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The role of kallikrein-kinin system in complex regional pain syndrome I (CRPS I) pathophysiologic mechanisms

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Inflammation, edema and local vascular permeability changes are essential features of the complex regional pain syndrome type I (CRPS I). The role of kallikrein-kinin system components as the major mediators in the development of these symptoms is poorly investigated.

The objective: **to investigate the role of kallikrein-kinin system in pathophysiologic mechanisms of CRPS I.**

Patients and methods**. We have investigated level of prekallikrein (PK), activity of fast-reacting (FRI) and time-dependent (TDI) inhibitors of plasma kallikrein, and blood plasma proteolytic activity (BPPA) in 45 patients with CRPS I and 15 healthy volunteers.**

Results**. Analysis of kininogenesis activity and sympathetic-adrenal system revealed their close interdependence. Our data corresponds well with the literature information about depressive effect of sympathetic nervous system on kininase activity. This leads to the accumulation of vasoactive peptides in the injures segment of the extremity. Decrease of neurogenic effects at the later stages of CRPS I leads to the fall of the basal kininogenesis level.**

Conclusion**. Local humoral factors such as the components of kallikrein-kinin system play an important role in CRPS I pathophysiologic mechanisms and are dependent on sympathetic-adrenal system activity.**

Key words: *complex regional pain syndrome, kallikrein-kinin system, sympathetic-adrenal system.*

Inflammation, edema and local vascular permeability changes are essential features of complex regional pain syndrome type I (CRPS I) [1–5]. Different pathophysiologic mechanisms were suggested and investigated. Nevertheless, the role of kallikrein-kinin system components as the major mediators in the development of these symptoms are still poorly explored. The peak of investigations of the kallikrein-kinin system fall within 1970–1990s. Not much has changed since that time.

There is the theory that bradykinin is the humoral factor that supports interrelations between regulation of blood vessels tone and rheological properties of blood. Its main role is the regulation of arterial vessels microvasculature and precapillary sphincters [6, 7]. Vessels permeability changes are mediated by kinins and their marked nociceptive effect are the important chain in the pathogenesis of different types of inflammation, edemas and vessel walls changes [8–14].

Kallikrein-kinin system activation is regarded now to have adaptive sanogenetic value. But failure of the regulatory mechanisms may lead to the non-controlled kininogenesis and subsequently to change the role of kinins from physiological adaptive to potentially pathological [14–15].

Thus we suggested that kallikrein-kinin system might play an important role in the pathogenesis of CRPS I.

The objective: to evaluate the role of kallikrein-kinin system in pathophysiologic mechanisms of CRPS I.

MATERIALS AND METHODS

We have investigated the function of kallikrein-kinin system in 45 patients with CRPS I. We divided them into two groups accordingly to the duration of the disease. The 1st group consisted of 21 patients with the early stages of the disease (6-8 weeks after the trauma). The 2nd group included 24 patients with the longer duration of CRPS I (9–14 weeks after the trauma). We also carried out investigations during the treatment process on the 21st and 45th days of treatment. The control group consisted of the 15 healthy volunteers.

There are no ideal diagnostic criteria of CRPS I at present. A number of patients that meet some criteria of CRPS I, don't meet other criteria [16]. We used Breuhl's criteria because of their greater sensitivity [17–19]. Not so great specificity is balanced out by exclusion of other diagnoses that could cause similar symptoms with help of instrumental and laboratory methods of investigation.

Regional kallikrein-kinin system activity was estimated using the level of prekallikrein (PK), activity of fast-reacting (FRI) and time-dependent (TDI) inhibitors of plasma kallikrein, and blood plasma proteolytic activity (BPPA). We investigated blood outflowing from the distal regions of the extremities (from the extremity with CRPS I symptoms and from the healthy contralateral extremity).

RESULTS AND DISCUSSION

We noticed significant decrease of PK (43,2±9,6), decrease of activity of FRI and TDI (FRI=7,91±1,54, TDI=0,68±0,28), and increase of BPPA (75,31±3,87) in CRPS I at the early stages of the disease. Contralateral extremity rates of PK were 169,59±4,7 ($p<0,01$). We also noted the decrease of FRI and TDI activity (FRI=21,58±1,6; TDI=1,7±0,2), and increase of BPPA (53,3±5,2). Contralateral healthy extremity figures were just a little bit changed than these in the control group subjects (Table 1). This fact may point to the overall activation of sympathicoadrenal and cellular structures synthetizing Fletcher factor (prekallikrein). The paradoxal decrease of prekallikrein and inhibitors of plasma kallikrein in the blood outflowing from the distal regions of the CRPS I extremities may be treated as kallikrein production increase or as the condition of its level maintenance.

