Effect of the Organophosphorus Pesticide Anthio on the Blood Supply to the Brain

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Experiments with cats using ultrasound show that exposure to the organophosphorus compound Anthio leads to a reduction of vascular resistance of the carotid and internal maxillary arteries. The bloodflow in these arteries does not decrease for a long time. The share of bloodflow in the internal maxillary artery is increased vis-a-vis the total flow in the carotid artery. A reduction of the blood supply to the brain is observed only by the end of the experiment with a blood pressure of 40 to 50 mm Hg.

Key Words: *organophosphorus compounds; blood supply to the brain; ultrasound; cat; narcosis*

Previously we demonstrated that exposure to the organophosphorus compound (OPC) Anthio used in agriculture leads to profound disorders in the pulmonary and systemic circulation and respiration [8,9]. The role of central and peripheral structures in the development of changes in arterial pressure (AP) and respiration, as well as in cardiac function during exposure to anticholinesterase agents, to which OPC belong, has been discussed [1,2]. Some authorities emphasize the priority of symptoms of irritation of the central and peripheral cholinergic systems as a result of the anticholinesterase action of the agents [2,10]. Disorders of central nervous system (CNS) function are reported to play an important role in OPC poisoning [2,4].

The hemodynamic and respiratory disorders which we detected may be to a certain measure related to changes in the regulatory functions of the CNS which, in turn, may be caused not only by a direct influence of OPC on the CNS structures, but also by changes in the blood supply to the brain.

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This research was aimed at investigating the blood supply to the brain during exposure to OPC.

MATERIALS AND METHODS

The linear and volumetric rates of the bloodflow in the common carotid artery and the internal maxillary artery, which is responsible for the blood supply to the brain in cats [3], were studied in acute experiments on 8 cats of both sexes weighing 2.7 to 4.4 kg under nembutal narcosis (40 mg/kg intraperitoneally) by the ultrasound method [5]. Bandage type ultrasonic transducers 0.5 to 1.5 mm in diameter operating at 27 mHz frequency were used. AP in the femoral artery was measured with a microelectromanometer [6]. The data on the bloodflow in the internal maxillary and carotid arteries and the AP obtained in the course of the procedure were fed into an analog computer in order to calculate the vascular resistance of the relevant sites. Heart rate was recorded with a cardiotachometer triggered by the bloodflow curve. Respiratory excursions of the thorax were recorded with a tensometric transducer. An emulsion of Anthio (Formathion) was administered in the stomach through a tube in a dose of 20% LD_{50} (42.6 mg/kg). As functional

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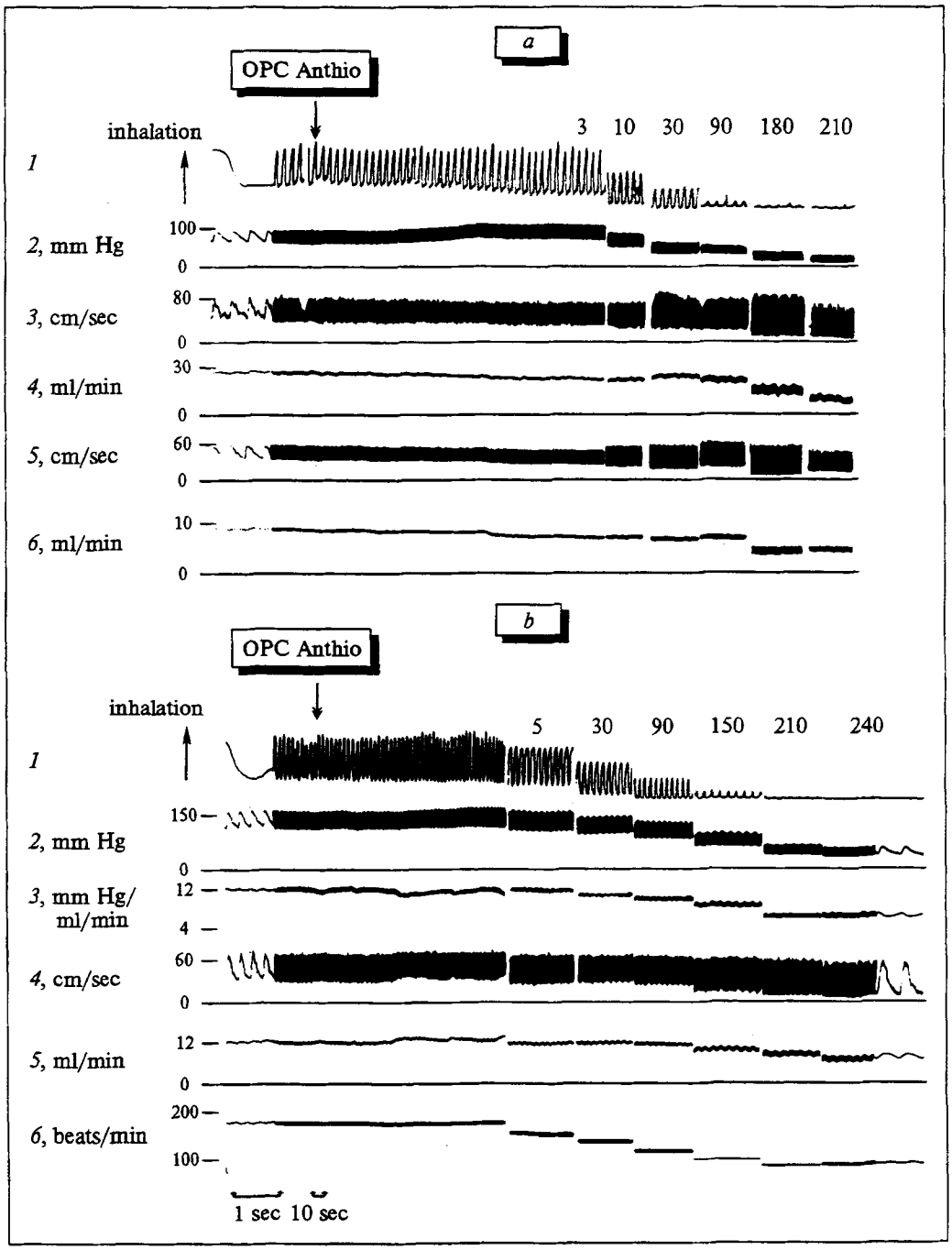

