PHYSIOLOGY

Effect of Tissue Phospholipid Composition on Synergistic Interactions between Sympathetic and Parasympathetic Systems

A. E. Lychkova and V. M. Smirnov

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 133, No. 4, pp. 364-366, April, 2002
Original article submitted October 23, 2001

The content of phospholipids in various tissues was studied during synergistic interaction between two branches of the autonomic nervous system. We found higher myocardial content of choline-containing phospholipids and lower rigidity of erythrocyte membranes in rabbits with pronounced sympathetic potentiation of the cardioinhibitory effect of the vagus nerve compared to rabbits without such potentiation.

Key Words: *heart*; *control*; *sympathetic and parasympathetic nervous system*; *phospholipids*

There is a concept that disturbed functional antagonism between sympathetic and parasympathetic regulation promotes damage to the myocardium [9,12,13]. Pathogenesis of reversible and irreversible myocardial injuries probably includes changes in the phospholipid metabolism and permeability of cardiomyocyte membranes [8,11].

It is commonly accepted that the effects of sympathetic and parasympathetic nerves on the viscera are opposite (they are usually called antagonistic, which is not correct, on our opinion). Opposite effects of the vagus and sympathetic nerves improve adaptive responses of internal organs. However, simultaneous stimulation of the vagus and sympathetic nerves under experimental conditions sometimes leads to their synergistic interaction. On our opinion, this synergism is mediated via preganglionic serotonergic nervous fibers going along the sympathetic trunk and making synapses on serotonergic intramural neurons [6].

In the early period after vagotomy (2-7 days), the content of lysophospholipids lysophosphatidylcholine (LPC) and lysophosphatidylethanolamine increased and returned to normal on day 20 after vagotomy. Sympathectomy induced opposite changes: the content of phosphatidylcholine (PC) and phosphatidylethanolamine increased, while the content of lysophospholipids decreased [2].

We hypothesized that sympathetic potentiation of the vagal inhibitory effect on the heart could be related to specific changes in phospholipid metabolism. Here we studied phospholipid composition of various tissues in animals with and without synergistic interactions not between the sympathetic and parasympathetic systems in the regulation of cardiac function.

MATERIALS AND METHODS

The experiments were performed on 15 rabbits weighing 2-5 kg. Potentiation of the vagal cardioinhibitory effect during simultaneous stimulation of the vagus and sympathetic nerves was found in 10 rabbits. These rabbits were divided into two groups according to their body weights. In group 1 rabbits (<3 kg) the effect appeared after administration of β-adrenoceptor blockers, while in group 2 rabbits (>3 kg) the sympathetic potentiation manifested without such pretreatment (group 2 rabbits were ~6 months older).

Department of Normal Physiology Russian State Medical University, Moscow

0007-4888/02/1334-0311$27.00

The third group consisted of 5 rabbits aged as group 1 animals and exhibiting no potentiation phenomenon even after β-adrenoceptor blockade.

Phospholipids were extracted from homogenates of the vagus nerve, stellate ganglion, liver, apex myocardium, plasma, and erythrocytes by the method of Folch and analyzed by thin-layer chromatography [6]. The blood was collected before testing of the autonomic responses. Erythrocytes were used for evaluation of differences in the composition of membrane phospholipids in rabbits with and without potentiation phenomenon. The data on membrane structure were obtained on whole erythrocytes but not their ghosts and should be considered as preliminary.

RESULTS

The content of phospholipids in rabbit erythrocyte membranes in group 1 rabbits 133% surpassed that in group 3 ($p<0.05$). The lowest phospholipid-to-cholesterol ratio was found in group 3 rabbits (0.5 *vs.* 2.5 and 1.5 in groups 1 and 2, respectively), which attested to high rigidity of erythrocyte membranes in animals without sympathetic potentiation of the vagal cardioinhibitory effect.

The highest levels of phospholipids in the vagus nerve homogenates were observed in group 1.

The relative content of phospholipids in the myocardium in group 1 was by 141% higher than in group 3. The opposite tendency was found in the stellate ganglion: the relative content of phospholipids in groups 2 (2.67±0.27) and 3 (3.75±0.35) were higher (by 234.4% and 136.6%, respectively) than in group 1 (1.6±0.3).

The concentration of glycerophosphate in the stellate ganglion was maximum in group 2 (52.3±2.7 mg/100 g tissue) and minimum (5.7±0.2 mg/100 g tissue) in group 1.

Thus, phospholipid degradation in the stellate ganglion in group 2 was more intensive than in group 1.

The content of sphingomyelin in the stellate ganglion was similar in all groups of rabbits, while in the vagus nerve it was by 18.8 and 30.7% higher in group 3 than in group 1 and 2, respectively ($p<0.05$). The content of sphingomyelin in the myocardium in group 3 was 7.8- and 1.7-fold higher than in groups 1 and 2, respectively. This agrees with published data on the important role of sphingomyelin cycle in the regulation of voltage-dependent channels. In particular, sphingosyl phosphocholine does not block calcium channels, but affects intracellular calcium depot [1].

Plasma content of sphingomyelin was similar in all groups. The content of sphingomyelin in erythrocyte membranes in group 2 rabbits surpassed that in groups 1 and 3 (by 50 and 33.4%, respectively). The high content of sphingomyelin in group 2 was associated with low functional activity of the sympathetic system.

