Synergism of Isothermal Regimen and Sodium Succinate in Experimental Therapy of Barbiturate Coma

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In rats with experimental thiopental coma rectal temperature decreased by 9.4°C, oxygen consumption 5-fold, and arteriovenous Po_2 gradient decreased 2-fold within 3 h; CO_2 accumulated in the blood and mixed type acidosis developed. Administration of sodium succinate under these conditions increased arteriovenous Po_2 gradient and reduced manifestations of metabolic acidosis. Maintenance of normal body temperature (warming) corrected primarily manifestations of respiratory acidosis. Each therapeutic agent reduced inhibition of O_2 consumption by $^1/_4$; animal survival tended to increase from 42 to 50%. Combined use of these treatments potentiated the antiacidotic effect and increased survival to 92%. The authors conclude that hypothermia inhibits the therapeutic effect of succinate in barbiturate coma.

Key Words: *barbiturate intoxication; hypothermia; oxygen consumption; acid base status; sodium succinate*

The initial period of barbiturate intoxication is characterized by hypothermia; its presumable causes are impairment of the thermoregulatory response to environment and reduction of thermogenesis. Body temperature decrease by 2°C characteristic of surgical anesthesia is fraught with the risk of a worse clinical outcome [4,5], which can be prevented by restoration of core temperature [6].

The content of Krebs cycle intermediates in the brain decreases in the presence of barbiturate concentrations possible *in situ*. The intensity of cell respiration in barbiturate coma can be limited by availability of Krebs cycle intermediates and be corrected by their injection [3]. Hypothermia can inhibit the resorption of exogenous carbonic acids and their incorporation into the Krebs cycle, and therefore warming can promote their therapeutic effect.

We evaluated the therapeutic effect of combined use of sodium succinate (SS) and external warming in barbiturate coma.

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MATERIALS AND METHODS

Female albino rats (n=149; 100-120 g) were distributed into 5 groups: control; sodium thiopental (ST) in a dose of 75 mg/kg (approximately LD_{50}) without subsequent treatment; treatment with SS (5 mmol/kg); isothermal regimen (IR; placing the animal into a 60-liter box ventilated with air warmed to 34°C for 3 h); combination of SS and IR. All agents were injected intraperitoneally (10 ml/kg).

Body temperature and oxygen consumption were measured before ST injection (initial level) and over 3 h with 30-min intervals; SS was injected after the 2nd measurement, IR was started after ST injection. The release of CO_2 with exhaled air and O_2 consumption were evaluated before ST injection (initial level) and 3 h after it. The effects of ST and/or therapeutic agents on acid base status and gaseous composition of the blood were evaluated in samples collected 3 h after injection of ST. The animals dead within 3 h after injection of ST were replaced.

Rectal temperature was measured with a mercuric thermometer with 0.1°C scale factor, oxygen

TABLE 1. Effects of SS and/or IR on Rat Survival in Thiopental Coma

Group	During 3 h			During 48 h		
	rats, total	survivors	survival, %	rats, total	survivors	survival, %
ST	47	21	45	12	5	42
ST+SS	34	25	74	12	6	50
ST+IR	34	20	59	12	6	50
ST+SS+IR	34	32	94**	12	11	92*+

Note. Here and in Table 2: *p<0.05, **p<0.01, ***p<0.001 compared to ST; +p<0.05, ++p<0.01 compared to ST+SS.

consumption (Qo_2) was evaluated at 18-20°C or at 34°C [1]. Excretion of CO_2 (Qco_2) was evaluated by absorbent titration. The respiratory coefficient was estimated for each animal ($RC=Qco_2/Qo_2$). In order to evaluate acid base status and gaseous composition of the blood, *a. abdominalis* and *v. cava inf.* caudally from *v. hepatica* were punctured. The blood (1 ml) was collected with heparinized syringes, placed on ice, and after 20-30 min analyzed on a Radiometer ABL 500 analyzer. In order to eliminate the effect of traumatic stress, control rats were also injected with ST (75 mg/kg), but blood samples were collected during animal transition into the lateral posture (after 1-2 min).

Statistical significance of intergroups differences for metabolic parameters and survival rates was evaluated using Student's t test and Fisher's exact test, respectively.