Fig. 1. Effect of OPC on the bloodflow in the carotid and internal maxillary arteries. *a*: *1*) respiration; *2*) *AP*; *3*) linear bloodflow velocity in carotid artery; *4*) volumetric bloodflow velocity in carotid artery; *5*) linear bloodflow velocity in internal maxillary artery, *6*) volumetric bloodflow velocity in internal maxillary artery. *b*: *1*) respiration; *2*) AP; *3*) vascular resistance of internal maxillary artery; *4*) linear bloodflow velocity in internal maxillary artery; *5*) volumetric bloodflow velocity in internal maxillary artery; *6*) heart rate. Here and in Figs. 2 and 3: thin lines under each curve show zero levels. Numbers in the upper part of the figures show the time (min) elapsed since OPC administration.

tests, 2-3-min inhalations of a gas mixture with 7% CO_2 were used.

RESULTS

The baseline volumetric rate of bloodflow in the carotid artery was 15.3 ml/min, on average (from 8 to 22 ml/min in different experiments). The mean volumetric bloodflow velocity in the internal maxillary artery was 10.1 ml/min (from 3.5 to 13 ml/min). The mean share of bloodflow in the internal maxillary artery vis-a-vis the bloodflow in the common carotid artery was initially 54%.

The mean maximal pulsed linear bloodflow velocity in the carotid artery was 37 cm/sec (from 18 to 90 cm/sec). The mean linear bloodflow velocity in the internal maxillary artery was 81 cm/sec (from 40 to 120 cm/sec). A constant constituent (diastolic flow) was always present in the bloodflow in both arteries. Quantitative changes in the volumetric bloodflow velocity coincided in time with the corresponding changes of the constant constituent.

