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MONOAMINE OXIDASE INHIBITING PROPERTIES OF SU-11,739 IN THE RAT. COMPARISON WITH PARGYLINE, TRANYLCYPROMINE AND IPRONIAZID

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ABSTRACT

MAÎTRE, L.: Monoamine oxidase inhibiting properties of Su-11,739 in the rat. Comparison with pargyline, tranylcypromine and iproniazid. J. Pharmacol. Exp. Therap. **157**: 81–88, 1967. Su-11,739, N-methyl-N-2-propynyl-1-indanamine, is a new nonhydrazine monoamine oxidase (MAO) inhibitor. It is characterized by a very high potency *in vitro* as well as by a relatively selective lack of action on liver MAO *in vivo*. A single s.c. injection of 1.5 mg/kg of Su-11,739 caused significant MAO inhibition for at least 3 weeks in the brain while the liver recovered normal MAO activity after about 1 week. *In vivo*, Su-11,739 was found to be 15 to 25 times more potent than pargyline and to differ qualitatively from tranylcypromine and iproniazid, principally by its selectivity for MAO of the central nervous system.

Su-11,739, N-methyl-N-2-propynyl-1-indanamine, is a new nonhydrazine long-lasting monoamine oxidase inhibitor (MAOI) (personal communications from A. J. Plummer and C. F. Huebner, and Schuler). Its effects on monoamine oxidase (MAO) activity of rat organs will be described and compared with those of other widely used MAOI. The following experiments have been carried out: 1) Characterization of the general MAO inhibiting properties of Su-11,739: potency *in vitro* and *in vivo*, duration of its action after giving a single dose and its cumulative effect. 2) Comparison of Su-11,739 with iproniazid, a representative of the hydrazine group, and also with tranylcypromine and pargyline, two other potent MAOI which represent two other chemical categories. The comparison of the four MAOI has been established from their respective action on three organs: brain, liver and heart, using two substrates of MAO, tyramine and 5-hydroxytryptamine (5-HT, serotonin). Finally, in order to gain a more complete view of the potency of these inhibitors, MAO activities have been determined *in vitro* as well as *in vivo*.

METHODS. *Mitochondrial suspensions.* The organs excised from five male albino rats (160–200 g b.wt.) were washed with cold 0.25 M sucrose, pooled and homogenized in 0.25 M sucrose. Mitochondria were isolated essentially according to the method of Schneider (1959). The mitochondrial fractions were suspended in M/15 phosphate buffer, pH 7.3, for enzyme assay. These mitochondrial suspensions were prepared such that a 2.0-ml suspension was equivalent to 0.2 g of liver, 0.5 g of brain or 0.4 g of heart, respectively. The nitrogen content of the mitochondrial fractions was of the same order of magnitude (7–8 mg) when expressed in terms of grams of tissue.

MAO activity. This activity was measured by manometric techniques. The oxygen taken up by the mitochondrial suspension was determined over a period of 2 hr at 37°C in a conventional Warburg respirometer. Air was used as the gas phase. The incubation mixture contained 2 ml of the mitochondrial suspension and 0.5 ml of the substrate solution. For *in vitro* experiments an additional 0.5 ml of the inhibitor solution was added. Tyramine (Fluka) and 5-hydroxytryptamine (Fluka) were used as substrates in a final concentration of 0.01 M. The inner well contained 50% KOH. Blank values were determined by omitting the substrate from the incubation mixture. The activity of each mitochondrial suspension was determined from duplicate analyses.

In vitro experiments. The inhibitors were added to the mitochondrial suspensions prepared

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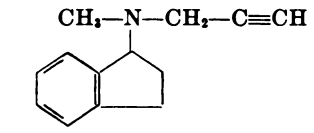
from organs of normal rats and preincubated for 30 min before additions of the substrate.