RESULTS

ST intoxication was associated with the development of hypothermia (Fig. 1, *a*). Injection of SS reduced hypothermia by no more than 1°C, while warming completely prevented it; SS against the background of IR did not modify rectal temperature. Hypothermia was not the main cause of animal death in barbiturate coma: IR had little effect on animal survival (Table 1). Three hours after ST injection, O_2 consumption decreased 5-fold (Fig. 1, *b*). This decrease was by ¼ corrected with IR or injection of SS, the effect being amplified by their combined use. After injection of SS, O_2 consumption and CO_2 release decreased proportionally. During IR alone or in combination with SS, CO_2 excretion increased to a greater extent than O_2 consumption (Table 2).

During barbiturate coma, arterial blood oxygenation little changed (Table 3), but arteriovenous Po_2 gradient decreased almost 2-fold. CO_2 accumulated in arterial and venous blood (primarily in the free form); blood alkaline reserve and pH decreased. Injection of SS increased arteriovenous Po_2 gradient 2.2 times. Blood content of CO_2 increased mainly at the expense of increased bicarbonate level; buffer base deficiency decreased. IR was associated with an increase in oxygenation of arterial and venous blood, arteriovenous Po_2 gradient increased by 1.5 times. CO_2 did not accumulate in the blood during IR, blood pH and alkaline reserve increased. Combination of IR with SS treatment increased arteriovenous Po_2 gradient by 1.9 times. The increase in blood pH, bicarbonate concentration, and buffer base excess exceeded the total increase caused by SS or IR alone.

These data indicate that tissue capacity to extract oxygen from the blood is reduced during barbiturate coma. It seems that decreased oxygen con-

TABLE 2. Effects of SS and/or IR on Rat Consumption of O_2 and Release of CO_2 with Exhaled Air 3 Hours after ST Injection ($M\pm m$)

Group	O_2 consumption, % of initial	CO_2 release, % of initial	Respiratory coefficient	
			before ST injection	3 h after ST injection
Control	95±3	94±5	0.81±0.03	0.79±0.03
ST	35±4	36±3	0.77±0.03	0.79±0.03
ST+SS	44±4	44±4	0.83±0.03	0.81±0.02
ST+IR	48±8	58±5**	0.79±0.02	1.05±0.07*
ST+SS+IR	56±6*	69±5***++	0.78±0.03	0.98±0.06*

