slightly more potent than 4-ethyl. Isopropyl was the least active of the derivatives tested causing only slight disruption at 4 mg/kg. It is noteworthy that the anti-5-hydroxytryptamine activity of the diisopropylamide of lysergic acid is much less than the dipropylamide[7]. In the case of both propyl and butyl derivatives a branched chain must not be complementary to the binding site for these compounds because iso-propyl is the least potent derivative in the series and tertiary butyl is inactive.

Discussion. The peripheral pharmacology of these substances is obviously quite different from their CNS properties perhaps suggesting a unique 5-HT receptor in the brain. The glaring example of this is 2-Bromo-LSD (BOL) which is a powerful uterine 5-HT antagonist[7] but has almost no hallucinogenic activity. Our results are in marked distinction to the effects reported by KULKARNI[12] on the behavior of mice. He reported that the 4-isopropyl analog was much more potent than the 4-ethyl or 4-methyl analog. We find that 4-isopropyl substitution gives rise to the least potent compound of the series. Given the comparison of the 6-membered rings of DOM and the hallucinogenic tryptamine moiety, it might be predicted that 4-methoxy-7-methyl-N,N-dimethyl tryptamine would be the hallucinogenic tryptamine analogue of DOM. If it can be shown that addition of a 7-methyl group to 5-methoxy-N,N-dimethyltryptamine results in a significant increase in hallucinogenic potency then this would be more proof of a common receptor mechanism. It will also be interesting to see if the effects of 4-substitution as reported in this paper would show the same relationship if substituted at C^7 in the tryptamine series.

Properties of 2,5-Dimethoxy-4-alkyl-amphetamines

Alkyl group	m.p.[a] HCl salt (°C)	Lit. m.p.[a] (°C)	Lit. reference
4-Ethyl	192–193	195	10
4-n-Propyl	181–182	182.5–183	11
4-Isopropyl	182–183	[b]	12
4-n-Butyl	145–147	—	[c]
4-t-Butyl	162–163	168	11
4-n-Amyl	139–140	—	[c]

[a] m.p., melting point. [b] Kulkarni[12] reported behavioral effects of this compound but no chemical properties or method of synthesis. [c] New compound.

Résumé. Le comportement des rats a été fortement influencé par des dérivés de la 2, 5-diméthoxyamphétamine Le mécanisme possible de l'action des hallucinogènes est discuté.

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Isoprotenerol Induction of Pineal Serotonin N-Acetyltransferase in Normotensive and Spontaneously Hypertensive Rats

Administration of β-adrenergic blockers during the development period of hypertension in spontaneously hypertensive rats delays the onset of the hypertension and prevents the development of pathological lesions[1]. Our preliminary studies have shown that the β-adrenergic stimulator isoprotenerol has a higher necrogenic effect on the myocardium of spontaneously hypertensive (SH) than of normotensive (N) controls. The common denominator of both observations might well be an altered reactivity of the beta receptor system to catecholamines in SH rats. Suppression of manifestations of this altered reactivity by beta-blockers would prevent the development of pathological lesions.

To test this hypothesis, we have chosen as a model system the enzyme forming the precursor of melatonin in the rat epiphysis, serotonin N-acetyltransferase[2]. β-adrenergic agonists induce more than a 10-fold increase in the activity of this enzyme, both in vitro in epiphyses maintained in tissue culture[3] and in vivo[4]. Administration of β-blockers suppresses this induction. We administered isoprotenerol to SH and N rats and followed the degree of induction of serotonin N-acetyl transferase in the epiphyses of both groups of animals.

Table I. Dependence of the degree of induction of serotonin N-acetyltransferase on the dosage of isoprotenerol

Dosage of isoprotenerol (mg/100 g b.w.)	Activity of serotonin N-acetyltransferase (pmoles of products per h/mg)
0	160 ± 15
0.2	1840 ± 360
0.5	1767 ± 272
1.0	1961 ± 40

Values presented are means from 5 animals ± SE. There were no significant differences between the experimental groups.

Materials and methods. Wistar-Konárovice normotensive and Wistar-Kyoto (the Okamoto-Aoki strain) spontaneously hypertensive rats were used. At least 1 week before the experiment, the animals were maintained on a standard regime of 6–18 h light and 18–6 h darkness. Isoprotenerol (Isuprel hydrochloride, Winthrop Products Co.) was administered s.c. at 10 h, and again at 12 h to experimental animals in a dose of 0.2 mg/100 g b.w. A control group received the same volume of physiological saline. At 14 h, both experimental and control animals were killed, the epiphyses were rapidly removed, weighed and placed on dry ice. Within 20 h of killing, the activity of serotonin N-acetyltransferase was determined by a modification of the method of KLEIN and WELLER[5]

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Table II. Induction of serotonin N-acetyltransferase by isoprotenerol in the epiphyses of normotensive (N) and spontaneously hypertensive (SH) rat males and females