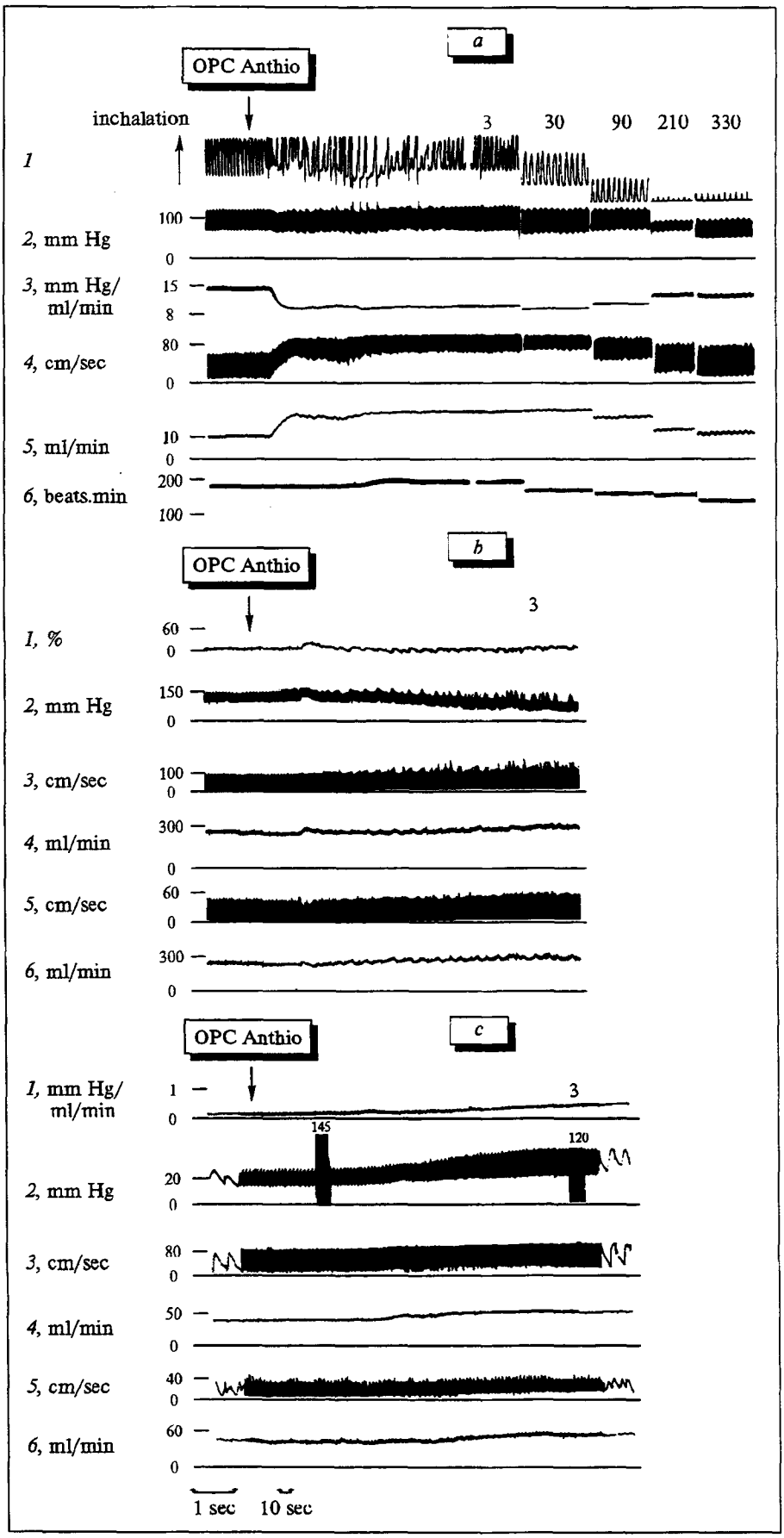

Fig. 2. Effect of OPC on the bloodflow and resistance in the internal maxillary artery and cardiac output during vomiting movements. *a*: *1*) respiration; *2*) AP; *3*) vascular resistance of internal maxillary artery; *4*) linear bloodflow velocity in internal maxillary artery; *5*) volumetric bloodflow velocity in internal maxillary artery; *6*) heart rate. *b*: *1*) balance between right and left ventricular output; *2*) AP in femoral artery; *3*) linear bloodflow velocity in ascending aorta; *4*) volumetric bloodflow velocity in ascending aorta; *5*) linear bloodflow velocity in pulmonary artery cone; *6*) volumetric bloodflow velocity in pulmonary artery cone. *c*: *1*) pulmonary vascular resistance; *2*) AP in pulmonary artery; *3*) linear bloodflow velocity in left pulmonary artery of lower lobe; *4*) volumetric bloodflow velocity in pulmonary artery of lower lobe; *5*) linear bloodflow velocity in pulmonary vein of lower lobe; *6*) volumetric bloodflow velocity in pulmonary vein of lower lobe.

The initial AP level was 140 to 150 mm Hg. AP started to decrease 5 to 30 min after exposure to OPC (in some experiments this drop was preceded by a short-term negligible rise). By the end of the experiment (4 to 5 h after administration of OPC) the mean AP level in the majority of animals was 33% of its initial level (from 21 to 40% in different experiments) (Fig. 1, *a*). In two experiments AP fell only to 70 and 80%. Previously we demonstrated that the total peripheral vascular resistance is sharply reduced under such conditions [8].