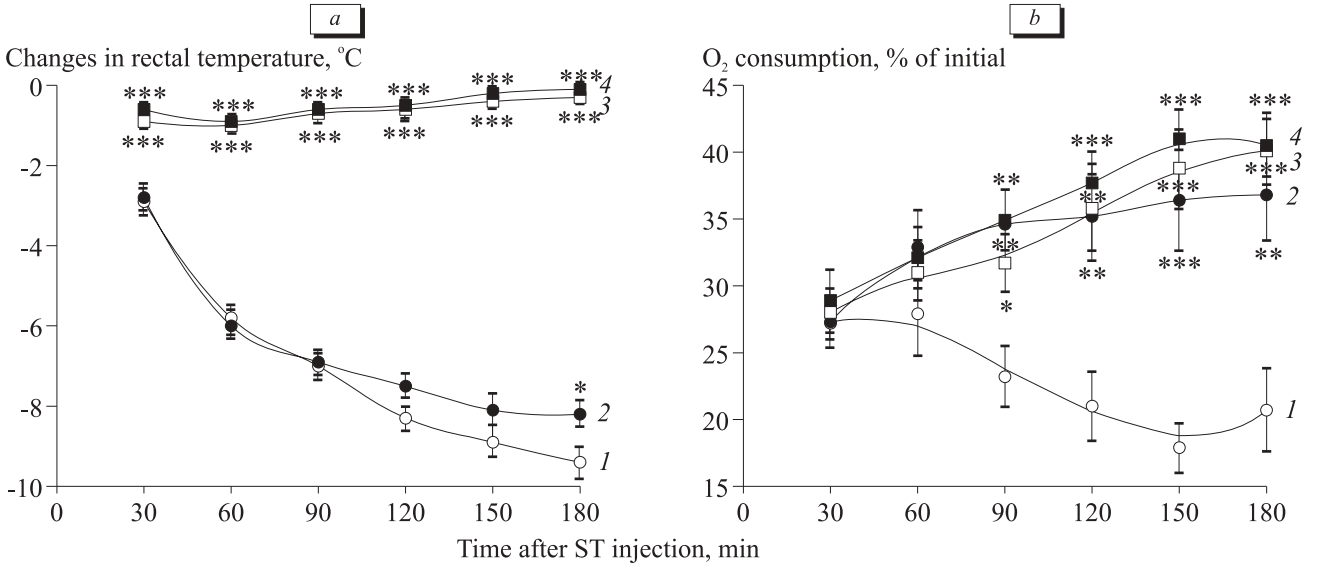

Fig. 1. Effects of SS and/or IR on body temperature (*a*) and oxygen consumption (*b*) in rats with thiopental coma (n=16). *1*) ST; *2*) ST+SS; *3*) ST+IR; *4*) ST+SS+IR. *p<0.05, **p<0.01, ***p<0.001 compared to ST.

TABLE 3. Effects of SS and/or IR on Rat Blood Gaseous Composition and Acid Base Status 3 Hours after ST Injection ($M\pm m$; n=8)

Parameter	Control	ST	ST+SS	ST+IR	ST+SS+IR
Blood gases					
Pco_2, mm Hg	41.7±3.3	81.5±6.8^{++}	94.6±5.4	48.9±1.4**	49.5±0.7**
	50.4±0.8	93.1±4.7^{+++}	108.3±5.7	60.3±3.7**	64.7±3.5**
Po_2, mm Hg	818.0±6.6	77.8±5.8	91.5±4.0	97.6±3.9*	88.7±9.7
	41.5±2.0	55.5±3.9^{+}	42.2±3.6*	64.2±1.3	46.9±3.1
So_2, %	91.0±3.1	87.1±4.0	93.1±0.8	96.3±0.8	95.4±0.7
	69.0±2.7	68.1±5.8	69.0±2.7	87.8±0.1***	75.8±4.2
tCO_2, vol.%	49.1±0.9	56.0±1.7^{+}	74.2±1.2***	52.7±1.4	71.2±2.2***
	55.0±0.8	60.1±0.8^{++}	79.2±1.1***	58.8±1.5	80.2±1.1***
Blood acid base status					
pH	7.32±0.02	7.08±0.05^{++}	7.14±0.05	7.28±0.04*	7.40±0.02**
	7.28±0.01	7.05±0.03^{+++}	7.11±0.05	7.23±0.04*	7.34±0.03***
HCO_3^-, mmol/liter	20.6±0.4	22.5±0.5^{+}	30.2±0.5***	21.0±0.3*	30.3±1.0***
	23.0±0.3	24.0±0.2^{+}	32.0±0.4***	24.4±0.8	33.8±0.5***
SBC, mmol/liter	20.3±0.3	16.6±0.4^{+++}	22.4±0.7***	20.6±0.8**	28.7±0.9***
	20.7±0.2	16.2±0.4^{+++}	21.8±0.8***	20.9±0.8**	29.3±0.5***
ABE, mmol/liter	-4.8±0.3	-9.9±0.4^{+++}	-4.7±0.3***	-4.8±1.0**	4.7±1.0***
	-3.7±0.4	-10.0±0.5^{+++}	-4.1±0.8**	-6.1±0.1***	6.0±0.5***
SBE, mmol/liter	-4.0±0.3	6.3±0.2^{+++}	2.4±0.6***	-0.4±0.3***	5.6±1.0***
	-2.8±0.3	-5.4±0.3^{+++}	3.4±0.3***	-3.2±0.5**	8.1±0.4***

Note. Numerator: *a. abdominalis*; denominator: *v. cava. inf.* *p<0.05, **p<0.01, ***p<0.001 compared to ST; ^{+}p<0.05, ^{++}p<0.01, ^{+++}p<0.001 compared to the control.

sumption in survivors is also due to this effect (Fig. 1, *b*; Table 2). Decrease in the metabolic component of acidosis under the effect of exogenous SS (Table 3) is in line with previous data and indicates redistribution of ATP resynthesis in the body in favor of the aerobic pathway.

Sodium succinate was injected, when body temperature decreased by about 3°C (30 min, Fig. 1, *a*). Obviously, prevention of hypothermia gave way to recruitment of exogenous SS into the Krebs cycle, which can explain the supra-additive increase in animal survival by 49-50% (Table 1) after combined use of IR and SS in barbiturate coma. Considering previous data [2,3], we can expect further amplification of the therapeutic effect after repeated injections of SS and prolongation of IR exposure.

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