Are Diabetic and Age-Related Angiopathies Based on Chronic Serotonin Insufficiency?

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 123, No. 1, pp. 103-110, January, 1997
Original article submitted October 25, 1996

The role of exo- and endogenous serotonin antagonists in the onset and maintenance of chronic serotonin insufficiency is demonstrated. Experimental and clinical administration of serotonin reduces tissue hypoxia in patients with diabetic and/or age-related angiopathy. It is demonstrated that chronic serotonin insufficiency plays a key role in the genesis of diabetic and age-related angiopathies.

Key Words: *serotonin; serotonin receptors; free hemoglobin; serotonin antagonists; diabetic and age-related angiopathies; acute and chronic serotonin insufficiency*

Considerable scientific effort has been focused on biological problems of aging. The understanding of the mechanisms of aging is necessary for the development of effective measures aimed at prolongation of active life. It is known that physiological aging is a slow process, while premature aging is often related to disease(s). Although there are different concepts of aging (more than 200 have been proposed during the last two decades [5,6,13,15]), it has been generally recognized that aging is a "by-product" of biological processes occurring in the organism. It should be noted that there is no universal theory explaining the mechanism of aging.

Aging is accompanied by cardiovascular, central nervous system, and other dysfunctions. The cardiovascular system is vital for maintaining homeostasis. It delivers nutrients and oxygen to tissue and removes waste products. Age-related angiopathy impairs oxygen transport, which leads to tissue hypoxia, dystrophy, and necrosis and results in mono- and polyorganic insufficiency and death. Therefore, we believe that special attention should be paid to the aging of blood vessels. It is known that in "aged" blood vessels the intima is more dense, the media is atrophied, and the vascular elasticity decreases. As a result, the ability of microvessels to dilate and contact rhythmically declines. This ability is determined by the automatism of smooth muscle fibers and is termed endogenous vasomotorics, vasomotion, myogenic regulation of microvessels, etc. [4, 10,16,20].

Aging of blood vessels is accompanied by degradation of their receptors, including the serotonin receptors (SR). Serotonin and SR play an important role in the maintenance of homeostasis. For instance, smooth muscle and platelet SR interact with ferroproteins (myoglobin and hemoglobin). Based on the new information about serotonin and its receptors [8-12], we decided to reconsider their role in some biological processes.

The present study is an attempt to evaluate the significance of serotonin and its antagonists in the genesis of diabetic and age-related angiopathies.

MATERIALS AND METHODS

Experiments with isolated segments of rabbit and guinea pig intestine showed that serotonin antagonists (papaverine, Novocain, dimedrol, Promedol, gentamycin, etc.) affect the serotonin—SR binding, inducing acute serotonin insufficiency which impairs automatism and contractility of smooth muscles. Exogenous serotonin restored

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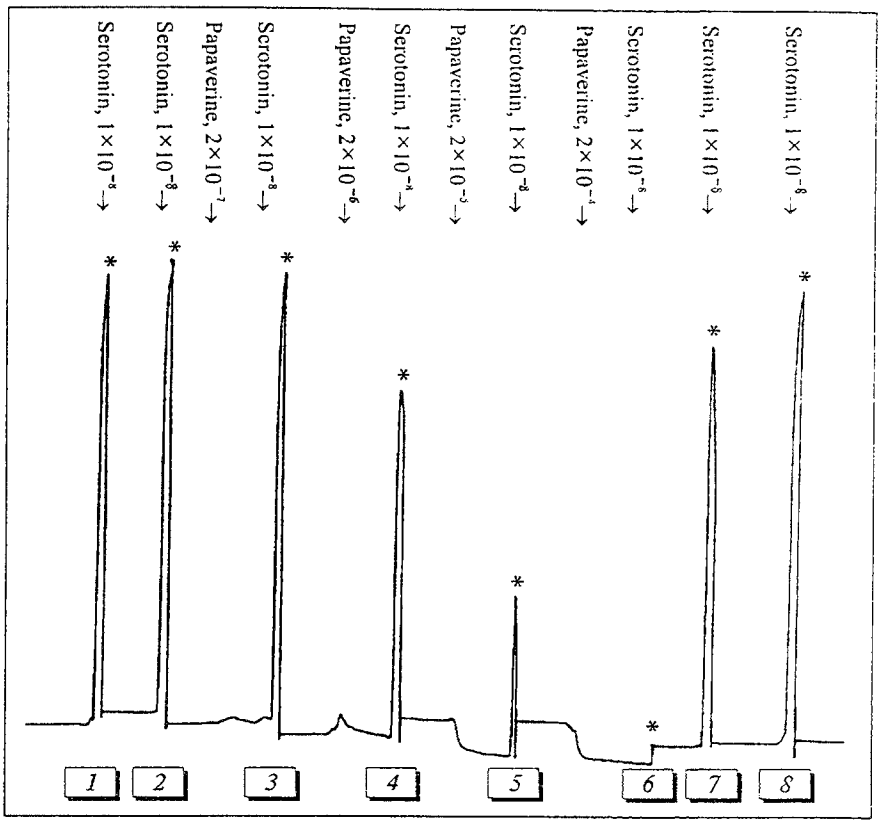