	Group	Dosage	Activity of serotonin N-acetyltransferase (pmoles of products per h/mg)
Males	N	Physiological saline	258 ± 14
	N	Isoprotenerol	3405 ± 240
	SH	Physiological saline	197 ± 18
	SH	Isoprotenerol	6196 ± 400
Females	N	Physiological saline	183 ± 13
	N	Isoprotenerol	2588 ± 340
	SH	Physiological saline	162 ± 15
	SH	Isoprotenerol	4023 ± 510

Values given are means from 5–7 animals ± SE. After administration of physiological saline there was a significantly higher activity in N males than in SH males ($p < 0.02$). in N females ($p < 0.01$) and SH females ($p < 0.001$). After administration of isoprotenerol there was a significantly higher activity in SH males than in N males ($p < 0.001$), in SH females than N females ($p < 0.05$), in SH males than in SH females ($p < 0.001$) and in SH males than in N females ($p < 0.001$).

described elsewhere[6]. The selected dose of 0.2 mg isoprenaline/100 g b.w., given 4 and 2 h before killing the animals, produced a maximal induction of serotonin N-acetyltransferase in the epiphyses of normotensive, 91-day-old females (Table I). The induction of N-acetyltransferase by isoprotenerol was investigated in N and SH males at age 87 days and in females in the age range 95–100 days. The significance of differences between different control and experimental groups was tested by the analysis of variance and Student's t-test; the 5% probability level criterion was used for the analysis of variance.

Results and discussion. The activity of serotonin N-acetyltransferase, after activation by isoprotenerol, reached practically twice the values in the epiphyses of SH males as those in N males, and more than 1.5 times the values in the epiphyses of SH females as those in N females (Table II). Control activities after administration of physiological saline were somewhat higher in the epiphyses of N than in SH males, in the females both values were the same (Table II). The induced activity of serotonin N-acetyltransferase was significantly higher in the epiphyses of SH males than in SH females. In normotensive rats there was no significant sex difference.

Exogenous, and probably also endogenous, catecholamines activate the adenyl cyclase system of pinealocytes by means of β-receptors[7,8]. The increased level of cAMP induces, by a still unknown mechanism, an increase in the synthesis of serotonin N-acetyltransferase[3,9]. The higher degree of induction of N-acetyltransferase by isoprotenerol in the epiphyses of SH rats can be conditioned by a higher activation of β-receptors, of the adenyl cyclase system or a further system mediating induction of the enzyme

If there was a higher activation of β-receptors of pinealocytes by catecholamines in SH rats, this increased activation could be produced either by a change in the sensitivity of SH rats to catecholamines- and therefore by an altered conformation of β-receptors, or by an increase in the number of β-receptors. The dosage of isoprotenerol used, 0.2 mg/100 g b.w. produced, however, maximal induction of serotonin N-acetyltransferase in N rats. Despite this, induction in SH rats was still higher. It would appear, therefore, that in the epiphyses of SH rats there is an increased density of β-receptors. This finding of an altered maximal response in induction of N-acetyltransferase is interesting in the light of the work of DEGUCHI and AXELROD[10], who showed that various amounts of endogenous or exogenous β-agonists could change the sensitivity of induction to various doses of isoprotenerol, but maximal responses remained unchanged. It is possible, therefore, that SH rats have a hereditarily increased tendency to a greater serotonin N-acetyltransferase induction, and possibly a higher tissue density of beta receptors in the epiphysis.

The reported sex differences in induction of N-acetyltransferase in the epiphyses of SH rats, and the insignificant difference in N rats, could be explained by various stages of the oestrus cycle of the females at the time of the experiment. The degree to which epiphyseal adenylcyclase can be activated by norepinephrine depends upon plasma levels of oestrogens; with high blood levels the degree of activation is very low or null[11]. If induction of N-acetyltransferase is a function of adenylcyclase activated by norepinephrine, than a similar dependence upon oestrogen levels should apply for activation of adenylcyclase and induction of N-acetyltransferase. Such a relation, however, has not been confirmed[12].

Zusammenfassung. Verabreichung von Isoprotenerol, eines β-adrenergen Agonisten, induziert einen signifikant höheren Anstieg der Aktivität der Serotonin-N-Acetyltransferase in der Epiphyse von spontan hypertensiven, im Vergleich mit normotensiven, Rattenmännchen. Derselbe Unterschied wurde auch bei Weibchen beobachtet, jedoch liegen die Aktivitätswerte bei spontan hypertensiven Männchen allgemein höher. Die durch Isoprotenerol erhöhte Induktion der Serotonin-N-Acetyltransferase erzeugt hinsichtlich der Catecholamine in den Pinealozyten von spontan hypertensiven Ratten eine veränderte Reaktivität der Achse β-Rezeptor-Adenylzyklasesystem-Serotonin-N-Acetyl transferase.

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