

EFFECT OF HYDRALLAZINE, OBSIDAN, AND
PROMETHAZINE AND THEIR COMBINATIONS ON THE
NAD AND NADH CONTENT IN THE LIVER AND BRAIN
OF HYPOXIC RATS

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Hydrallazine (2.5 mg/kg), obsidan (10 mg/kg, and promethazine (10 mg/kg) increased the NAD + NADH content in the liver and brain of intact rats without affecting their relative proportions. These drugs, in the same doses, especially if administered together, raised the NAD + NADH level if depressed by hypoxia and increased the NAD/NADH ratio. It is concluded that the antihypoxic action of hydrallazine, obsidan, and promethazine is perhaps connected with an increase in the total nicotinamide-adenine dinucleotide content and a relative increase in the content of its oxidized form. KEY WORDS: hydrallazine; obsidan; promethazine; hypoxia; nicotine-adenine dinucleotide.

The disorders associated with hypoxia are based on ATP deficiency, due to a disturbance of oxidative phosphorylation and glycolysis. One of the factors which inhibits these processes is inhibition of activity of NAD-dependent dehydrogenases, connected with a deficiency of nicotinamide coenzymes and predominance of their reduced forms [4-6].

The writers showed previously [2, 3] that hydrallazine, obsidan, and promethazine increase the resistance of animals to hypoxia. The antihypoxic action of these drugs is increased if they are administered together [1].

The object of the present investigation was to study the effect of hydrallazine, obsidan, promethazine, and their combinations on the NAD and NADH content in the liver and brain of animals exposed to acute hypoxic hypoxia.

EXPERIMENTAL METHOD

Experiments were carried out on 100 noninbred female albino rats weighing 150-200 g. Hydrallazine, obsidan, and promethazine were given as a single subcutaneous injection in doses of 2.5, 10, and 10 mg/kg respectively, and also of a combination of all three in the same doses. Control animals received the corresponding volumes of 0.85% NaCl solution. Some of the animals were placed 60 min later in a chamber ventilated with a hypoxic gas mixture (6.66% O₂, 93.34% N₂), in which they remained for 30 min. At the end of this period the rats were decapitated and the brain and liver immersed in liquid nitrogen. The content of NAD and NADH in homogenates of these organs was determined fluorometrically [7] and expressed in micrograms per gram wet weight of tissue. On the basis of these results the values of NAD + NADH and NAD/NADH were calculated.

EXPERIMENTAL RESULTS

After administration of hydrallazine, obsidan, and promethazine to intact rats the NAD + NADH content in the liver was increased significantly by 30, 33.9, and 24.7%, and in the brain by 14.6, 11.7, and 10.8% respectively. The NAD/NADH ratio was unchanged (Table 1).

In hypoxia the total level of this coenzyme in the liver was significantly reduced by 16.7%, whereas in the

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TABLE 1. Effect of Hydrallazine, Obsidan, Promethazine, and Combinations of Them on Content of NAD and NADH in Liver and Brain (in $\mu\text{g/g}$ wet weight of tissue) of Intact Hypoxic Rats ($M \pm m$)

Drugs and doses, mg/kg	NAD	NADH	NAD + NADH	NAD/NADH
Control	$\frac{502 \pm 40.0}{248 \pm 6.5}$	$\frac{199 \pm 7.4}{93 \pm 6.6}$	$\frac{702 \pm 43.0}{341 \pm 9.1}$	$\frac{2.52 \pm 0.19}{2.73 \pm 0.21}$
Hydrallazine (2.5)	$\frac{682 \pm 19.3^*}{285 \pm 7.0^*}$	$\frac{240 \pm 10.6^*}{108 \pm 8.4}$	$\frac{918 \pm 25.1^*}{391 \pm 9.7^*}$	$\frac{2.84 \pm 0.13}{2.7 \pm 0.22}$
Obsidan (10)	$\frac{675 \pm 12.5^*}{269 \pm 7.2}$	$\frac{265 \pm 11.5^*}{114 \pm 5.7^*}$	$\frac{940 \pm 23.8^*}{381 \pm 7.5^*}$	$\frac{2.55 \pm 0.07}{2.37 \pm 0.16}$
Promethazine (10)	$\frac{638 \pm 13.3^*}{273 \pm 8.2}$	$\frac{238 \pm 7.5^*}{105 \pm 8.6}$	$\frac{876 \pm 13.8^*}{378 \pm 12.8}$	$\frac{2.69 \pm 0.11}{2.7 \pm 0.26}$
Hypoxia	$\frac{332 \pm 10.6^*}{199 \pm 7.7^*}$	$\frac{251 \pm 8.9^*}{142 \pm 5.1^*}$	$\frac{585 \pm 16.3^*}{341 \pm 11.9}$	$\frac{1.32 \pm 0.04^*}{1.4 \pm 0.04^*}$
Hypoxia + hydrallazine (2.5)	$\frac{420 \pm 12.1^\dagger}{230 \pm 8.2^\dagger}$	$\frac{220 \pm 10.6^\dagger}{123 \pm 6.2^\dagger}$	$\frac{638 \pm 8.3^\dagger}{353 \pm 9.7}$	$\frac{1.93 \pm 0.13^\dagger}{1.89 \pm 0.13^\dagger}$
Hypoxia + obsidan (10)	$\frac{400 \pm 16.7^\dagger}{228 \pm 7.6^\dagger}$	$\frac{227 \pm 4.2}{127 \pm 4.3}$	$\frac{627 \pm 18.3}{355 \pm 10.4}$	$\frac{1.75 \pm 0.08^\dagger}{1.8 \pm 0.06^\dagger}$
Hypoxia + promethazine (10)	$\frac{413 \pm 6.5^\dagger}{235 \pm 7.5^\dagger}$	$\frac{221 \pm 6.0^\dagger}{130 \pm 7.7}$	$\frac{635 \pm 20.0^\dagger}{365 \pm 7.2}$	$\frac{1.86 \pm 0.08^\dagger}{1.85 \pm 0.16^\dagger}$
Hypoxia + hydrallazine (2.5), obsidan (10), promethazine (10)	$\frac{449 \pm 11.3^\dagger}{239 \pm 6.8^\dagger}$	$\frac{209 \pm 6.1^\dagger}{118 \pm 3.7^\dagger}$	$\frac{651 \pm 9.2^\dagger}{357 \pm 7.4}$	$\frac{2.13 \pm 0.13^\dagger}{2.02 \pm 0.08^\dagger}$

Legend. 1) Values for liver given in numerator, for brain in denominator. 2) *) $P < 0.05$ compared with control, †) $P < 0.05$ compared with hypoxia.

brain it showed no significant change; the NAD/NADH ratio was reduced by 47.7 and 48.8% respectively, mainly on account of a relatively greater increase in the content of reduced forms.

After prophylactic separate administration of hydrallazine, obsidan, and promethazine to these animals the NAD + NADH content in the liver was increased, as also was the NAD/NADH ratio, by 46, 32.5, and 40.9%, and in the brain by 35, 28.5, and 32% respectively. After combined administration of the drugs their efficiency increased: the content of coenzyme in the liver was raised by 11.2% and the NAD/NADH ratio rose in the liver by 62.8% and in the brain by 44.2%.

The results indicate that one mechanism of the increased resistance of the recipient to hypoxia due to the action of hydrallazine, obsidan, and promethazine is an increase in the total content of nicotinamide-adenine dinucleotide and an increase in the reserves of its oxidized form, which activates NAD-dependent dehydrogenases and, consequently, the ATP-generating systems.

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