Fig. 1. Serotonin-induced decrease in the amplitude of contractions of a guinea pig ileum segment caused by the addition of increased concentrations of papaverine to the incubation medium. *1*) baseline level of contractions (serotonin concentration 10^{-8} g/ml); *2*) contractions in response to the same concentration of serotonin after washing (control); *3-6*) decreased amplitude of contractions in response to 10^{-8} g/ml serotonin after the addition of increasing concentrations of papaverine; *7*, *8*) restoration of the amplitude of contractions to baseline level after the addition of 10^{-8} g/ml serotonin. Incubation with papaverine 3 min, addition of serotonin after 7 min. Asterisk indicates washing.

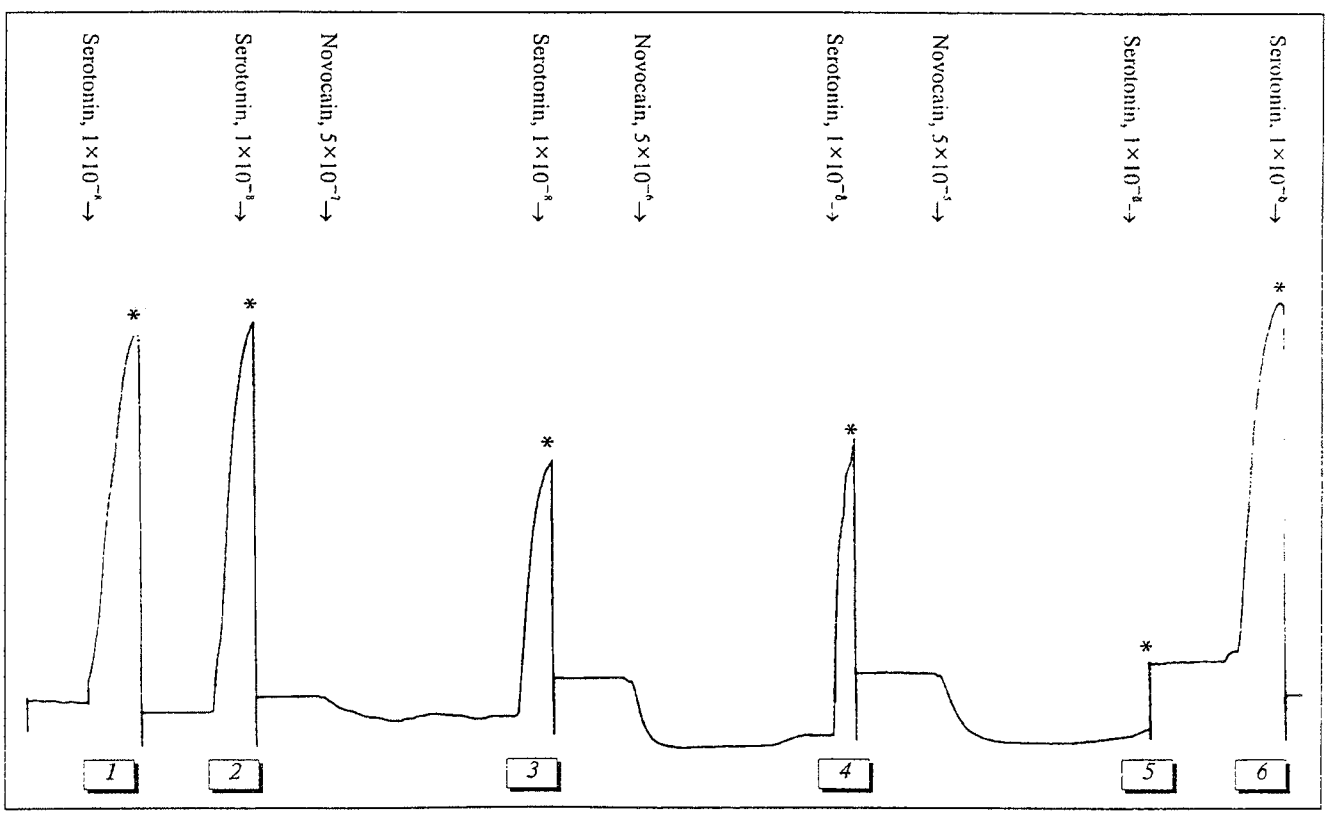

Fig. 2. Serotonin-induced decrease in the amplitude of contractions of a guinea pig ileum segment caused by the addition of increased concentrations of Novocain to the incubation medium. *1*) baseline contractions (serotonin concentration 10^{-8} g/ml); *2*) contractions in response to the same concentration of serotonin after washing (control); *3-5*) decreased amplitude of contractions in response to 10^{-8} g/ml serotonin after the addition of increasing concentrations of Novocain; *6*) restoration of the amplitude of contractions to baseline level after the addition of 10^{-8} g/ml serotonin. Incubation with Novocain 3 min, addition of serotonin after 7 min. Asterisk indicates washing.

