisons produced by living organisms have fascinated man for many centuries, and various of them have been exploited for good and devious ends from ancient times down to the present. Unlike most of the man-made environmental poisons that pervade the industrialized world today, most of the natural poisons produced by living things are unstable in nature, and nearly all cases of accidental poisoning by such toxins involve direct contact with the organisms that produce them. In most of the industrialized nations of the world, natural toxins are not serious problems because, owing to climatic conditions and urbanization, poisonous insects and animals are rare, and in the case of microorganisms, because contacts have been minimized by better hygiene and controls on the production and distribution of foodstuffs and water or because the unpleasant consequences of such contacts have been largely eliminated by immunization. However, the tropical climates of most developing countries favor proliferation of all forms of life. Serious and even fatal diseases in man and livestock caused by toxins of various microorganisms are often endemic, and more than 100 000 human deaths occur each year as a consequence of bites or stings by poisonous snakes, insects and spiders. Diarrhea diseases caused by various microorganisms are the major cause of infant mortality in the world. Furthermore, the mycotoxins produced by certain molds render a very large fraction of the cereal and peanut production of many developing countries unfit for consumption by man or beast. The latter toxins are especially dangerous owing to the insidious nature of their effects.

For two reasons, natural toxins have received steadily increasing attention during the last two decades: firstly, because we realize that better methods for their detection and the diagnosis, treatment and prevention of the diseases that they cause are among the prerequisites for social and economic progress in many of the developing nations of the world. The second reason is the realisation that the often awesome potency of the most powerful natural toxins is due to very specific interference with vital molecular processes involved in the maintenance of cell integrity and in the communication among different cells. Natural toxins are thus emerging in their own right as extremely valuable tools for the study of some of the most fundamental mechanisms of life.

The concensus among the participants was that the 6th International Symposium on Animal, Plant and Microbial Toxins held in Uppsala in August 1979 under the co-sponsorship of the International Society on Toxinology and the University of Uppsala was a great success both scientifically and socially. The scientific success relects in no small part the high relevance of the subject matter and the competence of the chairmen who put together the 16 different sessions. The meeting was attended by 319 registered participants, and including non-registered locals attendance exceeded 400 on most days. The next international meeting of the International Society on Toxinology will be held in Brisbane, Australia, during July 1982.

Of the 235 abstracts submitted for the meeting, 209 arrived in time for publication in the special issue of TOXICON (volume 17, supplement 1, 1979). 207 papers were actually presented at the meeting: 78 orally and 129 in poster form. Although nearly all of the papers presented were worthy of publication, it did not seem feasible to publish the entire proceedings, which might have run to well over 2000 pages. Working within a page limit of 800 - 1000 pages, we therefore decided to invite submission of manuscripts of only the invited oral papers, which were mainly of review character, and the special workshop presentations, which were tightly organized and also contained considerable amounts of review material. We felt that the remaining free communications, which mainly represented new, original research on a broad range of topics would inevitably be published elsewhere anyway. In any case, the publication of the abstracts meant that all participants had the opportunity

to record their participation in print.

Of the 124 manuscripts thus requested for these proceedings, 83 were received and appear here under the authorship of 228 authors. Although we had correctly estimated the time required for the editorial work at two full months, most of the manuscripts arrived late in October 1979, toward the end of the period that we had reserved for the job, and owing to teaching and other committments we were unable to return in earnest to the task until mid-Spring of this year. A delay of somewhat more than one month in the submission of the manuscripts has thus delayed completion of the book by about half a year. We hope that you readers will find the volume worth waiting for.

Uppsala, June 1, 1980

David Eaker Torkel Wadström

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Plenary Lectures

VENOM GLANDS, VENOM SYNTHESIS, VENOM SECRETION AND EVOLUTION

E. Kochva, U. Oron, M. Ovadia, T. Simon and A. Bdolah

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ABSTRACT

This paper reviews the embryonic development, structure and function of the compound oral glands of non-venomous and venomous snakes in comparison with other exocrine glands, mainly the pancreas. It discusses the phylogenesis of the snake venom glands and proposes a hypothesis for the co-evolution of the two-component, phospholipase-containing toxin and the anti-toxic factor(s) found in the blood serum of snakes.