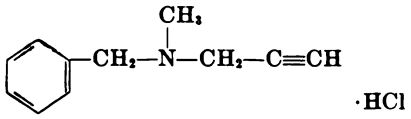
In vivo experiments. The inhibitors were administered to the rats by s.c. injection. The organs were removed after a given time and MAO activity was estimated in the corresponding mitochondrial suspension, as described above. For the comparison of the *in vivo* potencies of the four MAOI mentioned, the organs were removed for assay 16 hr after the injection. In this context, this can be considered a suitable period of time after which to study the effects of a single administration of long-acting MAOI.

Statistical methods. The statistical methods of Lord (1947) and Hogben (1964) were used.

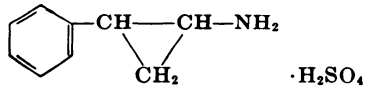
Inhibitors. The following inhibitors were used:



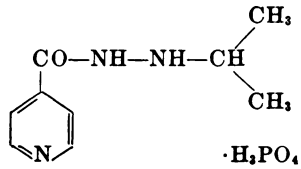
Su-11,739



Pargyline (Eutonyl)



Tranylcypromine (Parnate)



Iproniazid (Marsilid)

RESULTS. *Effects of Su-11,739 on MAO activity of liver, brain and heart in vitro and in vivo.* When Su-11,739 was added to mitochondria isolated from liver, brain or heart, it produced a dose-dependent inhibition of the MAO activity (fig. 1). When Su-11,739 was administered to the rats it also produced a dose-dependent inhibition of MAO in the three organs studied (table 1). The calculated ED50's are shown in table 2. *In vitro,* Su-11,739 exhibited the greatest potency on heart mitochondria. The inhibitions shown with liver and brain mitochondria were practically the same. The respective activities contrast with those obtained from *in vivo* experiments: after *in vivo* application the inhibition was more pronounced in the brain than in the heart, whereas relatively little inhibition was seen in the liver.

Duration of action of Su-11,739 after giving a single dose. A single s.c. application of Su-11,739 (1.5 mg/kg) produced a very long-lasting MAO inhibition (fig. 2). The MAO inhibition was always more pronounced in

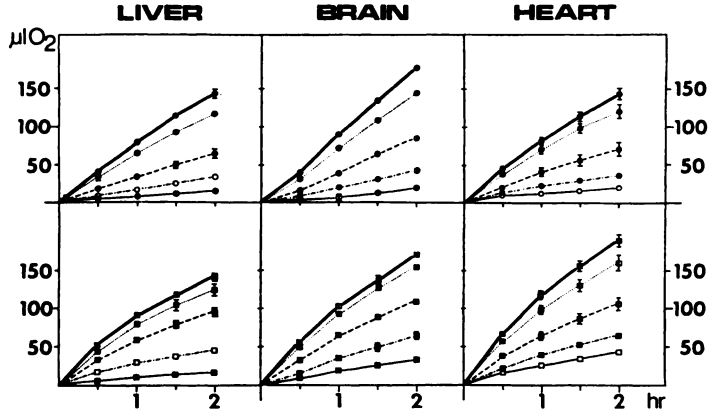


FIG. 1. MAO inhibiting potency of Su-11,739 *in vitro.* Mitochondria were isolated from livers, brains and hearts of normal rats and incubated with Su-11,739 for 2 hr. Upper half, microliters of oxygen consumed when tyramine was used as substrate; lower half, microliters of oxygen consumed when 5-hydroxytryptamine was used as substrate. ——, control values. The following concentrations of Su-11,739 were used for liver and brain: 1×10^{-8}, 3×10^{-8}, 5×10^{-8} and 7×10^{-8}, g/ml, respectively; for heart: 1×10^{-9}, 1.5×10^{-8}, 3×10^{-8} and 6×10^{-8} g/ml, respectively. Each symbol represents the mean value obtained from three to six extracts, excepting the open symbols which are mean values of two extracts. The vertical bars represent the S.E.M., which, when the horizontal limit lines are omitted, are smaller than the symbols.

the brain than in the liver. In addition, it should be pointed out that the inhibiting effect of Su-11,739 also lasted much longer in the brain than in the liver. Eight days after treatment normal values were found for liver MAO, whereas cerebral MAO was still inhibited by 50% and MAO inhibition could still be detected in the brain as long as 2 weeks after hepatic MAO had returned to control values.