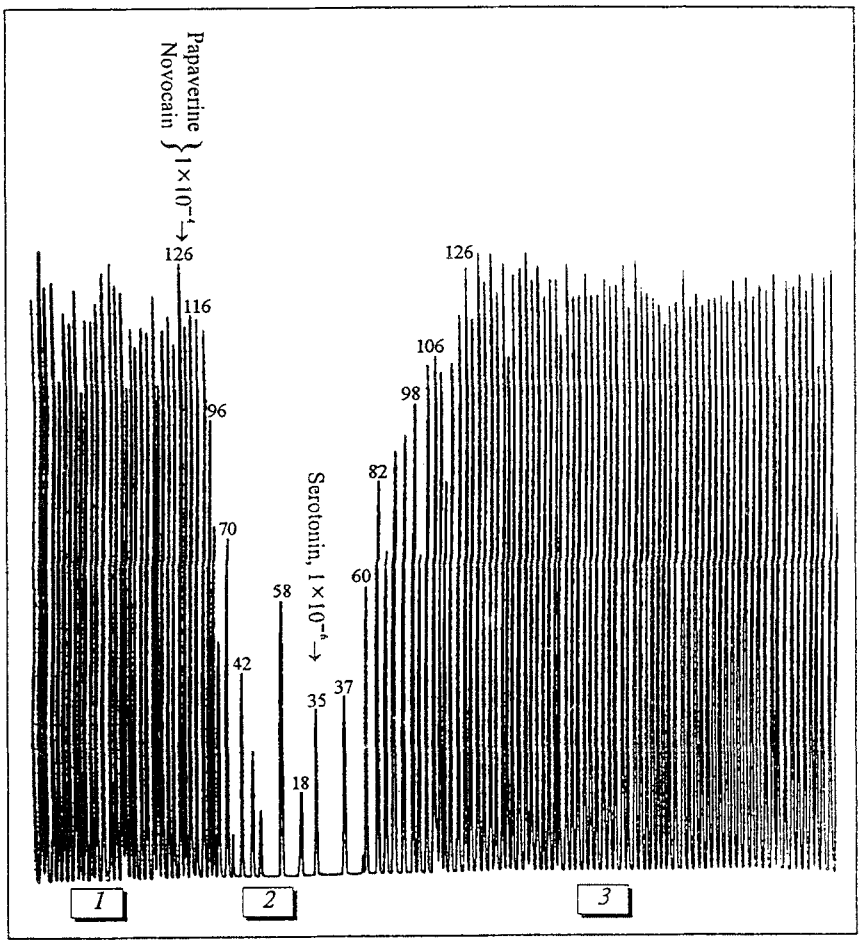

Fig. 3. Inhibition of contractile activity of a rabbit ileum segment by papaverine and Novocain and its restoration with serotonin. *1*) normal automatism and contractile activity; 2) partial inhibition of contractile activity by papaverine and Novocain and preserved automatism; *3*) restoration of contractile activity after the addition of serotonin.

automatism and contractility of intestinal smooth muscles (Figs. 1-4).

In clinical practice, acute serotonin insufficiency is observed in intoxication with psychotropic preparations and other serotonin antagonists (drugs, toxins, etc.). Administration of serotonin eliminates the symptoms of acute serotonin insufficiency (disturbance of consciousness, intestinal obstruction, and/or vascular insufficiency).

Some endogenous substances act as serotonin antagonists. High concentrations of hemoglobin inhibit serotonin-induced contractions of guinea pig intestinal segments. The addition of a 10-fold higher dose of serotonin increases the amplitude of contractions, i.e., partially restores smooth muscle contractility. An erythrocyte normally lives for 100-130 days, about 1% of erythrocytes is destroyed every day, and certain amount of hemoglobin circulates in the bloodstream [3,18,20]. Normal plasma free hemoglobin contents varies from 10 to 40 mg/liter [1,3, 5,14]. The haptoglobin system prevents elevation of free hemoglobin in the blood and its interaction with SR, thus providing normal functioning of vascular smooth muscle cells.

In a living organism, circulating free hemoglobin gradually induces changes in SR similar to those observed in acute experiments. It was demonstrated that the binding of serotonin antagonists to SR is reversible (Figs. 1-5): the antagonist—SR complex dissociates after washing and addition of free serotonin. However, the interactions between SR and