INCREASE IN ANTI-5HT ACTIVITY BY 1-METHYLATION OF CLAVINE-TYPE ERGOT ALKALOIDS

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In the previous paper (1), we reported that the clavine-type ergot alkaloids including agroclavine, elymoclavine and their dihydro derivatives had moderate anti-5HT activity *in vitro* and *in vivo*. Recently it has been described by Fanchamps *et al.* (2) that methylation at 1-position of several lysergic acid derivatives showed more active anti-5HT property than their original compounds.

From these results, we have also tested how 1-methylation of the clavine-type alkaloids modifies the anti-5HT property of the original ones. The methods employed were the isolated rat's uterus,

TABLE 1. Chemical structures of clavine-type ergot alkaloids and their 1-methyl derivatives.

Compounds	Abbreviation	Chemical structure		
		R ₁	R ₂	double bond
Agroclavine	AGR	H	CH ₃	8-9
1-Methyl-agroclavine	MAGR	CH ₃	CH ₃	8-9
Dihydroagroclavine	DHA	H	CH ₃	—
1-Methyl-dihydro-agroclavine	MDHA	CH ₃	CH ₃	—
Elymoclavine	ELY	H	CH ₂ OH	8-9
1-Methyl-elymoclavine	MELY	CH ₃	CH ₂ OH	8-9

TABLE 2. Anti-5HT activities *in vitro* and *in vivo*.

Compounds	Anti-5HT activities			
	<i>In vitro</i>	<i>In vivo</i>		
	Isol. rat's uterus relative activity	5HT-edema of rat's hind paw ED 50 mg/kg s.c.	5HT pressor of dog's b.p. relative activity	5HT pressor of dog's b.p. ED 50 µg/kg i.v.
AGR	13.7	7.0	3.6	50
MAGR	72.9	2.6	9.6	50
DHA	2.8	4.0	—	—
MDHA	23.5	2.0	12.5	—
ELY	9.2	4.3	5.8	100
MELY	157.7	0.88	28.4	30
Methergine*	64.5	0.21	120.0	—
Deseril**	162.0	0.038	651.0	12
LSD-25	100.0	0.25	100.0	—

* Lysergic acid butanolamide

** 1-Methyl-lysergic acid butanolamide

edema of rat's hind paw and blood pressure of dog for determination of maximal anti-5HT activity, and the onset and duration of the action were measured by varying the time-interval between treatment of antagonists and 5HT using rat's hind paw.

As shown by the data in Table 2, 1-methylation generally increased the anti-5HT activity of the original alkaloids 5-10 times *in vitro*. Especially 1-methyl-clymoclavine (MELY) was the most potent in this type of derivatives and nearly the same active as Deseril which has been known as the most potent 5HT-antagonist. However, judging from the rapid elimination of anti-5HT activity of MELY washing with normal Tyrode solution *in vitro* and the fast onset and short duration of its action *in vivo*, it can be suggested that 1-methyl derivatives of the clavine-type ergot alkaloids may have relatively loose binding to 5HT-receptor and a fast degradation and/or excretion in comparison with 1-methyl derivative of lysergic acid butanolamide.

REFERENCES

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