TABLE 1

Percentage of inhibition produced by varying doses of Su-11,739

Organ	Control O_2 Uptake	Dose of Su-11,739 (mg/kg s.c.)[a]					
		0.03	0.1	0.3	1.5	3.0	10.0
	$\mu l/g$[b]	% inhibition					
Liver							
Tyramine	780		15.2	31.4	49.4	57.0	64.3
Serotonin	680		0	18.5	29.1	36.8	46.1
Brain							
Tyramine	354	23.8	42.0	67.8	91.4	93.5	
Serotonin	348	11.2	24.5	53.6	87.1	88.7	
Heart							
Tyramine	225	20.6	32.2	49.7	85.6	89.9	89.8
Serotonin	295	23.4	27.5	50.0	80.5	81.9	85.9

[a] Organs were removed 16 hr after giving the inhibitor. Inhibitions were calculated for an incubation period of 2 hr. Each number represents the mean value of two to five extracts.

[b] O_2 uptake for control tissues, expressed as $\mu l/g$ wet weight/2 hr of incubation (n = 4).

Cumulative effect of Su-11,739. Daily treatment with Su-11,739 (50 $\mu g/kg$/day s.c.) resulted in a cumulative effect in all three organs (fig. 3). Moreover, under these conditions the inhibition was more pronounced in the brain than in the peripheral organs, particularly the liver.

Comparison of the activities of Su-11,739 with those of pargyline, tranylcypromine and iproniazid. The activities of the four MAOI are shown in figure 4. The ED50 values are indicated in table 2. Figure 4 and table 2 show that Su-11,739 is by far the most potent *in vitro* and *in vivo* inhibitor of the cerebral and cardiac MAO in the rat. *In vivo,* and as calculated from their respective ED50's, Su-11,739 was found to be over 20 times more potent than pargyline on brain MAO, 5 to 8 times more potent than tranylcy-

TABLE 2

Doses or concentrations of Su-11,739, pargyline, tranylcypromine and iproniazid required to produce a 50% inhibition of MAO[a]

Organ	Tyramine				Serotonin			
	Su-11,739	Pargyline	Tranyl-cypromine	Iproniazid	Su-11,739	Pargyline	Tranyl-cypromine	Iproniazid
	$\mu mol/kg$				$\mu mol/kg$			
In vivo								
Brain	0.65	16	5	31	1.20	26	6.5	40
	(1)	(24.6)	(7.7)	(47.7)	(1)	(21.6)	(5.4)	(33.3)
Liver	6.50	100	12	7.25	>45	>184	15	7.5
	(1)	(15.4)	(1.85)	(1.13)	(1)	(—[b])	(—[b])	(—[b])
Heart	1.35	21	8	≥100	1.35	23	8	≥100
	(1)	(15.5)	(5.9)	(≥74)	(1)	(17.1)	(5.9)	(≥74)
	$\mu mol/l$				$\mu mol/l$			
In vitro								
Brain	0.126	0.85	3.9	144	0.180	1.8	4.4	144
	(1)	(6.75)	(31)	(1140)	(1)	(10)	(24.4)	(800)
Liver	0.126	0.68	8	8	0.170	1.6	8.8	7
	(1)	(5.4)	(63.5)	(63.5)	(1)	(9.4)	(51.8)	(41.2)
Heart	0.068	1.3	1.2	16	0.085	1.6	1.4	19
	(1)	(19.1)	(17.6)	(235)	(1)	(18.8)	(16.5)	(224)

[a] Inhibitions were calculated for an incubation period of 2 hr. Values in parentheses represent the doses or concentrations required for 50% inhibition relative to those of Su-11,739.