The studies showed that the carotid artery basin also contributes to the reduction of the total peripheral vascular resistance. The resistance in the common carotid and internal maxillary arteries started to decrease just 10 min after administration of OPC. It reached the minimal values (64%, on average, in the carotid artery and 55% of the initial level in the internal maxillary artery) after 60 to 90 min and remained so for some time (Fig. 1, *b*). By the end of the experiment the resistance of both arteries somewhat increased, but was always lower than initially.

Due to the reduced resistance, the bloodflow in the common carotid artery was stable for some time, even though the AP had begun to drop; hence, the phenomenon of cerebrovascular autoregulation manifested itself under these conditions as well [7].

Bloodflow in the internal maxillary artery delivering blood directly to brain structures was stable as well. Reduction of the bloodflow in this artery started somewhat later than in the common carotid artery (Fig. 1, *a*). This was paralleled by an increase in the share of bloodflow in the internal maxillary artery vis-a-vis the bloodflow in the carotid artery (in the period from 10 to 150 min after administration of OPC). By the end of the experiment these ratios had normalized. Reduction of the resistance and increase of the bloodflow in the carotid arteries may be to a certain degree related to metabolic acidosis which develops with exposure to OPC [9].

In four experiments short-term vomiting movements were observed immediately after administration of OPC; the OPC could not be regurgitated, because the larynx was closed off with a cotton plug. The vomiting movements went along with a drastic reduction of vascular resistance in the internal maxillary artery and a 2-3-fold increase of the bloodflow, with the AP unchanged (Fig. 2, *a*). Vomiting movements were observed in some experiments during our previous study, when we investigated cardiac output [8], and so we can correlate the time course of bloodflow changes in the internal maxillary artery with other hemodynamic parameters: vomiting movements do not cause changes in the systemic AP or cardiac output (Fig. 2, *b*), but the pulmonary AP is negligibly increased in this case (Fig. 2, *c*). It is possible that the reduction of cerebrovascular resistance and the increase of bloodflow in this case are a separate reflex reaction unrelated to changes in systemic AP and cardiac output. Although the vomiting movements lasted only 1-2 min, the increased bloodflow persisted much longer (up to 60 to 90 min) in these experiments.

Bloodflow in the common carotid and internal maxillary arteries fell to approximately 52% of its initial level (from 28 to 70% in different experiments) only in the terminal stage in parallel with an AP decrease to 40-50 mm Hg. In two animals bloodflow did not decrease right up to the end of the experiment (with a rather high AP in one case and with markedly reduced AP in the other).

The baseline heart rate was 180 to 210 beats/min. Similarly as in the previous study [8], a reduction of heart rate was observed starting from the 45th to 120th min after administration of OPC. In some experiments a short-term increase of the heart rate preceded this decrease. By the end of the experiment the heart rate was 53% of its initial level, on average. In one experiment the parameter decreased negligibly: to 93%.

The initial respiration rate was 24 to 34 resp/min. A drop of the respiration rate, starting 10 to 45 min after OPC administration, was observed. In 4 experiments it was preceded by an increase of respiration frequency. By the end of the experiment the respiration rate have dropped to 44% of its initial level, on average. Weakening of the electrical activity of the intercostal respiratory muscles and enhancement of the electrical activity of the diaphragm under the effect of OPC had been observed [9]. The figures show abatement of the respiratory movements, because the respiration transducer was placed on the thorax and we could observe more intensive respiratory movements of the diaphragm only visually; a more detailed investigation of the respiratory function was not our purpose in the present research.

In order to study the reactivity of the vessels delivering blood to the brain, functional tests with short-term (2-3 min) inhalation of a hypercapnic gas mixture (7% CO_2 in air) were carried out. Experiments demonstrated that the reactivity of cerebral vessels to hypercapnia persisted for a long time: inhalation of the mixture was associated