Intensive kallikrein synthesis decreases prekallikrein deposits. Low activity of inhibitors develops due to their consumption and participation in blood coagulation and fibrinolytic system. It promotes the high level of kallikrein maintenance in the pathologic focus. This complex of disturbances together with the decrease of kininase activity leads to the excess accumulation of kinins in the pathologic focus.

As it is shown in table 2, treatment of the patients from 1st group (local non-steroidal anti-inflammatory remedies, electroneurostimulation, antidepressants, anticonvulsants) had resulted in significant increase of the studied variables on the 21st day, which had correlated to the clinical symptoms in the damaged zone – decrease of pain and edema and increase of motion range. On the 45th day of the treatment physiologic activity of kallikrein-kinin system returned to its normal level in those patients.

Table 1

Indices of kallikrein-kinin system activity [arginine μmol / min / L]

Components of kallikrein-kinin system		Blood plasma proteolytic activity (BPPA)	Prekallikrein (PK)	Fast-reacting inhibitors of plasma kallikrein (FRI)	Time-dependent inhibitors of plasma kallikrein (TDI)
Groups	Statistical key figures				
Control	M	42,50	126,50	13,90	1,60
	m	5,30	5,90	1,90	0,10
	n	15	15	15	15
Group I	M	75,31	43,20	7,91	0,68
	m	3,87	9,60	1,54	0,28
	n	12	12	10	11
	P1	<0,001	<0,001	>0,5	<0,01
	P2	>0,5	<0,01	<0,001	<0,01
Group II	M	53,30	169,59	21,58	1,70
	m	5,20	4,70	1,60	0,20
	n	12	12	12	10
	P3	<0,01	< 0,001	<0,001	<0,001

P_1 – statistical difference between control and group I; P_2 – statistical difference between group I and II; P_3 – statistical difference between control and group II.

Patients of 2nd group were studied in 2,5 and 3,5 months after the beginning of treatment and demonstrated significant increase in prekallikrein level (169,59±4,7), FRI (21,58±1,6) and TDI (1,7±0,2) inhibitors of plasma kallikrein activity in contrast to the 1st group patients. These parameters were increased even in comparison with the control group (Table 1). Disease pattern in these patients was characterized by the minor edema of the distal segment of the injured extremity, the skin turgor decrease, moderate intensity pain (VAS score 1–2), together with the ROM decrease.

The data from the 2nd group patients had shown the accumulation of the components of kallikrein-kinin system in the injured region which may be related to their metabolism and/or kininase activity decrease.

Analysis of kininogenesis activity changes and sympathetic-adrenal system state revealed their close interdependence. Thus marked increase in kallikrein-kinin system activity on the early stage of the disease developed on the background of norepinephrine increase. This fact points to the enhancement of neurogenic adrenergic effects. We also noted the accumulation of precursors of kallikrein and its inhibitors activity increase in the injured region on late stages of CRPS I. These changes come along with the decrease of epinephrine and norepinephrine release concurrently. This interdependence represents adrenergic effects depression.

Our data corresponds with the other investigators information about depressive effect of sympathetic nervous system on kininase activity. This leads to the accumulation of vasoactive peptides in the injures segment of the extremity. Decrease of neurogenic effects at the later stages of CRPS I leads to the fall of the basal kininogenesis level.

CONCLUSION

Local humoral factors such as the components of kallikrein-kinin system play an important role in CRPS I pathophysiologic mechanisms and are dependent on sympathetic-adrenal system activity.