[b] Not calculated because Su-11,739 and pargyline were unable to produce a 50% inhibition even at subtoxic doses.

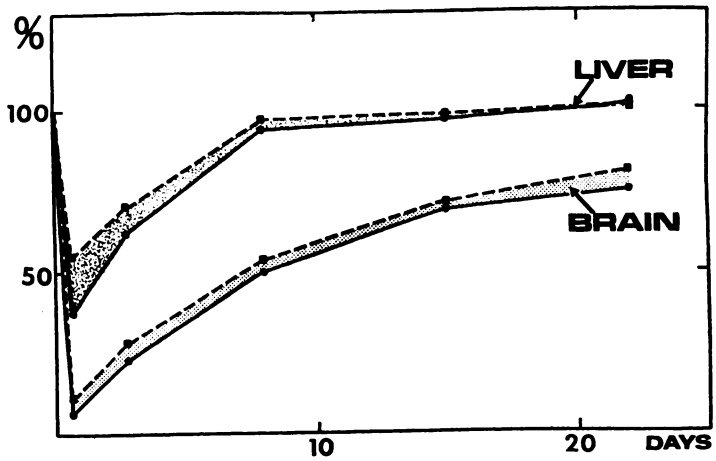


FIG. 2. Percentage of MAO inhibition produced by a single s.c. injection of Su-11,739 (1.5 mg/kg), as a function of time. - - -, inhibition found when 5-hydroxytryptamine was used as substrate; ——, inhibition found when tyramine was used as substrate. Each symbol represents the mean value obtained from two or three extracts. Inhibitions were calculated for an incubation period of 2 hr.

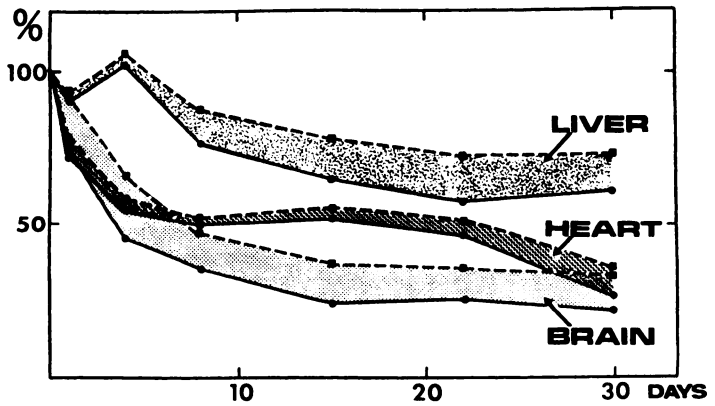


FIG. 3. Percentage of MAO inhibition produced by daily s.c. injections of Su-11,739 (50 μg/kg/day). - - -, inhibition found when 5-hydroxytryptamine was used as substrate. ——, inhibition found when tyramine was used as substrate. Each symbol represents the mean value obtained from two or three extracts. Inhibitions were calculated for an incubation period of 2 hr.

promine and 30 to 50 times more potent than iproniazid. On liver MAO, Su-11,739 was about 15 times more potent than pargyline and showed about the same activity as tranylcypromine and iproniazid. On heart MAO, Su-11,739 was 15 to 17 times more potent than pargyline, about 6 times more potent than tranylcypromine and more than 74 times more potent than iproniazid. The respective affinities of MAOI for the different organs are more apparent when we study the inhibitions produced in liver and heart by the same doses required to produce 50% inhibition of cerebral activity (table 3). From this table it is evident that Su-11,739 showed *in vivo* the most selective MAO inhibition in the brain.

