The neuromuscular blocking activity of M&B 15,944 in various species compared with that of suxamethonium bromide

Species	Preparation	M&B 15,944		Suxamethonium	
		i.v. ED50 (mg/kg)	Duration at ED50 (min)	i.v. ED50 (mg/kg)	Duration at ED50 (min)
Cat	Sciatic nerve tibialis muscle	0.97 (10) [a]	3.5		
		1.1 (5) [b]	3.0	0.013 (4)	4.3
	Sciatic nerve soleus muscle	1.8 (5) [b]	5.3	0.020 (4)	4.3
Dog	Sciatic nerve tibialis muscle	1.43 (4) [a]	7.5	0.02 (4)	5.6
Rhesus monkey	Sciatic nerve tibialis muscle	0.44 (2) [b]	4.0	—	—
	Sciatic nerve soleus muscle	0.28 (2) [b]	2.5	0.35 (3)	4.0
Baboon	Sciatic nerve tibialis muscle	0.34 (3) [b]	3.5	0.21 (1)	1.7
Chicken	Sciatic nerve gastrocnemius muscle	1.37 (3) [a]	5.3	—	—

Effective doses (ED50) are those required to reduce to 50% the heights of the muscle twitches produced by stimulation of the motor nerve in the anaesthetised animal. The compound was used either as the chloride or iodide. Doses refer to the cation. Figures in () refer to the number of experiments. [a] Iodide used. [b] Chloride used.

Résumé. Le M&B 15.944 (éthiodide de *p*-diméthylaminophényl heptyl cétone thiosémicarbazone) est un curarisant dont la brève durée d'action est comparable à celle de la succinylcholine chez divers espèces y compris le singe. Le méchanisme du blocage neuromusculaire provoqué par le M&B 15.944 est compétitif.

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Effect of Ketamine Hydrochloride on Oxygen and Glucose Uptake by Brain Tissue in vitro

Ketamine hydrochloride (CI-581) is a dissociative anesthesic agent which was introduced by DOMINO et al.[1]. There are contradictory data about the effect of this drug on cerebral utilization of oxygen in vivo. KREUSCHER et al.[2] reported a decrease of brain oxygen uptake in dogs treated with Ketamine hydrochloride, whereas DAWSON et al.[3] found that the drug increased the oxygen uptake, an effect which was abolished by prior administration of Thiopental. We have studied the effect of ketamine hydrochloride on the oxygen and glucose utilization by rat brain slices and brain homogenates. Since the depressing action of brain oxygen uptake elicited by some anesthesic agents is more evident when the tissue respiration has been stimulated by high potassium concentrations (GHOSH and QUASTEL[4]; TAMARIT[5]). We also studied the effect of ketamine hydrochloride at low and high potassium concentrations.

Materials and methods. Brain slices and brain homogenates were prepared from adult male albino rats (150–200 g body wt.) killed by decapitation. The slices were obtained as described by MCILWAIN and BUDDLE[6] and were incubated in Krebs-Ringer phosphate medium (pH 7.4), which contained 10 m*M* glucose and 5 m*M* or 100 m*M* potassium. Whole brain homogenates were prepared at 2–4 °C in a Potter-Elvehjen homogenizer, mixing 1 g tissue samples with 9 ml of a solution containing 0.25 *M* sucrose and 0.1 *M* phosphate buffer (pH 7.4).

Oxygen utilization at 37 °C was determined by direct manometric technique (UMBREIT et al.[7]), using a conventional Warburg apparatus with air as gas phase. Glucose uptake was estimated by measuring the glucose concentration in the medium at the end of incubation with a glucose oxidase method (SOLS and DE LA FUENTE[8]). Student's *t*-test was applied for the statistic significance of the data (SNEDECOR[9]).

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Table I. Effect of ketamine hydrochloride on oxygen and glucose uptake by brain slices

