Propranolol (10 mg/kg i.p.) or atropine (10 mg/kg i.p.) administered 10 min prior to physostigmine, successfully blocked the physostigmine-induced stimulation of brain oxygen uptake (table 1). Under these conditions, neither propranolol nor atropine alone altered the rate of brain oxygen uptake in control animals (table 1). Unlike the low doses of physostigmine, higher (sub-lethal) doses inhibited oxygen consumption in the rat brain cerebral cortex. The significant decrease of oxygen uptake (about 18%) was found after i.v. injection of 0.4 mg/kg of physostigmine (table 2). This effect was antagonized by atropine (10 mg/kg 10 min prior to physostigmine). The injection of neostigmine, which was tested at a wide dose range (0.025–0.2 mg/kg), was without effect upon oxygen uptake in rat cerebral cortex (table 2).

Discussion. The results obtained show that physostigmine injected i.v. in a dose of 0.1 mg/kg expressly stimulates oxygen uptake in rat cerebral cortex tissue. This increase of oxygen uptake in rat cerebral tissue is certainly due to the central action of physostigmine since neostigmine, a cholinesterase inhibitor, which does not readily cross the blood-brain barrier, is unable to produce a similar effect. The stimulant effect of physostigmine may be considered as a result of adrenergic activation in the central nervous system. The antagonism by propranolol supports this hypothesis. Our earlier results have also shown that propranolol successfully blocked the stimulant effect of adrenergic substances on the oxygen uptake in rat cerebral cortical slices[8].

On the other hand, the fact that atropine also antagonized the stimulant effect of physostigmine on the brain tissue respiration suggests the possibility that the action of physostigmine is primarily cholinergic and that the adrenergic effect is a secondary phenomenon.

The injection of a higher dose of physostigmine did not produce a further increase in the stimulation of brain respiration, but a pronounced depression. This result is in agreement with other reports[9,10] which indicate that anticholinesterase substances in massive systemic doses depress brain oxygen uptake. The exact mechanism whereby anticholinesterase compounds depress cellular respiration remains to be determined. However, it is interesting to note that some sympathomimetic drugs in high concentrations also cause a reduction in cerebral metabolism[11].

Table 2. The effect of neostigmine and physostigmine on the oxygen uptake in rat cerebral cortex slices

Treatment* (mg/kg)	QO_2 (μM O_2/g/h)**	Change of controls (%)
Saline	71.6±4.3	-
Neostigmine		
(0.025)	69.4±3.9	−3.0
(0.1)	70.4±4.2	−1.6
Physostigmine		
(0.3)	65.7±3.8	−8.3
(0.4)	58.9±2.1	−17.7***
Physostigmine (0.4)+		
Atropine (10.0)	66.2±4.2	−7.7

* See results. ** The figures represent the mean value (of 10–15 experiments)±SE. *** $p<0.01$.

1 This work was supported by a grant from Serbian Republic Scientific Fund (ZMNU SR Srbija), Belgrade (Yugoslavia).
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Effect of dichloromethane on the sciatic motor conduction velocity of rats

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Summary. There is a correlation between dichloromethane dosis (X) of 1–6 mmole/kg administered i.p. to rats and the sciatic motor conduction velocity (Y): $Y=57.1-1.091\,X$. The correlation coefficient 'r' is 0.437 ($p<0.01$). Presumably, the decrease of nerve conduction velocity is caused by the endogenous carbon monoxide production due to dichloromethane biotransformation.

There are 2 aspects which prompted us to study the effect of dichloromethane (CH_2Cl_2) on motor nerve conduction velocity of rats: (a) Carbon monoxide (CO) induces a decrease of conduction velocity[1-3] and (b) an increase of endogenous CO production and in blood carboxyhemoglobin (COHb) concentration was observed when humans or laboratory animals were exposed to CH_2Cl_2[4-21].

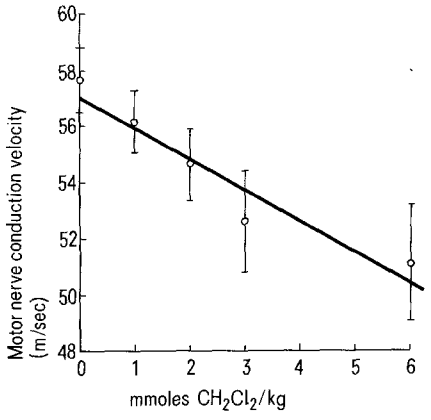
Methods. Male albino rats of our colony-bred strain weighing between 160 and 200 g (age: 60 days) were used. They were maintained on standard laboratory diet and tap water ad libitum. CH_2Cl_2 was administered by i.p. injection. The rats were anaesthetized by hexobarbital and the sciatic motor conduction velocity (SMCV) determined according to the method of Glatzel et al.[22] at room temperature (24±1 °C). COHb concentration in blood was determined using the equation

$$\%\ \mathrm{COHb}=\frac{75.1\ (\mathrm{ml\ CO/100\ ml\ blood})}{\mathrm{g\ Hb/100\ ml\ blood}}$$

with the CO capacity of 1.331 ml/g Hb[23]. Hemoglobin (Hb) concentration was determined as cyanmethemoglobin, CO

in blood by means of the palladium-II-chloride method[24,25]. The analysis for dichloromethane concentration in blood was done by gas chromatography after extraction with toluene, using benzene as internal standard. Blood samples were taken from retroorbital plexus. All measurements were performed 2 h after CH_2Cl_2 injection.

Results. There is a correlation between CH_2Cl_2 doses of 1–6 mmoles/kg (X) and the SMCV (Y): $Y = 57.1 - 1.091\,X$ (figure). The correlation coefficient 'r' is 0.437 ($p < 0.01$). In separate experiments we found 4.1 ± 0.5, 6.2 ± 0.3, 5.4 ± 0.7, and 6.8 ± 1.9 (controls: 0.8 ± 0.2) % COHb ($n = 5$ in each case) following injection of 1, 2, 3, and 6 mmoles of CH_2Cl_2/kg, respectively. The corresponding CH_2Cl_2 concentrations in blood are 26.6 ± 4.4, 85.3 ± 23.6, 99.4 ± 15.2, and 325 ± 81 µmoles/l.



Discussion. The predominant toxic effect of dichloromethane is its narcotic action[26]. In regard to behavioral effects of CH_2Cl_2 and CO as assessed by sensory and psychomotor performance in human exposure studies, impairment of performance was shown after 3–4 h of exposure to 300 ppm CH_2Cl_2. No comparable effects could be detected after 5 h of exposure to 100 ppm CO[27]. Winneke[27] concludes that endogenous CO production after exposure to CH_2Cl_2 cannot be considered responsible for the signs of depressant effect on the central nervous system. The results of the present experiments confirm our assumption that CH_2Cl_2 produces a decrease of SMCV indicating an effect on the peripheral nerve. The cause of this response seems to be the endogenous CO production in consequence of CH_2Cl_2 biotransformation: 9.1 ± 1.5% COHb due to CO retard the SMCV of rats by 16%[3], 6.8 ± 1.9% COHb due to CH_2Cl_2 by 11%. The cause for the discontinuity of COHb increase 2 h following increasing CH_2Cl_2 doses is still obscure. Taking in account the known SMCV decreasing properties of carbon tetrachloride[28,29], it is not possible to exclude that a direct effect of CH_2Cl_2 may play a role.

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