Specificity of the four MAOI toward substrates. Mitochondrial suspensions do not oxidize tyramine and 5-hydroxytryptamine equally; the volume of oxygen consumed by a mitochondrial suspension in the presence of tyramine can differ significantly from that consumed by the same mitochondrial suspension in the presence of 5-hydroxytryptamine under otherwise identical conditions. In control experiments the ratio of the 5-hydroxytryptamine activity to the tyramine activity (5-HT/tyr) was 1.00 in the brain, 0.86

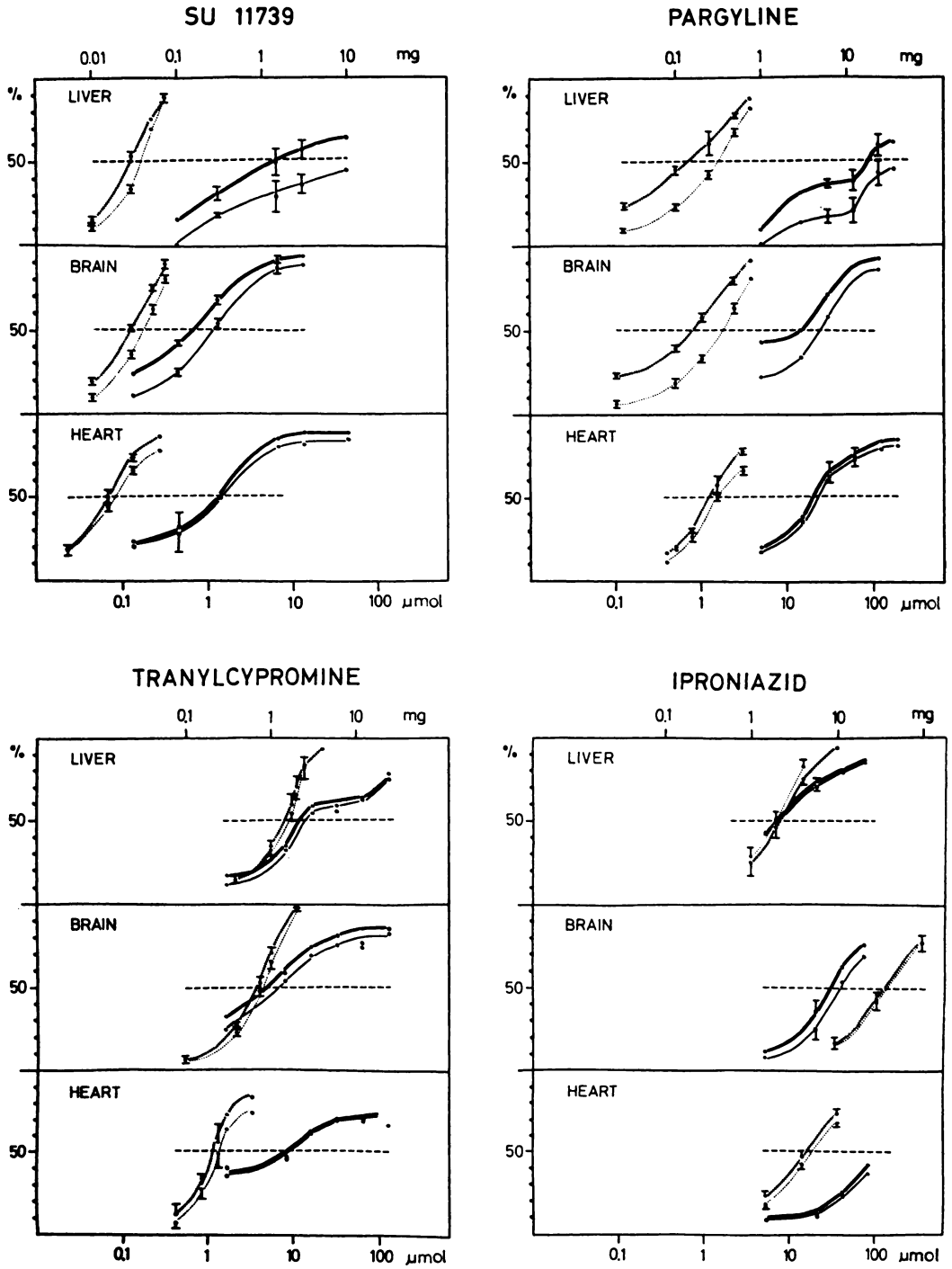


FIG. 4. MAO inhibiting properties of Su-11,739, pargyline, tranylcypromine and iproniazid *in vitro* and *in vivo*. Abscissae: Inhibitor doses or concentrations, expressed in micromoles per kilogram (*in vivo*) or micromoles per liter (*in vitro*). Ordinates: percentage inhibition. ——, tyramine used as substrate *in vivo*; ——, 5-hydroxytryptamine used as substrate *in vivo*; -----, tyramine used as substrate *in vitro*; ·····, 5-hydroxytryptamine used as substrate *in vitro*. Each symbol represents the mean value obtained from two to six extracts. Inhibitions were calculated for an incubation period of 2 hr.

TABLE 3

Relative activities of Su-11,739, pargyline, tranylcypromine and iproniazid on brain, liver and heart MAO[a]

Organ	Tyramine				Serotonin			
	Su-11,739	Pargyline	Tranyl-cypromine	Iproniazid	Su-11,739	Pargyline	Tranyl-cypromine	Iproniazid
	% inhibition				*% inhibition*			
In vivo								
Brain	50	50	50	50	50	50	50	50
Liver	20	31	25	78	16	16	26	80
Heart	37	40	44	18	46	58	47	24
In vitro								
Brain	50	50	50	50	50	50	50	50
Liver	52	55	25	>90	56	54	25	>85