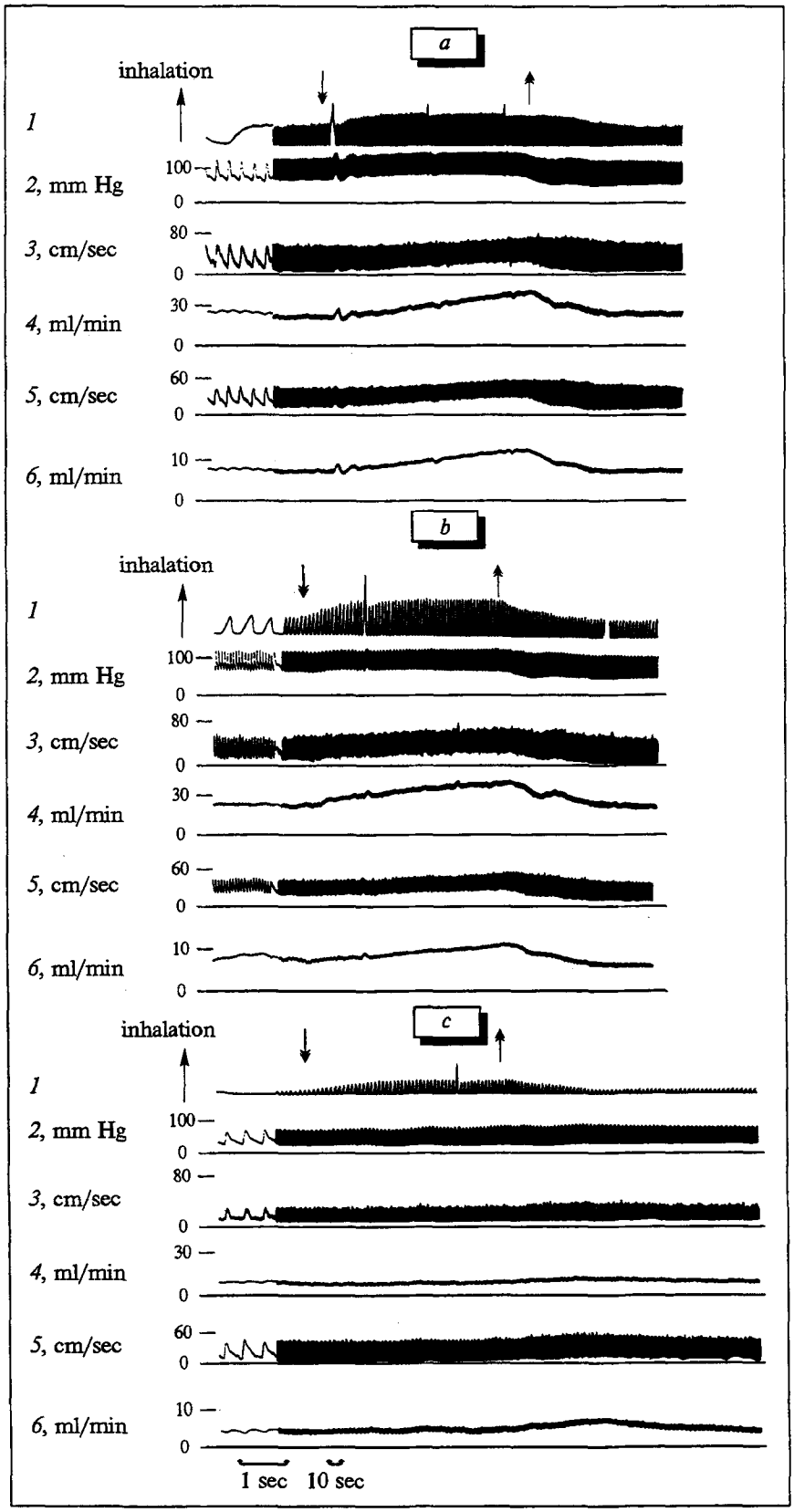

Fig. 3. Effect of inhalation of a gas mixture with 7% CO_2 on the bloodflow in the carotid and internal maxillary arteries before (*a*), 1 h (*b*), and 4 h (*c*) after exposure to OPC. Legends to curves as in Fig. 1, *a*. Arrows show the beginning and end of inhalation of the mixture.

with a decrease of vascular resistance and increase of the bloodflow in the common carotid and internal maxillary arteries. This reaction disappeared or faded toward the end of the experiment, 3-4 h after administration of OPC. A respiratory reaction to hypercapnia (increased amplitude of res-

piratory movements) was observed till the end of the experiment, when bloodflow evidently normalized (Fig. 3).

Hence, the blood supply to the brain was shown to be unchanged for quite a long time or even to be increased after exposure to the OPC Anthio. Bloodflow started to be reduced only in the terminal stage (4 to 5 h after exposure), and in some experiments its level remained close to normal. Previously observed disorders of the pulmonary and systemic circulation [8] and respiration [9] develop at a later stage, 30 to 90 min after exposure to OPC. This gives grounds for assuming that the detected disorders of pulmonary and systemic hemodynamics and respiration are not caused by insufficient blood supply to the brain.

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