Experimental Model of Depletion of the Blood Kallikrein-Kinin Systems

S. P. Shumilov

UDC 616.133.1:577.152.34]+616.154:577.175.85]-092.9-07

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 116, № 10, pp. 343-344, October, 1993
Original article submitted May 20, 1993

Key Words: *kallikrein-kinin system; kallikrein; kininogen; kininases; kinins*

The blood level of active kinins is determined by the rate of kinin formation and destruction. Hence, different states of the kallikrein-kinin system (KKS) can be observed in the organism, namely activation, inhibition, deficiency and depletion [3]. By depletion we mean a low level of active kinins and the impossibility of their formation according to the organism's requirements with maintained synthesis of the KKS components. A long-term subcutaneous administration of L-thyroxine causes a considerable decrease in kallikrein and prekallikrein activity in the blood of experimental animals [8]. As the activity of the kallikrein system falls off, the kininogen content increases. This response of the kinin system to L-thyroxine can be thought of as a variant of KKS depletion. However, the possibility of the formation of active kinins from kininogens under the action of other blood proteolytic enzymes (trypsin, urokinase, thrombin, etc.) is retained [9-11].

On the basis of these considerations, we propose a new method for more rapid and complete depletion of the blood KKS: a simultaneous promotion of kinin formation and kinin destruction.

MATERIALS AND METHODS

Experiments were performed on 32 white outbred male rats weighing 230-260 g. The animals were divided into three groups and injected intravenously with varied doses of andecalin (5, 10 and 40 U/kg body weight). Intact animals served as controls. Blood was collected from the posterior vena cava under ether anesthesia. Prekallikrein and kallikrein levels [6], total kallikrein activity [7], total kininogen and kinin contents [5], and activity of kininases [1] were determined in the plasma.

RESULTS

Kinin formation can be activated by systemic injection of kallikrein, trypsin, and catecholamines and upon ischemia of any organ [2,4,9-11], which is generally followed by kinin destruction. The simultaneous activation of kinin formation and destruction has been observed after administration of andecalin [3,4]. Andecalin is a tissue kallikrein (purified extract of pig pancreas) which is contaminated by kininases. The activity of these kininases proved to be 1300-1500 μg bradykinin/ml plasma/min. Administration of andecalin in a dose of 5 U/kg induced an increase in the kallikrein activity and a decrease in the kininogen content (Table 1), i.e., it activated kinin formation. Kinin destruction was also activated. However, this did not lead to the depletion of blood KKS, since the bradykinin content was elevated. When andecalin was administered in a dose of 20 or 40 U/kg, activation of both kinin formation and destruction was observed. At the same time, there was no increase in the content of active kinins, which may be regarded as indicative of a depletion of blood KKS.

Department of Physiology, Siberian Medical University, Tomsk.. (Presented by M. A. Medvedev, Member of the Russian Academy of Medical Sciences)

0007-4888/93/0010-1189$12.50

TABLE 1. Levels and Activities of the Blood KKS Components 2 h after Intravenous Injection of Andecalin ($M \pm m$)

KKS component	Control (n=10)	Intravenous injection of andecalin, U/kg		
		5 (n=9)	20 (n=6)	40 (n=7)
Prekallikrein, U/liter	246.0±8.78	223.0±5.99	141.6±3.94*	95.4±8.84*
Kallikrein, U/liter	12.1±0.53	280.0±22.5*	320.0±51.5*	396.0±34.0*
Total kallikrein, μM/liter	0.37±0.03	0.62±0.07*	0.93±0.07*	1.89±0.08*
Kallikrein inhibitors, rel. units	1.10±0.04	1.02±0.05	0.82±0.12*	0.33±0.02*
Kininogen, μM/liter	3.73±0.10	2.60±0.07*	1.56±0.19*	0.99±0.11*
Kininases, μM/liter	82.28±4.80	115.2±9.60*	301.6±4.80*	472.2±16.2*
Bradykinin, nM/liter	3.90±0.30	6.38±0.30*	3.06±0.10	3.40±0.10

Note. Asterisk indicates values statistically different from the control at $p<0.05$. n = number of experiments

It is concluded that for the activation of kinin formation it is reasonable and physiologically advantageous to employ kallikrein in doses which increase its blood content 1.5- to 3-fold. Injection of kininase in doses which induce a 3- to 6-fold increase in its blood content is feasible for the activation of kinin destruction.

REFERENCES

1. P. Ya. Gaponyuk and E. M. Umarkhodzhaev, *Pat. Fiziol.*, **13**, № 5, 80-82 (1969).
2. V. I. Kiselev, A. A. Ryzhkov, and A. L. Panchenko, *Fiziol. Zh. SSSR*, **67**, № 4, 561-567 (1981).
3. V. I. Kiselev, *Mechanisms of Neuronal, Humoral, Hormonal, and Autoregulation of the Activity of the Blood Kallikrein-Kinin System*, Doctoral thesis, Moscow (1985).
4. A. L. Panchenko and V. I. Kiselev, *Byull. Eksp. Biol. Med.*, **98**, № 10, 469-471 (1984).
5. T. S. Paskhina, *Modern Methods in Biochemistry* [in Russian], Moscow (1968).
6. T. S. Paskhina and A. V. Krinskaya, *Vopr. Med. Khimii*, № 6, 660-663 (1974).
7. M. S. Surovikina, G. V. Maslova, and E. E. Fomina, *Byull. Eksp. Biol. Med.*, **95**, № 5, 106-109 (1983).
8. V. A. Treshutin, in: *Thrombus Formation and Pathology of Hemostasis* [in Russian], Tomsk (1982), pp. 70-73.
9. M. Buluk, M. Gzokalo, and M. Malofieew, *Thrombos. Diathes. Haemorrh. (Stuttg.)*, **24**, 548-558 (1970).
10. M. Rocha e Sieva, W. T. Beraldo, and G. Rosenfeld, *Amer. J. Physiol.*, **136**, 261-273 (1949).
11. W. Vogt and W. Wawretschek, *Naunyn-Schmeideberg's Arch. Exp. Path. Pharmak.*, **260**, 223-230 (1968).