The content of phosphatidylethanolamine in liver homogenates was maximum in group 1 (39.8±3.5 *vs.* 1.9±3.5 and 5.3±0.4 mg/100 g in groups 2 and 3, respectively).

The animals exhibiting the potentiation phenomenon were more mature. This is confirmed by increased contents of phosphatidylethanolamine in the stellate ganglion (22.3±10.5 mg/100 g) and vagus nerve (27.3±2.8 mg/100 g) in group 2 rabbits compared with group 3 animals (14.0±3.0 and 17.7±3.4 mg/100 g, respectively). Increased concentration of choline-containing phospholipids (CCP) in the stellate ganglion homogenates attests to their possible involvement in transmitter metabolism and modulation of β-adrenoceptor activity in the myocardium [8].

In all tissues except erythrocytes, PC content in groups 1 and 2 was higher than in group 3.

In group 1, the transported PC pool and the content of PC in the stellate ganglion (playing the major role in the potentiation phenomenon) were increased.

It was of special interest to measure the contents of lysophosphatidylcholine (LPC), the modulator of presynaptic membrane conductivity and choline metabolism [3], and the total content of CCP. Catecholamines play the major role in PC synthesis [5] and determine high level of sympathetic activity in groups 1 and 3.

In group 2, the contents of LPC in the liver, plasma, and erythrocytes were increased by 31.5, 71.3, and 95.3%, compared with group 1, respectively.

The PC/LPC ratio in erythrocyte membranes reflecting the rate of PC synthesis from lyso PC [4] was higher of group 3 rabbits compared to groups 1 and 2 (6.3±1.2 *vs.* 1.5±0.5 and 3.0±0.8, respectively).

In group 1, the content of CCP in the stellate ganglion was higher than in group 3. CCP concentration in the vagus nerve, myocardium, and erythrocytes differed insignificantly.

In group 1 and 2 rabbits plasma contents of CCP were increased. This attests to intensive function of the phospholipid transporting system and increased concentrations of acetylcholine precursors in the blood of animals exhibiting pronounced potentiation phenomenon.

The increased content of CCP and high PC/LPC ratio in the liver of rabbits exhibiting pronounced potentiation phenomenon (groups 1 and 2), suggest enhanced synthesis and reduced degradation of CCP in the liver of these animals compared to group 3 rabbits.

In group 1, the total content of CCP in homogenates of the stellate ganglion (including preganglionic serotonergic fibers passing through it) and in the

plasma was higher than in group 3. Acetylcholine synthesized from choline released during CCP degradation can also contribute to potentiation of the vagal inhibitory effect. This agrees with published data [7].

Replacement of 2.3% cell phospholipids with LPC considerably changed electrophysiological properties of Purkinje fibers [10]. In group 2 rabbits, the relatively high myocardial content of LPC was associated with maximum instability of cardiac function at the peak of the potentiation effect. Thus, high levels of CCP in rabbits exhibiting pronounced sympathetic potentiation of the vagal cardioinhibitory effect confirms the important role of CCP in the mechanisms of this phenomenon.

The plasma content of CCP in group 1 and 2 rabbits was increased and the content of sphingomyelins also tended to increase, which indicated activation of CCP transport in rabbits exhibiting pronounced potentiation effect.

Thus, the animals with pronounced sympathetic potentiation of the vagal cardioinhibitory effect (group 2) are the most mature in biochemical respect. This biochemical maturity is probably responsible for relatively low activity of the sympathetic system, higher membrane permeability for transmitters in nerve endings, and most pronounced potentiation phenomenon.

REFERENCES

1. O. M. Vekshina, *Biol. Membrany*, **17**, No. 4, 341-367 (2000).
2. I. P. Gereliuk, *Pat. Fiziol.*, No. 3, 32-35 (1981).
3. I. K. Kolomiitseva, N. I. Potekhina, and T. P. Semenova, *Byull. Eksp. Biol. Med.*, **129**, No. 6, 629-632 (2000).
4. T. P. Kulagina, I. K. Kolomiitseva, and V. I. Arkhipov, *Ibid.*, **130**, No. 9, 292-294 (2000).
5. N. Yu. Novoselova, A. N. Moskvin, P. A. Torkunov, *et al.*, *Ibid.*, **128**, No. 9, 261-263 (1999).
6. E. Shtal', *Thin Layer Chromotography* [in Russian], Moscow 1969.
7. C. Aussel, C. Pelassy, and B. Rossi, *J. Lipid, Mediat.*, **2,** No. 2, 103-116.
8. V. E. Benediktsdottir, J. Curvers, and S. Gudbjarnason, *J. Mol. Cell Cardiol.*, **31**, No. 5, 1105-1115 (1999).
9. J. Fotheringham, F. Y. Xu, M. Nemer, *et al.*, *Biochim. Biophys. Acta,* **1485**, No. 1, 1-10 (2000).
10. R. W. Gross, P. B. Carr, B. J. Lee, *et al.*, *Curc. Res.*, **51**, No. 1, 27-36 (1982).
11. S. Gudbjarnason and V. E. Benediktsdottir, *Mol. Cell Biochem.*, **163-164**, 137-143 (1996).
12. O. Novakova, J. Drnkova, V. Kubista, and F. Novak, *Physiol. Res.*, **43**, No. 3, 151-156 (1994).
13. V. V. Panagia, Y. Taira, G. L. Bryson, *et al., J. Cardiovasc. Pharmacol. Ther.*, No. 3, 239-246 (1998).