Heart	72	33	>85	>80	73	54	>75	>70

[a] Numbers were calculated from figure 4. They represent the percentage of inhibition of liver and heart MAO activities for doses or concentrations producing a 50% inhibition in the brain.

TABLE 4

Effect of Su-11,739 on the ratio 5-HT/tyr[a]

Organ	Su-11,739	Ratio after Incubation for			
		30 min	60 min	90 min	120 min
	mg/kg				
Liver	0	1.01 ± 0.010	0.94 ± 0.010	0.88 ± 0.008	0.86 ± 0.009
	0.1	1.29	1.16	1.06	1.02
	0.3	1.17	1.12	1.05	1.01
	1.5	1.39	1.37	1.26	1.21
	3	1.37	1.38	1.32	1.26
	10	1.34	1.41	1.33	1.29
Brain	0	1.31 ± 0.019	1.14 ± 0.011	1.05 ± 0.012	1.00 ± 0.014
	0.03	1.45	1.32	1.22	1.16
	0.1	1.91	1.57	1.41	1.30
	0.3	2.09	1.70	1.58	1.44
	1.5	—[b]	1.80	1.59	1.49
	3	—[b]	1.42	1.40	1.74
Heart	0	1.55 ± 0.034	1.38 ± 0.025	1.30 ± 0.027	1.27 ± 0.026
	0.03	1.33	1.23	1.20	1.22
	0.1	1.68	1.43	1.38	1.35
	0.3	1.48	1.32	1.28	1.26
	1.5	1.79	1.67	1.66	1.72
	3	—[b]	2.87	2.18	2.26
	10	—[b]	2.07	1.79	1.76

[a] Rats were pretreated with a single s.c. injection of Su-11,739. The mitochondrial fractions of the organs were prepared 16 hr later and incubated as described in the text.

[b] Not calculated because the volume of oxygen taken up was very low: <15 µl with 5-hydroxytryptamine as substrate.

in the liver and 1.27 in the heart, for a 2-hr incubation period. For all organs the ratio 5HT/tyr diminished progressively with time of incubation (table 4), thus indicating that 5-hydroxytryptamine is deaminated more rapidly than tyramine at the beginning of an experiment and, after as short a period as 30 min later, the rate of tyramine deamination is relatively enhanced.

