THE PATHOGENESIS OF CARBON MONOXIDE POISONING AND ITS COMBINED TREATMENT

(UDC 615.712.1-099)

V. A. Pukhov

S. M. Kirov Military Medical Academy, Leningrad. Scientific Director of Laboratory Active Member AMN SSSR Professor I. R. Petrov

(Presented by Active Member AMN SSSR I. R. Petrov)
Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 60, No. 11, pp. 39-42, November, 1965
Original article submitted April 23, 1964

The objects of this investigation were to study the course of CO poisoning in relation to differences in the functional state of the central nervous system and adrenals, and to attempt to improve the combination of measures used in the treatment of experimental CO poisoning.

METHOD

Experiments were conducted on 278 albino mice and 90 rats of both sexes. Carbon monoxide poisoning was caused by the static method of administration [7], in which various concentrations of the gas were given for different periods. In the respective series of experiments the mice received intramuscular injections of caffeine (30 mg/kg), adrenalin (0.5 mg/kg), barbital sodium (150 mg/kg), and ACTH (3-4 units/kg daily for 1 week). The rats received amphetamine before being poisoned, in a dose of 0.06-0.12 mg/100 g body weight. After the rats had been poisoned with CO in a concentration of 1.6 mg/liter for a period of exposure of 3 h, a combination of therapeutic measures was applied, consisting of barbital sodium, adrenalin, and ACTH-zinc phosphate in the above-mentioned doses, after which some rats were maintained on artificial respiration. Immediately after exposure to CO, the rats were kept for 12-18 h in a chamber continuously supplied with a mixture of oxygen and CO_2 (2%).

The brain and adrenals of the rats were investigated histologically. Brain sections were stained with hematoxylin-eosin and by Van Gieson's and Nissl's methods, and sections of the adrenals were stained with Sudan III. The reaction of the animals to a strong acoustic stimulus was recorded.

RESULTS

Depending on the character of the functional changes and of the resistance to anoxia caused by CO poisoning the animals as a whole could be divided into two groups. In the mice and rats of group 1 during poisoning excitation of the central nervous system was predominant (frequent attacks of motor excitation and clonic convulsions). The number of such mice rose progressively with an increase in the toxic concentration of CO (see table). In the animals of group 2, throughout the period of poisoning inhibition of the central nervous system was predominant, and attacks of motor excitation and of convulsions were rare and of short duration. The mice showing predominance of excitation died in 100% of cases during poisoning. Their mean period of survival during poisoning was 9 min, while death of the mice with predominance of inhibition took place on the average after 21 min ($P = 0.02$). As a result of poisoning of the rats with CO in a concentration of 1.6 mg/liter and for an exposure period of 3 h, about 50% of the animals with predominance of inhibition perished, while the rats in which convulsions developed died in 100% of cases during or after poisoning.

All the animals with a convulsive reaction to a strong acoustic stimulus (15%), i.e., mice and rats with a relatively inadequate level of internal inhibition [4], were included in the group with predominance of excitation of the central nervous system, and they were found to be most sensitive to CO poisoning. After CO poisoning, the rectal temperature of the overwhelming majority of rats fell, as also did their oxygen consumption and their

Resistance of Mice to Poisoning with CO in Various Concentrations. Duration of Poisoning 30 min

Series of expts.	CO conc. in mg/liter	No. of mice			Course of anoxia	
		total	surviving	dying	convulsive	inhibitory
Control	10,1	30	10	20	14	16
	12,0	30	4	26	20	10
	14,1	30	—	30	22	8
	16,2	20	—	20	18	2
After administration of caffeine	10,1	20	—	20	14	6
After administration of adrenalin	10,1	15	10	5	7	8
After administration of barbital sodium	12,0	16	6	10	4	12
After admin. of ACTH	12,0	16	6	10	3	13
After administration of barbital sodium and adrenalin						
After poisoning—artificial respiration	10,1	20	19	1	1	19
	12,0	20	20	—	1	19
	14,1	21	7	14	13	8
	16,2	10	2	8	6	4
After administration of ACTH, barbital sodium and adrenalin. Artificial respiration and addition of carbon dioxide	14,1	20	20	—	1	19
	16,2	10	3	7	5	5

Note. All the mice died during CO poisoning. The drugs were injected 20-30 min before poisoning.

respiration rate. Various pathological changes were observed in the brain of the rats dying at different stages after poisoning (signs of edema, chromatolysis, hyperchromatosis, and areas of ghost cells). These changes were most marked in animals with predominance of excitation of the central nervous system.