Drug concentration (M)	Potasium concentration (mM)	Oxygen uptake µl/100 mg wet tissue, during incubation (min) 15	30	45	60	Glucose (mg/100 mg wet tissue/60 min)
Control	5	14.17 ± 1.06 (28)	29.14 ± 1.57 (28)	46.75 ± 2.65 (28)	61.42 ± 2.85 (28)	1.17 ± 0.13 (11)
	100	18.92 ± 1.16 (12)	38.68 ± 1.46 (12)	60.93 ± 3.15 (12)	84.90 ± 3.58 (12)	1.66 ± 0.19 (13)
1×10^{-3}	5	18.06 ± 1.15[b] (32)	34.16 ± 2.17 (32)	54.96 ± 3.70 (32)	75.85 ± 4.45[b] (32)	1.43 ± 0.13 (11)
	100	20.75 ± 1.45 (13)	44.50 ± 2.19[a] (13)	67.67 ± 3.50 (13)	89.61 ± 4.89 (13)	1.66 ± 0.12 (13)
1×10^{-4}	5	17.45 ± 1.45 (18)	34.54 ± 1.90[a] (18)	56.50 ± 4.77 (18)	74.56 ± 6.09 (18)	1.26 ± 0.19 (12)
	100	22.57 ± 1.07[a] (13)	45.81 ± 2.24[b] (13)	71.22 ± 3.42[a] (13)	92.08 ± 3.97 (13)	1.67 ± 0.15 (13)

[a] $P < 0.05$; [b] $P < 0.02$. The figures are means ± S.E.M. In parentheses the number of slices.

Table II. Effect of ketamine hydrochloride on oxygen uptake by brain homogenates

Drug concentration (M)	No. of experiments	Oxygen uptake µl/100 mg wet mg wet tissue, during incubation (min) 15	30	45	60
Control	9	22.68 ± 1.69	39.87 ± 2.33	56.22 ± 2.72	69.75 ± 2.80
1×10^{-3}	8	20.87 ± 1.43	39.41 ± 1.64	58.23 ± 3.84	70.32 ± 2.73
1×10^{-4}	8	20.22 ± 1.53	38.47 ± 2.20	53.99 ± 2.88	69.42 ± 2.96
1×10^{-5}	9	17.21 ± 1.93[a]	35.53 ± 2.45	53.39 ± 2.81	66.71 ± 2.78

[a] $P < 0.05$. The figures are means ± S.E.M.

Results. The data on oxigen and glucose uptake by brain slices are shown in Table I. It can be seen that, in normal Krebs-Ringer phosphate medium (5 mM potassium), Ketamine hydrochloride increases the oxygen uptake by the tissue; this increase of respiration is the same (about 20%) in the drug concentrations tested ($1\times10^{-3}M$ and $1\times10^{-4}M$). The glucose uptake by the slices seems to be also enhanced in these conditions, which is more evident at the highest concentration of the drug; nevertheless, the differences in the glucose uptake between 'control' and 'experimental' slices failed to show statistic significance at the 5% level.

In Krebs-Ringer phosphate medium with high potassium concentration (100 mM), both the oxygen and glucose uptake by brain slices are about 40% increased. In these conditions, the addition of ketamine hydrochloride to the medium further raises the respiration of the tissue, but not to greater extent than at low potassium concentration. In this case, the drug does not modify the glucose uptake by the slices.

The data on oxygen uptake by brain homogenates are shown in Table II. Ketamine hydrochloride does not seem to have any significant effect on the respiration of tissue homogenates, even if it is noted that in Table II there is a statistically significant diminution ($P < 0.05$) of the oxygen uptake at a drug concentration of $1\times10^{-5}M$ in the first 15 min of incubation.

Discussion. The results of our experiments with rat brain slices agree with those obtained in vivo by DAWSON et al.[3] in the dog, both showing that ketamine hydrochloride causes an increase of oxygen uptake by brain tissue. This effect elicited by an anesthesic agent is at variance with the more common observation that central depressor drugs cause inhibition by brain oxygen utilization (QUASTEL[10]; MCILWAIN[11]), and it could be related to the stimulant and hallucinogenic properties of ketamine hydrochloride described by DOMINO et al.[1].

The enhancing effect of ketamine hydrochloride on the oxygen uptake by brain slices seems to be independent of potassium concentration in the medium of incubation. Also the enhancing effect on respiration is not always accompanied by a parallel increase of glucose uptake by the tissue. However, the fact that drug does not have any apparent effect on oxygen uptake by brain homogenates points to some action of ketamine hydrochloride on cell membrane as the basic mechanism causing the stimulation of respiration elicited in the intact tissue.

Resumen. El clorhidrato de Ketamina (1×10^{-3} M y 1×10^{-4} M) incrementa el consumo de oxígeno de cortes de cerebro de rata incubados en Krebs-Ringer fosfato conteniendo 5 mM ó 100 mM de potasio. La droga no modifica el consumo de oxígeno de homogeneizado de cerebro total.

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