KEYWORDS

Venom; snake; evolution; phospholipase A; toxin; embryonic development; exocrine glands; anti-toxin; enzyme inhibitor; Viperidae.

INTRODUCTION

In his paper on the evolution of enterosecretory proteins, Adelson (1971) states that "genetic changes in the time and location of expression of the functionally different, related genes led to the evolution of functionally specialized regions of the gut" and that "the ability to secrete related proteins remained constant among the gut-derived glands." He sees as a special case "the ability of several specialized non-entodermal tissues to secrete proteins related to entodermal proteins", which could evolve by "a change in the pattern of gene-activation..... allowing expression of a formerly repressed entodermal gene in a non-entodermal tissue". Extensive evidence in support of these suggestions has since been accumulated (Dayhoff and co-workers, 1975), and hypotheses on the evolution of toxins from certain pancreatic enzymes have been proposed (Eaker, 1975; Heinrikson, Krueger and Keim, 1977; Ivanov and Ivanov, 1979; Strydom, 1977). Given these hypotheses one might expect to find similarities also in the morphology of the glands secreting these compounds, i.e. the pancreas and the compound oral glands of snakes; these similarities should then be more evident in the more primitive glands of the non-venomous species.

EMBRYOLOGY AND MORPHOLOGY

Snakes have developed a variety of exocrine glands in the mouth. The two major types are found in the supra-labial region and are represented by Duvernoy's glands in the colubrid snakes and by the venom glands in the Viperidae and Elapidae *sensu lato* (Kochva, 1978b).

We shall start this comparison with the embryonic development of Duvernoy's glands and the venom glands of Viperidae. In all species thus far examined the gland develops from a common, ectodermal primordium, together with the dental lamina of the maxilla (Fig. 1a). At later stages, the primordium of Duvernoy's gland branches in a symmetrical pattern, while in the Viperidae branching is restricted to the posterior region of the gland (Figs. 1b-d). From what meager evidence is available, the development of the venom glands of the Elapidae and the Atractaspidinae seem to resemble the pattern of Duvernoy's glands rather than the viperid venom glands.

In general terms, the embryonic development already provides some clues suggesting that the venom glands of the Viperidae are the more specialized and should be expected to differ from other glands also in the adult. The similarities with other exocrine glands such as the pancreas, should be looked for among Duvernoy's glands of the non-venomous snakes. The great variability of these glands should facilitate the search and make it possible to find glands with a general pattern not dissimilar to that of the pancreas. An example of such a gland is given in Fig. 2. The venomous snakes, and mainly the vipers, show a different morphology

