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Stimulation of Human Prolactin Secretion by Mescaline

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Abstract. Prolactin (PRL) and Growth Hormone (GH) secretions were studied in human serum after the oral administration of 5 mg/kg mescaline (3,4,5-trimethoxy-β-phenylethylamine) or 2,3,4-trimethoxy-β-phenylethylamine (2,3,4-TMPEA) respectively. Mescaline stimulated the secretion of PRL more than four-fold above base-line levels. Peak concentrations were found 90 – 120 min after drug intake. Five hours later serum PRL was still markedly increased. Mescaline also triggered GH secretion. There was no alteration of serum PRL and GH concentrations after intake of the non-hallucinogenic 2,3,4-TMPEA.

Key words: Mescaline-2,3,4-trimethoxy-phenylethylamine – Prolactin secretion – Humans

Since the first hypothesis of Gaddum (1953) and Woolley (1954) that indolamine hallucinogens might act on 5-HT receptors, substantial evidence from biochemical (Freedman, 1961; Freedman et al., 1970; Aden et al., 1968, 1974) neurophysiological (Aghajanian et al., 1970; Aghajanian, 1977; Haigler et al., 1973; De Montigny and Aghajanian, 1977) and behavioral studies (Winter, 1975; Schoenfeld, 1976; Kuhn et al., 1978; Nakamura and Fukushima, 1978) in animals supports the view that hallucinogenic drugs may exert their major effects by acting on pre- and/or postsynaptic 5-HT receptors in the CNS. However, there is little evidence to suggest that hallucinogens act in this way in human brain. Recently Meltzer and coworkers (1978a, 1978b) demonstrated that psychotomimetic drugs of the indolamine and mescaline types increase PRL secretion in the rat by direct stimulation of 5-HT receptors. The present study on the influence of mescaline and its non-hallucinogenic isomer 2,3,4-trimethoxyphenylethylamine on human PRL and GH secretions was undertaken to confirm these results in man.

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Materials and Methods

Subjects and Materials

The subjects consisted of healthy volunteers, four male and one female, aged 27 – 34 (31 ± 2). They had no medication for the last 4 weeks and had fasted for about 12 h before the experiment was started. All subjects were fully informed and gave a written consent. Mescaline sulphate (E. Merck, Darmstadt, FRG) and 2,3,4-trimethoxy-phenylethylamine · HCl (Aldrich Chem. Comp., Milwaukee, Wisc. U.S.A.) were dissolved in 50 ml water. Two subjects received 5 mg/kg mescaline by drinking the drug solution at about 10 a.m., three others ingested the same mg/kg dose of a 2,3,4-TMPEA · HCl solution. One subject, who received 2,3,4-TMPEA, ingested after an interval of 4 weeks the same mg/kg dose of mescaline. During the following 5 h the subjects were allowed to take water or bread. They could walk around in a non-experimental environment and were asked for a report of their hallucinogenic experiences.

Venipuncture was performed by inserting a butterfly set (Vigolette, Braun-Melsungen, FRG) into a forearm vein before drug intake. Ten milliliter blood samples were drawn into polypropylene tubes every 30 min (−30, 0, 30, 60, 90, 120) and 3, 4, and 5 h after ingestion of the drugs. The blood samples were stored at room temperature for about 3 h. After clotting, serum samples were obtained by centrifugation (15 min at 3000 × g) and stored frozen (−20° C) until they were used.

PRL and GH Determinations

All samples were analysed in duplicate on the same day. PRL and GH were determined radioimmunologically using commercially available kits of International CIS. The results were expressed in ng/ml. One nanogram CIS standard is equivalent to 14 micro U MRC 71/222 (PRL) and to 2 micro U MRC 66/217 (GH) respectively. Intra-assay coefficient of variation was below ± 5%.

Results and Discussion

Figure 1 shows the temporal response of PRL secretion to a mescaline dose sufficient to induce hallucinations