The ratio 5-HT/tyr can be influenced by the MAOI. After treatment of the rats with Su-11,739 the ratio was definitely increased in all organs (table 4). It was increased in a similar manner after adding graded concentration of the inhibitor *in vitro*. Thus it must be considered that tyramine oxidation by partially inactivated MAO is more sensitive to inhibition than 5-hydroxytryptamine oxidation. In table 5 the effects of the MAOI on the ratio of 5-HT/tyr are compared. Pargyline produced similar changes to those produced by Su-11,739; it increased the ratio markedly in all organs, *in vitro* and *in vivo*. Tranylcypromine increased this ratio only slightly in the brain and in cardiac mitochondria *in vitro*. Iproniazid produced a small increase of this ratio in the brain *in vivo;* it increased the ratio significantly when incubated with cardiac mitochondria and even decreased it in the case of liver at the highest concentration, tested *in vitro* and *in vivo*.

Discussion. Su-11,739 qualitatively resembles pargyline but it is more potent, especially in its ability to inhibit cerebral MAO. The effects of iproniazid are very different, whereas tranylcypromine occupies a somewhat intermediate position, *i.e.*, Su-11,739 and pargyline *in vivo* inhibited the cerebral MAO more than the hepatic MAO. Tranylcypromine produced similar but less pronounced ef-

TABLE 5

Effects of Su-11,739, pargyline, tranylcypromine and iproniazid on the ratio 5-HT/tyr[a]

Organ	Su-11,739				Pargyline				Tranylcypromine				Iproniazid			
	In vitro		*In vivo*		*In vitro*		*In vivo*		*In vitro*		*In vivo*		*In vitro*		*In vivo*	
	Dose	Ratio	Dose	Ratio	Dose	Ratio	Dose	Ratio	Dose	Ratio	Dose	Ratio	Dose	Ratio	Dose	Ratio
	g/ml $\times 10^{-8}$		*mg/kg*		*g/ml* $\times 10^{-7}$		*mg/kg*		*g/ml* $\times 10^{-7}$		*mg/kg*		*g/ml* $\times 10^{-6}$		*mg/kg*	
Liver	1	1.05	0.3	1.01	0.25	1.02	3	1.08	4	0.88	0.3	0.92	1	0.96	1.5	0.87
	3	1.43	1.5	1.21	1	1.24	6	1.13	10	0.87	1.5	0.89	2	0.91	6	0.90
	5	1.30	3	1.26	2.5	1.27	12	1.11	17.5	0.97	3	0.95	4	0.70	12	0.92
	7	1.05	10	1.29	5	1.25	24	1.19	20	1.04	12	0.84	—	—	24	0.69
Brain	1	1.08	0.03	1.16	0.2	1.25	3	1.33	1	1.01	0.3	1.11	10	0.98	1.5	1.05
	3	1.28	0.1	1.30	1	1.37	6	1.44	4	1.09	1.5	1.10	30	0.99	6	1.10
	5	1.47	0.3	1.44	2	1.61	12	1.66	7.5	1.16	3	1.22	100	0.95	12	1.24
	7	1.71	1.5	1.49	5	1.78	24	1.93	10	1.27	12	1.11	—	—	24	1.27
Heart	0.5	1.33	0.03	1.22	1	1.34	3	1.31	1.5	1.40	0.3	1.39	1.5	1.42	1.5	1.39
	1.5	1.51	0.1	1.34	1.5	1.37	6	1.41	2.5	1.64	1.5	1.25	4	1.43	6	1.25
	3	1.76	0.3	1.36	3	1.57	12	1.36	3	1.85	3	1.25	10	1.69	12	1.30
	6	2.18	1.5	1.72	6	2.00	24	1.72	6	2.29	12	1.29	—	—	24	1.39

[a] Ratios were calculated for an incubation period of 2 hr. Control values are shown in table 4.

fects. Iproniazid, in contrast, produced a much greater inhibition of hepatic MAO than of cerebral MAO.