Table 2

Indices of kallikrein-kinin system activity in CRPS I patients during treatment [arginine μmol / min / L]

Components of kallikrein-kinin system		Blood plasma proteolytic activity (BPPA)	Prekallikrein (PK)	Fast-reacting inhibitors of plasma kallikrein (FRI)	Time-dependent inhibitors of plasma kallikrein (TDI)
Groups	Statistical key figures				
Initial indices	M	75,31	43,20	7,91	0,68
	m	3,87	9,60	1,54	0,28
	n	12	12	10	11
21st day	M	23,50	164,70	17,09	1,31
	m	6,70	2,20	1,82	0,25
	n	18	18	12	12
	P1	<0,001	<0,001	<0,001	<0,05
	P2	<0,001	<0,001	<0,001	<0,001
45th day	M	49,02	138,40	13,48	1,79
	m	4,70	13,35	2,54	0,34
	n	12	15	15	15
	P3	<0,001	<0,001	>0,2	>0,1

P_1 – statistical difference between initial indices and 21st day of monitoring; P_2 – statistical difference between initial indices and 45th day of monitoring; P_3 – statistical difference between 21st and 45th days of monitoring.

Роль калликреин-кининовой системы в патогенезе комплексного регионарного болевого синдрома (КРБС I)

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Воспаление, отек и изменения локальной сосудистой проницаемости – основополагающие черты комплексного регионарного болевого синдрома (КРБС I). Роль компонентов калликреин-кининовой системы как основных медиаторов в развитии этих процессов изучена недостаточно.

Цель исследования: изучение роли калликреин-кининовой системы в патофизиологических механизмах формирования КРБС I.

Материалы и методы. Исследован уровень прекалликреина (ПК), активность быстореагирующего ингибитора (БРИ) и медленно-реагирующего ингибитора (МРИ) плазменного калликреина, а также протеолитическая активность плазмы (ПАП) у 45 пациентов с КРБС I и 15 здоровых добровольцев.

Результаты. Анализ активности кининогенеза и симпато-адреналовой системы выявил их тесную взаимосвязь. Полученные нами результаты подтверждают литературные данные о подавляющем влиянии симпатической нервной системы на кининазную активность, что приводит к накоплению вазоактивных пептидов в поврежденном сегменте конечности. Снижение нейрогенного влияния на более поздних стадиях КРБС I приводит к падению базального уровня выделения кининов.

Заключение. Местные гуморальные факторы, такие как компоненты калликреин-кининовой системы играют важную роль в патогенезе КРБС I и зависят от активности симпато-адреналовой системы.

Ключевые слова: *комплексный регионарный болевой синдром, калликреин-кининовая система, симпато-адреналовая система.*

Роль каллікреїн-кінінової системи у патогенезі комплексного реґіонарного больового синдрому (КРБС I)

О. Бур'янов, Л. Хіміон, В. Котюк

Запалення, набряк та зміни локальної проникності судин – основні ризики комплексного регіонарного больового синдрому (КРБС I). роль компонентів каллікреїн-кінінової системи як основних медіаторів розвитку цих процесів вивчена недостатньо.

Мета дослідження: вивчення ролі каллікреїн-кінінової системи у патофізіологічних механізмах формування КРБС I.

Матеріали та методи. Досліджено рівень прекалліkреїна (ПК), активність швидко реагуючого інгібітора (ШРІ) та повільно реагуючого інгібітора (ПРІ) плазмового каллікреїну, а також протеолітична активність плазми (ПАП) у 45 пацієнтів із КРБС I і 15 здорових добровольців.

Результати. Аналіз активності кініногенезу і симпато-адреналової системи виявив їхній тісний взаємозв'язок. Одержані результати тісно кореспондують із даними літератури про пригнічення симпатичною нервовою системою кініназної активності, що призводить до накопичення вазоактивних пептидів в ушкодженому сегменті кінцівки. Зниження нейрогенного впливу на більш пізніх стадіях КРБС I приводить до падіння базального рівня кінінів.

Заключення. Місцеві гуморальні фактори, такі, як компоненти каллікреїн-кінінової системи відіграють важливу роль у патогенезі КРБС I та залежать від активності симпатоадреналової системи.

Ключові слова: *комплексний регіонарний больовий синдром, калікреїн-кінінова система, симпато-адреналова система.*

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REFERENCES

1. Sandroni P. Factor III: Sudomotor Changes and Edema – Pathophysiology and Measurement / P. Sandroni, P.R. Wilson // КРБС: Current Diagnosis and Therapy. Progress in Pain Research and Management. Vol. 32, Edited by P. Wilson, M. Stanton-Hicks, R.N. Harden–Seattle: IASP Press, 2005. – P. 59–79.

2. Evidence for local inflammation in complex regional pain syndrome type 1 / F.J.P.M. Huygen, A.G.J. de Bruijn, M.T. de Bruin et al. // Mediators of Inflammation. – 2002. – V. 11, № 1. – P. 47–51.