hemoglobin in the organism create conditions for pathological changes in the entire circulation system. Blood serotonin concentration normally ranges from 20 to 200 μg/liter and does not increase with age [8,10], presumably, as a result of degradation of vascular SR caused by free Hb and dystrophic changes in surrounding tissues.

Serotonin is produced by enterochromaffin cells of the alimentary canal. Changes in the blood vessels supplying the alimentary canal lead to tissue hypoxia and decrease serotonin production. Serotonin from enterochromaffin cells is adsorbed by platelets. In the microcirculatory vascular bed, serotonin is released

from platelets and interacts with smooth muscle SR, inducing periodical dilation-constriction waves necessary for normal tissue metabolism and homeostasis [10].

It can be hypothesized that circulating serotonin antagonists (free hemoglobin and some metabolites) affect normal interactions between serotonin and SR, leading to irreversible changes in SR. Degradation of these receptors alters functional and morphological properties of the microvessel smooth muscles. To certain age the amount of circulating serotonin is sufficient for the maintenance of normal endogenous vasomotorics; however, with age greater amounts of serotonin are necessary due to chronic serotonin insufficiency, which is accompanied by impaired automatism and contractility of vascular smooth muscles and decreased elasticity of blood vessels leading to endogenous microcirculatory disorders, hypoxia, dystrophy, and tissue necrosis which manifest themselves as functional and morphological alterations in blood vessels and dystrophy of the organs supplied by them. These processes develop gradually as a result of physiological aging and are accelerated in some diseases, when more potent serotonin antagonists (pathological metabolites) appear in the bloodstream.