Comparison of the *in vitro* and *in vivo* activities emphasizes the important possibility of preferential accumulation of the inhibitors in different tissues. It would be erroneous to assume a certain activity *in vivo* from the data obtained by *in vitro* experiments, since these data do not show to what extent the inhibitors enter the cells, nor do they indicate how long these inhibitors are retained in the tissues in an active form. It is not possible to make any assumption, even if the MAOI, for instance Su-11,739 and pargyline, present similar properties. The different activities obtained *in vitro* and *in vivo* for each inhibitor become more apparent when the number of micromoles of inhibitor added to a liter of mitochondrial suspension is related to the number of micromoles administered per 1 kg b.wt.

As shown in table 6, Su-11,739 was 5.1 times more active *in vitro* than *in vivo* on brain MAO, and it was 51 times more active *in vitro* than *in vivo* on liver MAO. Since Su-11,739 showed the same potency *in vitro* on both cerebral and hepatic mitochondria, it must be assumed that *in vivo*, 16 hr after application, the inhibitor was available for brain MAO sites in an effective concentration 10 times greater than for liver MAO sites. Table 6 shows further that the ratios varied considerably from organ to organ for any one inhibitor and from inhibitor to inhibitor for any one organ.

TABLE 6

Ratios of the in vitro activities to in vivo activities of the four MAOI[a]

Inhibitor	Brain	Liver	Heart
Su-11,739	5.1	51.0	19.9
Pargyline	18.8	147.0	16.2
Tranylcypromine	1.3	1.5	6.7
Iproniazid	0.2	0.9	≥6.2

[a] Ratios were calculated from the respective doses or concentrations required to produce a 50% MAO inhibition (fig. 4) when tyramine was used as substrate.

It is particularly interesting to note that iproniazid was relatively more potent *in vivo* than *in vitro* on brain MAO. This effect could be due to a selective accumulation as well as to a very slow metabolic rate of the inhibitor in the brain or to the formation of an active metabolite which could also disappear more slowly from the brain than from peripheral organs. The latter explanation is favored by studies of Seiden and Westley (1963) and of Smith *et al.* (1963). These

authors have shown independently that iproniazid is converted to the MAOI isopropylhydrazine, or to a more highly oxidized product derived from isopropylhydrazine, when incubated with rat brain mitochondria (Seiden and Westley, 1963) or with guinea-pig liver mitochondria (Smith *et al.*, 1963).

In vivo experiments, of course, give a more adequate picture of the pharmacologic effects which one might expect from these inhibitors. This view has been substantiated by another type of *in vivo* experiment using a characteristic property of MAOI, namely the reversal of the sedative effect of reserpine or reserpine derivatives to one of stimulation (Plummer and Furness, 1963). Su-11,739 has been found to cause such a reversal and, in comparative experiments where graded doses of pargyline and of Su-11,739 have been administered, it has been found to be at least 20 times more effective than pargyline (Huebner *et al.*, 1966). This observation agrees with the values presented here, obtained from the direct determination of MAO activity in the brain after pretreatment of animals with Su-11,739 or pargyline.

The present results, obtained from preparations of various tissues, show clear differences in substrate specificities and inhibitor sensitivities. The experimental design has not been established in order to elucidate some characteristics of the heterogeneity of the MAO. Nevertheless, the differences noted provide further evidence that various tissues of the same animal species contain more than one single MAO and that the proportions of the different MAO vary considerably from one organ to another. This has already been suggested by other multiple substrate and/or inhibitor studies (Blaschko *et al.*, 1937; Weiner, 1960; Sarkar and Zeller, 1961; Kobayashi and Schayer, 1955; Oswald and Strittmatter, 1963; Gorkin *et al.*, 1964; Severina and Gorkin, 1965).

In conclusion, Su-11,739 has been shown to be a very potent MAOI with long-lasting and cumulative inhibiting capacities. Its effects on cerebral MAO were more pronounced and long-lasting than those on hepatic MAO. This selectivity for MAO of the central nervous system was also demonstrable with pargyline but to a lesser extent. The effects of tranylcypromine and of iproniazid are qualitatively and quantitatively different, *e.g.*, they show a relatively higher affinity for liver MAO.

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