3. Differential expression patterns of cytokines in complex regional pain syndrome / N. Üçeyler, T. Eberle, R. Rolke et al. // Pain. – 2007. – V. 132, № 1–2. – P. 195–205.

4. Regulation of peripheral blood flow in Complex Regional Pain Syndrome: clinical implication for symptomatic relief and pain management / G. Groeneweg, F.J.P.M. Huygen, T.J. Coderre, F.J. Zijlstra // BMC Musculoskeletal Disorders. – 2009. – V. 10:116. doi:10.1186/1471-2474-10-116.

5. Endothelial dysfunction in cold type complex regional pain syndrome / Schattschneider J., Hartung K., Stengel M. et al. // Neurology. – 2006. – V. 67, № 4. – P. 673–675.

6. Local regulation of vascular tone by bradykinin and angiotensin converting enzyme inhibitors / Auch-Schwelk W., Kuchenbuch C., Claus M. et al. // Eur Heart J. – 1993. – Suppl I. – P. 154–60.

7. Дзизинский А.А. Кинины в физиологии и патологии сердечно-сосудистой системы / Дзизинский А.А., Гомазков О.А. // Новосибирск. – 1976. – 207 с.

8. Acute NADPH oxidase activation potentiates cerebrovascular permeability response to bradykinin in ischemia–reperfusion / Abigail Woodfin, De-En Hu, Mosharraf Sarker, Tsuyoshi Kurokawa, and Paul Fraser // Free Radic Biol Med. – 2011. – V. 50, № 4. – P. 518–524.

9. Histamine and interstitial pulmonary edema in the dog / Pietra G.G., Szidon J.P., Leventhal M.M., Fishman A.P. // Circ Res. – 1971. – V. 29, № 4. – P. 323–337.

10. Bradykinin derivatives as permeability factors / Reis M.L., Okino L. & Rocha e Silva M. // Agents and Actions. – 1973. – V. 3, Issue 5. – P. 383–383.

11. Involvement of bradykinin in endotoxin-induced vascular permeability increase in the skin of rats / Ueno A., Tokumasu T., Naraba H., Oh-ishi S. // Eur J Pharmacol. – 1995. – V. 284, № 1–2. – P. 211–214.

12. Rothschild A.M. Contribution of vasopressor and plasma kininogen changes towards acute adrenaline pulmonary edema in the rat / Rothschild A.M., Castania A. // Naunyn Schmiedebergs Arch Pharmacol. – 1976. – V. 295, № 2. – P. 177– 181.

13. Суровикина М.С. Кининовая система плазмы крови при воспалительных и аллергических процессах (экспериментально-клиническое исследование). – Автореф. дис. ... д-ра мед. наук. – М., 1975.

14. Киселев В.И. Методические аспекты оценки состояния калликреин-кининовой системы крови. (Обзор литературы) / В.И. Киселев, В.П. Куликов // Лаб. дело. – 1988. – № 7. – С. 27-–2.

15. Bulletin of Experimental Biology and Medicipe. – 1997. – V. 123, № 1. – P. 96–99. 1997 Experimental methods for clinical practice. Colorimetric Determination of Three Forms of Plasma Kallikrein and Its Adsorption on Kaolin M.S. Surovikina, M.V. Stamm, and V.V. Surovikin.

16. Complex regional pain syndrome (type 1). A comparison of two diagnostic criteria methods / McBride A., Barnett A.J., Livingstone J.A., Atkins R.M. // Journal of Bone and Joint Surgery, British Volume. – 2006. – V. 88-B, supp I. – P. 178.

17. Proposed New Diagnostic Criteria for Complex Regional Pain Syndrome / Harden R.N., Bruehl S., Stanton-Hicks M., Wilson P.R. // Pain Medicine. – 2007. – V. 8, № 4. – P. 326–331.

18. Validation of proposed diagnostic criteria (the «Budapest Criteria») for Complex Regional Pain Syndrome / Harden R.N., Bruehl S., Perez R.S, et al. // Pain. – 2010. – V. 150, № 2. – P. 268–274.

19. Incidence of complex regional pain syndrome type I after fractures of the distal radius / Dijkstra P.U., Groothoff J.W., ten Duis H.J., Geertzen J.H. // European Journal of Pain. – 2003. – V. 7, № 5. – P. 457–462.

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