This hypothesis is supported by results obtained during the treatment of patients with diabetes mellitus. Diabetic patients develop angiopathy similar to

TABLE 1. Changes in Transcutaneous Po_2 During Administration of Serotonin Adipinate to Patients with Diabetic Angiopathy

Age, years	Po_2, mm Hg	
	baseline	serotonin infusion, 5-10 mg/h*
28	46	61
39	43	57
40	25	34
43	35	52
43	33	43
46	47	52
48	14	31
54	18	30
54	16	27
55	12	21
56	27	37
57	28	42
58	22	40
58	34	47
59	18	28
60	38	48
61	26	32
62	31	44
64	21	30
68	28	51
68	23	37
69	19	36
71	17	34
75	21	38
76	12	23
80	12	26

Note. *$p<0.05$ compared with baseline value.

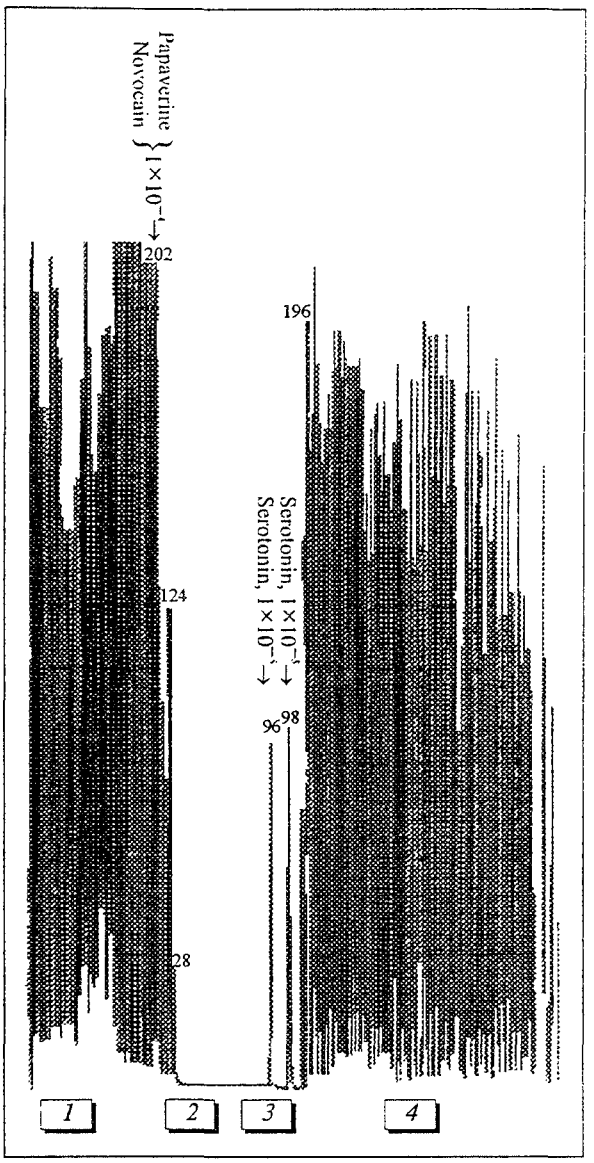

Fig. 4. Inhibition of automatism and contractile activity of a rabbit ileum segment by papaverine and Novocain and its restoration with serotonin. *1*) normal automatism and contractile activity; *2*) complete inhibition of contractile activity by papaverine and preserved automatism; *3*) complete restoration of contractile activity and partial restoration of automatism after the addition of serotonin: *4*) restoration of automatism and contractile activity after a second addition of serotonin.

