Bradykinin Kallidin and Kallikrein

Supplement

Editor E. G. Erdös

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Continuation of Handbuch der experimentellen Pharmakologie

Vol. XXV Supplement

Preface

Volume XXV of the Handbook of Experimental Pharmacology series entitled "Bradykinin, Kallidin, and Kallikrein" was published in 1970. My aim in editing this volume of the series is not to replace, but to update the 1970 edition. During the decade preceding the publication of Vol. XXV, the existence of kinins and kallikreins gained acceptance, the protein components of the system were purified and characterized and the peptides were synthesized. Even after these accomplishments, interest in the subject has not abated, but has increased substantially. We have learned a great deal about the role that components of the kallikrein–kinin system play in other systems and about the immensely complex and intricate interactions in blood. Directly or indirectly, kallikrein and kinins affect the coagulation of blood, the activation of complement, and the generation of angiotensin. Kinins release or modulate the actions of other agents, including prostaglandins, histamine, and catecholamines. Inhibitors of kallikrein or kininase II are employed, for example, in extracorporeal circulation or in hypertension. Kallikrein, kinins, and kininases, present in urine, were described first in 1925 and 1954, but have been ignored for decades. These substances are now studied extensively because of their possible role in blood pressure regulation. The evidence that kinins have a metabolic function is also increasing. The abundance of active components of the system in genital organs suggests a role in the fertilization process.

The book is organized into chapters which bear upon these issues. The first four chapters discuss kininogenases, the enzymes which release kinins and their inhibitors. Plasma kallikrein, its substrates and its inhibitors and the interrelationships with other blood-borne systems are reviewed in the first chapter. This is followed by a discussion of kininogenases in blood cells including acid kininogenases which form an alternate kinin system.

Reviews of the extensive studies on the structure of glandular kallikreins and their inhibitors are next, summarizing the achievements of a very enlightening period of protein research.

The next section deals with kinins. Structure-activity studies on peptides of the kinin system and on bradykinin potentiators have lead to the synthesis of effective kininase II inhibitors and hopefully, in the future, will lead to the development of specific kinin antagonists. Free, naturally occurring bradykinin and related peptides are next. If we wish to understand the actions of kinins, we must learn about their sites of action and we must be able to assay them accurately and in minute quantities. Chapters on bradykinin receptors and on radioimmunoassay contribute an up-to-date review of these problems. The actions of kinins and kallikrein in the central nervous system and other tissues are described next. Some of the investigations

described here may be only initial observations, but might later open new areas of research. Among the most intriguing aspects of research on kinins are studies of their indirect actions, especially their interrelationships with prostaglandins (Chap. XI). Kinins are not stable in the organism; they are rapidly inactivated in blood and kininases in tissues limit their actions. The functioning of kininase I as an anaphylatoxin inactivator and kininase II as the angiotensin I converting enzyme emphasizes the importance of these proteins.

Glandular kallikrein and urinary kallikrein have been scrutinized by many researchers since excretion of the latter seems to be connected with hypertension. Chapters XIII, XIV, and XV describe the results of experimental work on glandular, renal, and urinary kallikrein in laboratory animals and man. Kinins may have a more important role in pathological than in physiological processes, as surveyed in Chap. XVI. The final chapter summarizes the extensive literature published in Russian because it is not easily accessible to readers outside of the U.S.S.R.

In 1966 I wrote in a review (Adv. Pharmacol. *4*, 1–90) "... the status of kinins somewhat resembles that of acetylcholine or histamine. Bradykinin may never become a therapeutically important agent. Nevertheless, if kinins play a significant role in some physiological or pathological conditions, agents which block the effects or inhibit their enzymic metabolism would be of prime importance." Since half of the second prediction seems to be fulfilled by the development of kininase II inhibitors, we may look forward to finding kininase I inhibitors that work in the whole organism, and to the development of active kinin blocking agents.

Finally, I mention with deep regret that Professor EUGEN WERLE is no longer with us; thus he can not witness the exciting developments in the field where he achieved so much, so early, and so far ahead of others.

Dallas, June 1979 E. G. ERDÖS

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