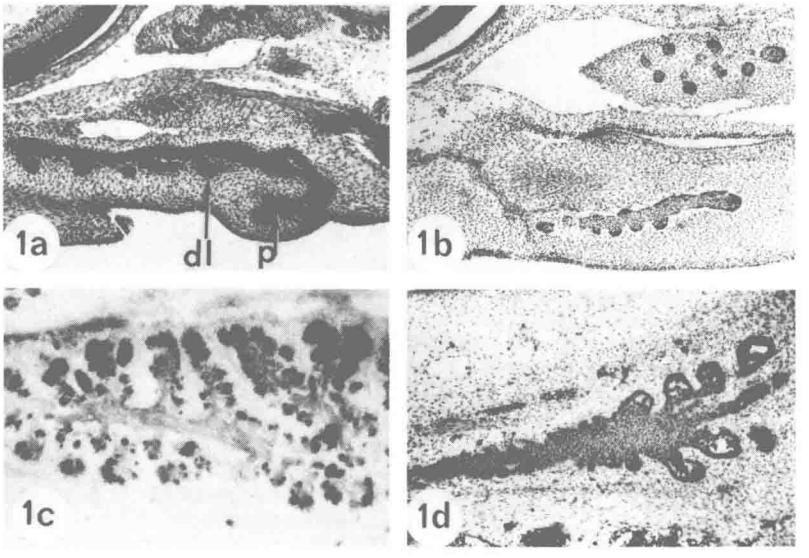

Fig. 1. Embryonic development of oral glands. a) Early stage of dental lamina with gland primordium in *Natrix tesselata*; approx. 80x. b) First branching of gland primordium in *Spalerosophis cliffordi*; approx. 50x. c) Later branching of gland in *Spalerosophis*; approx. 40x. d) Branching of venom gland primordium in *Vipera palaestinae*; approx. 60x. dl - dental lamina; p - primordium of Duvernoy's gland.

that can be clearly seen even at lower magnifications of the light microscope (Figs. 3a-c). At the ultrastructural level the differences are more evident: In all glands examined, including the Elapidae, the cells are filled with secretory granules; only the Viperidae and Crotalidae show a very small number of granules, compensated for by the wide lumina that store large amounts of venom (Figs. 4a-c). *Vipera palaestinae* and the other Viperidae and Crotalidae thus show a gland that is well adapted for having a large amount of venom in store to use effectively even in several consecutive strikes, in connection with a simple and efficient way of replenishing the dose(s) injected (Kochva, 1978a).

Looking at the amounts of venom found in the gland lumina and the small number of secretory granules in the cells, the question was asked whether these secretory granules are the only avenue of venom secretion or whether there was an alternative, direct route of secretion, e.g. from the cisternae of the rough endoplasmic reticulum into the lumen. The latter pathway was suggested for other exocrine glands (cf. Isenman and Rothman, 1979).

In order to answer this question, some histochemical and immunohistochemical techniques were applied, at the level of the light and electron microscopes (Figs. 5a-d). The results show that all secretory cells contain the venom components examined, some of which could be identified in the same secretory granules. Admittedly, not all our evidence is direct and overlapping, but it appears nevertheless that the venom is secreted through these granules, despite their scarcity.

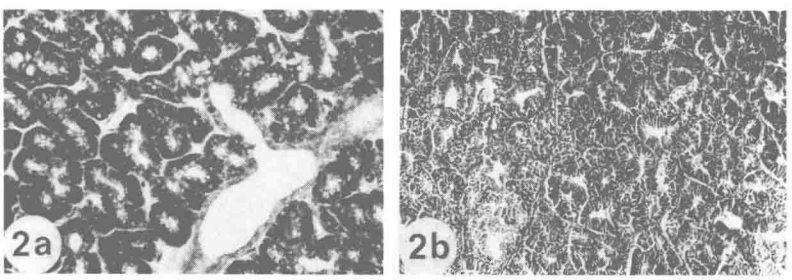

Fig. 2. Comparison of pancreas and Duvernoy's gland. a) Pancreas of *Vipera palaestinae*; approx. 200x. b) Duvernoy's gland of *Aparallactus modestus*; approx. 200x.

PHYSIOLOGY

Quantitative evidence on the synthesis and secretion of venom is now available from work done on the Cascavel, *Crotalus durissus terrificus* at Riberão Preto by Marchi, Haddad and De Lucca (1978), on the Tsefa, *Vipera palaestinae*, by Oron and Bdolah (1978b) in Tel Aviv and on the sea snake *Laticauda semifasciata* by Takeda, Yoshida and Tamiya (1974). Radioautographic and morphometric calculations (Fig. 6) support the assumption that the intracellular transport of venom proteins in both *Crotalus* and *Vipera* follows the conventional pattern of exocrine glands, as documented by Palade (1975) for the mammalian pancreas. In *Crotalus* there is a variable number of intracisternal granules (Brasileiro, 1976) that follows a different labelling pattern.

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