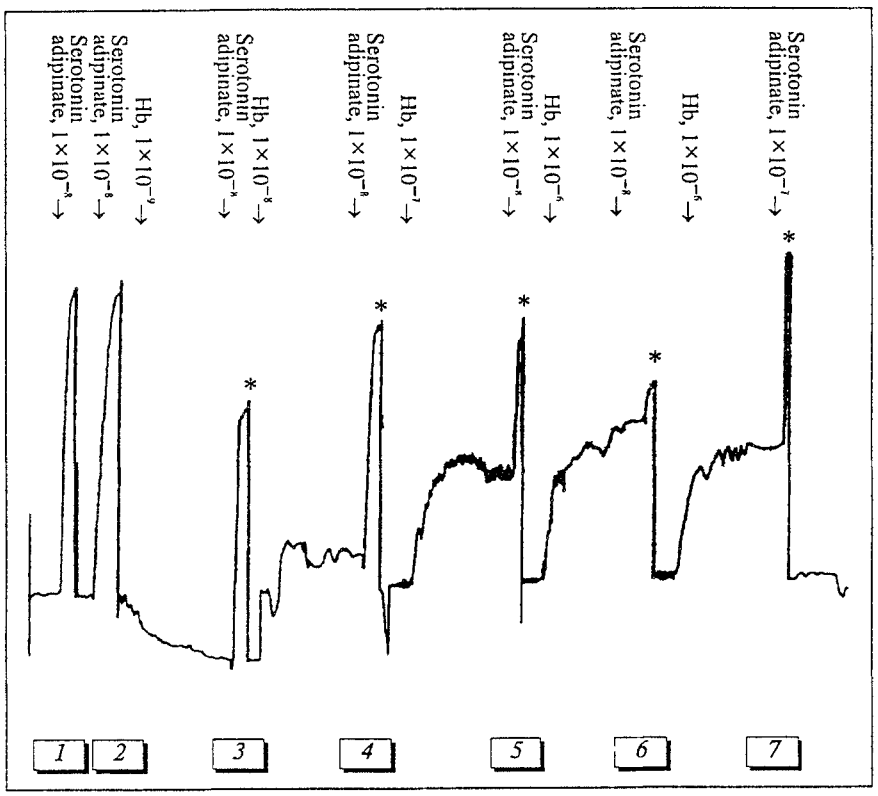

Fig. 5. Serotonin-induced changes in the amplitude of contractions of a guinea pig ileum segment caused by the addition of increased concentrations of hemoglobin (Hb) to the incubation medium. *1*) baseline contractions (serotonin concentration 10^{-8} g/ml); *2*) contractions in response to the same concentration of serotonin after washing (control); *3-6*) decreased amplitude of contractions in response to 10^{-8} g/ml serotonin after the addition of increasing concentrations of Hb; *7*) restoration of the amplitude of contractions after the addition of 10^{-7} g/ml serotonin against the background of 10^{-5} g/ml Hb. Incubation with Hb 5 min, addition of serotonin after 7 min. Asterisk indicates washing.

that observed in aged people. The mechanisms of this angiopathy is unknown [2,5,14,19]. Based on the hypothesis of impaired serotonin—SR binding, we have suggested that diabetic angiopathy is associated with chronic serotonin insufficiency, and the function of vascular smooth muscles in these patients, at least partially, can be normalized by administration of serotonin. We anticipated that serotonin improves automatism and contractility of vascular smooth muscles and eliminates tissue hypoxia.

RESULTS

Group 1 included 26 patients (11 women and 15 men). Four patients had type I diabetes mellitus and 22 patients had type II diabetes mellitus. In 6 patients the disease duration was <10 years, and in 20 patients it was >10 years. In patients with diabetic angiopathy (foot or toe necrosis), local changes in Po_2 were measured transcutaneously with a Radiometer apparatus before and after infusion of serotonin adipinate. The sensor was placed near necrotic focus. In 14 patients, electromyogram was recorded simultaneously with Po_2. Serotonin adipinate 10 mg (1%) was dissolved in 100-200 ml normal saline and infused intravenously at a rate of 2.5 or 5-10 mg/h.

At an infusion rate of 2.5 mg/h (12 patients) serotonin induced no statistically significant changes in microcirculation.

At an infusion rate of 5-10 mg/h (mean age 57.4 years) Po_2 increased by 50.4% compared with the initial value (Table 1). Tissue Po_2 and electrical activity of smooth muscles increased in all 14 patients. The majority of patients (25 out of 26) were older than 35, i.e., they had both age-related and diabetic angiopathies of various intensity. Figure 6 shows electromyogram and Po_2 dynamics during serotonin infusion in patient A. (75 years old, type II diabetes mellitus with microangiopathy of leg blood vessels and purulent-necrotic ulcer of the right foot).

Thus, we have demonstrated that in patients with age-related and diabetic angiopathies both electrical activity and Po_2 in pathologically changed tissues increase during intravenous infusion of serotonin. The finding that even clinically pronounced angiopathy can be at least partially normalized imply that the pathological processes occurring in the vascular wall are reversible, i.e., under certain conditions age-related angiopathy and, consequently, aging can be slowed down. This suggestion is consistent with the observation that changes in the structure and function of smooth muscles are reversible to a certain extent [7].