During the first few hours after poisoning the number of eosinophils in the blood fell, which may be regarded as a sign of an increased blood level of glucocorticoid hormones. Further evidence of this was given by the marked decrease in the content of lipid granules in the zona fasciculata of the adrenal cortex. In later periods (2-3 days) the blood eosinophil level began to increase, and the fall in the content of lipid granules now affected all the zones of the adrenal cortex, indirect evidence of the gradual development of their hyperfunction [9]. It was thus shown that the course of anoxia caused by CO poisoning is largely determined by the character of the changes in the function of the central nervous system and by the difference in the type of nervous activity of different animals. On the other hand, changes were observed which could be regarded as an indication of disturbance of the function of the pituitary-adrenal system, which is known to play a role in determining the course of anoxia [1, 2, 5, 8]. In order to study the relationship between the character of the course of anoxia and the functional state of these systems, experiments were conducted in which their function was modified artificially.

Artificial excitation of the central nervous system, produced by injecting the animals with caffeine (see table), led to an increase in mortality during CO poisoning ($P = 0.001$) and also to an increase in the number of mice with predominance of excitation ($P = 0.01$). Of the 20 rats receiving amphetamine, 15 died during CO poisoning, whereas in the control series only 17% of the rats died in this period.

When, on the other hand, the central nervous system was artificially inhibited by administration of barbital sodium (see table), the resistance of the mice to CO poisoning was slightly increased ($P = 0.02$). The number of mice with predominance of excitation also fell significantly ($P = 0.02$). As a result of the artificial increase in the adrenal cortical function caused by administration of adrenalin and ACTH (see table), a slight increase in the resistance of the mice to CO poisoning took place ($P = 0.05$).

During the study of the effect of barbital sodium on the course of CO poisoning, its beneficial action was found to be accompanied by a harmful effect: the early depression of respiration and, in some cases (14%), the rapid death of the animals. The latter was evidently connected with the spreading of deep inhibition to the vitally important structures of the brain and, in particular, to the respiratory center. To prevent this harmful action, combinations of drugs and agents causing excitation (adrenalin, carbon dioxide) and inhibition of the central nervous system (barbital sodium and, to some degree, ACTH) were tried, and were administered to the mice before exposure to carbon monoxide. As the table shows, this enabled most of the mice to survive, even after exposure to highly toxic concentrations of CO. On the basis of these findings it was decided to use this combination of substances for the treatment of rats poisoned by carbon monoxide.

As a result of exposure of rats to CO in a concentration of 1.6 mg/liter for 3 h, 15 of the 35 rats died during exposure or soon after, while 20 animals receiving combined treatment survived and were sacrificed 10-15 days after poisoning. In the control series of experiments, only 7 of the 35 rats survived. In the rats receiving treatment, respiration was restored sooner and the eosinopenia lasted longer than in the controls. Together with the comparative integrity of the lipid content of the adrenal cortex, this fact shows that the treatment given prevented the onset of hyperfunction of the adrenal cortex. The effectiveness of treatment was also demonstrated by the fact that although pathological changes were present in the brain of the rats, they were less marked than in the animals not receiving treatment. Hence, the animals with predominance of excitation of the central nervous system and also the animals receiving stimulants were most sensitive to anoxia. I. R. Petrov and V. S. Shapot and co-workers [3], who obtained similar findings, consider that as a result of preliminary excitation of the central nervous system of the animals, the subsequent anoxia develops in these animals against the background of an established decompensation of the metabolism of high-energy phosphorus compounds in the brain. It has previously been shown [6] that the mechanism of the positive action of artificial intensification of inhibition of the central nervous system on the course of anoxia is associated with the sharp decrease in the breakdown of high-energy compounds in the brain tissues.

The positive result of treatment is evidently associated with the intensification of the protective inhibition of the central nervous system under the influence of barbital sodium, the improvement of the blood supply to the brain as a result of the action of CO_2 and adrenalin, and the stimulation of the glucocorticoid function of the adrenals under the influence of ACTH [1-3, 5, 6].

LITERATURE CITED

1. V. B. Antonov and V. A. Pukhov, Pat. fiziol., 4, 25 (1962).
2. Z. I. Barbashova, Acclimatization to Hypoxia and Its Physiological Mechanisms [in Russian], Moscow-Leningrad (1960).
3. I. R. Petrov, V. S. Shapot, and K. G. Gromova et al., In book: Collected Abstracts of Scientific Research in 1951-52 at the Military Medical Academy [in Russian], Leningrad (1955), p. 18.
4. L. V. Krushinskii, The Formation of Animal Behavior in Normal and Pathological Conditions [in Russian], Moscow (1960).
5. T. M. Malikova, Pat. fiziol., 6, 17 (1962).
6. I. R. Petrov, Role of the Nervous System in Anoxia [in Russian], Leningrad (1952).
7. S. D. Radaikin, Practical Manual of Toxicology, Pathology, and Therapy of Lesions Due to War Gases [in Russian], Moscow-Leningrad (1940).
8. E. I. van Leer, Anoxia and Its Influence on the Organism [in Russian], Moscow (1947).
9. H. Selye, The Physiology and Pathology of Exposure to Stress, Montreal (1950).