Our results indicate that diabetic and age-related angiopathies are accompanied by changes in SR of vascular smooth muscles and chronic serotonin insufficiency. These changes induce vascular disorders and dystrophy of tissues and organs leading to mono- and polyorganic insufficiency and death.

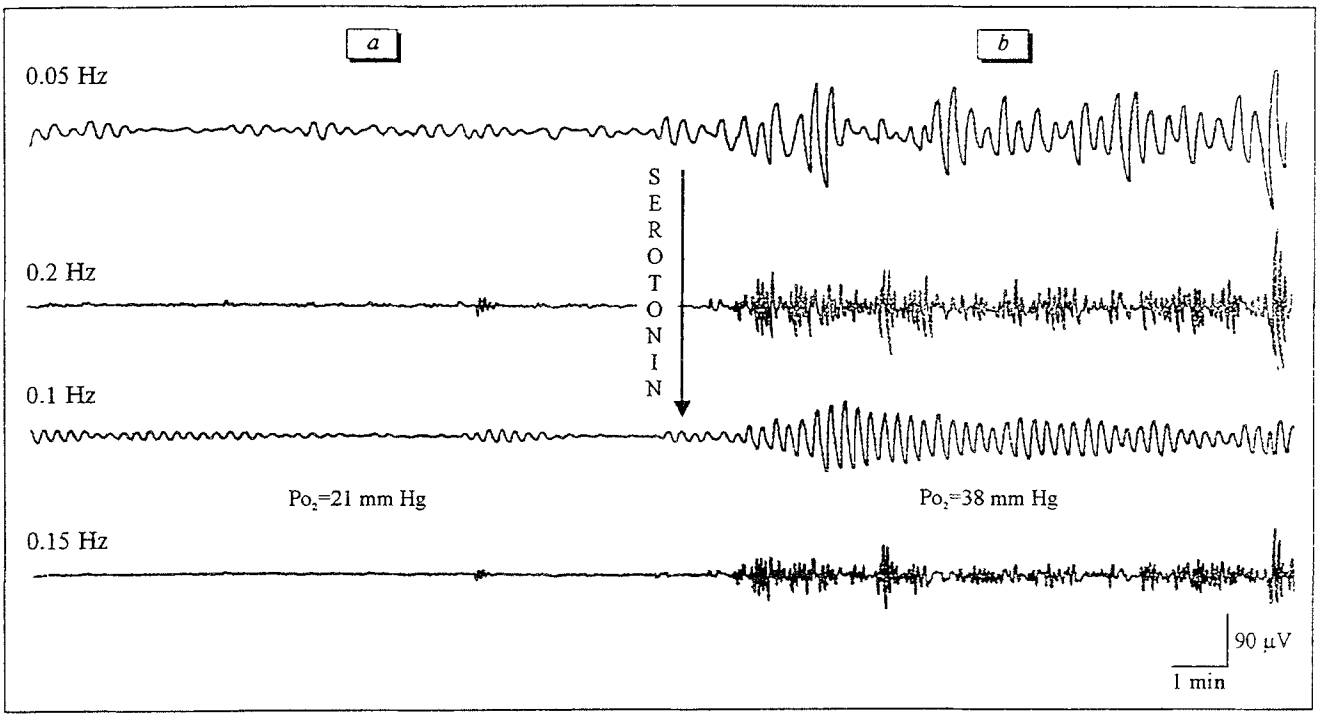

Fig. 6. Electromyogram (*a*) and Po_2 (*b*) record of a patient with age-related and diabetic angiopathies before and after intravenous infusion of serotonin. *a*) baseline electrical activity of smooth muscles and baseline Po_2 (21 mm Hg); *b*) increased electrical activity of smooth muscles and Po_2 elevation (38 mm Hg) during serotonin infusion.

Further studies are necessary for optimization of therapy and prevention of diabetic and age-related angiopathy with serotonin.

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