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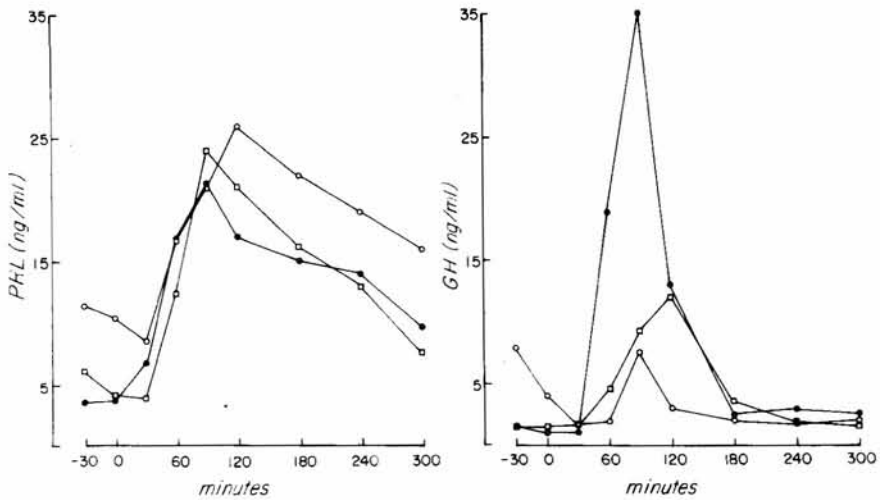

Fig. 1
Time course of prolactin (*PRL*) and growth hormone (*GH*) concentrations in human serum after the oral ingestion of 5 mg/kg mescaline

in man (that is 400 mg of mescaline sulphate for an average weight of 70 kg). Serum PRL increased more than 4-fold above base-line levels in all subjects investigated. This finding confirms recent results of Meltzer and coworkers (1978a) in rats. However, there are some notable differences. In humans a smaller oral dose of mescaline (5 mg/kg) triggered a longer lasting elevation of PRL secretion compared to the stimulation of plasma PRL in rats after injection of the 5-fold higher dose (25 mg/kg). After i.p. injection of mescaline in rats maximal concentrations were reached at 15 min with return to base-line levels by 30 min (Meltzer et al., 1978). After oral intake, peak concentrations in human serum were reached between 90 – 120 min. PRL concentrations decreased linearly, but were still markedly increased about 5 h later in all subjects ($p < 0.01$; paired students' *t*-test).

The half-life of PRL in human plasma is about 20 – 30 min (Boyd and Reichlin, 1978). Therefore the kinetics of PRL decline after stimulation of its secretion cannot be explained by the half-life of PRL in plasma, but suggest a prolonged stimulation by mescaline or mescaline metabolites on those receptors in the human brain, that are responsible for triggering PRL in man.

The beginning of hallucinations coincided in all three subjects with the maximal stimulation of PRL secretion, whereas no correlation could be established between the decreasing PRL concentrations that followed 2 h after mescaline intake and the time course and magnitude of hallucinations, which were reported by the subjects retrospectively. On the contrary two subjects reported long-lasting psychotomimetic experiences 6 – 8 h after drug intake. At this time, PRL concentrations were already probably within the range of the base-line levels.

Mescaline was also found to trigger GH secretion. However, the time course of GH stimulation differed from that of PRL. Three hours after mescaline intake, GH levels were within the range of the base-line concentrations (see Fig. 1). In addition, triggering of GH secretion differed among the subjects investigated, and could, with one exception have been just normal fluctuations. It is well known that GH is a highly stress-responsive hormone. However, as summarized recently by Brown and coworkers (1978), several kinds of emotional stress (e.g. antipication, film-induced anxiety or sexual arousal) did not trigger GH secretion in contrast to several physical stresses such as venipuncture or cardiac catheterization. Therefore it is interesting to note, that the smallest GH increase occured in the subject, who reacted most sensitively to venipuncture. Because of the different extent of GH stimulation and the small number of subjects, the present data do not provide a basis for conclusions. However, more attention should be paid to the influence of psychotomimetic drugs on GH secretion, particularly as not data seem to have been published.

In contrast to mescaline the non-hallucinogenic isomer 2,3,4-trimethoxy-phenylethylamine had no effect either on PRL or GH secretion. This fact should be interpreted cautiously because of the different distribution and metabolism of these two compounds in the brain (Seiler and Demisch, 1971, 1974). The radioactivity present in the hypothalamus and other brain regions of the mice 1 h after i.p. injection of ^{3}H-2,3,4-TMPEA consisted almost exclusively of metabolites, whereas mescaline concentrations were always higher than those of its acidic and neutral metabolites in the same brain areas (Seiler and Demisch, 1974). 2,3,4-TMPEA is rapidly metabolized by brain MAO in vivo and in vitro in contrast to mescaline, so that the non-hallucinogenic amine may never reach the receptor sites in the brain.

Evidence from animal work supports conclusion that stimulation of PRL secretion both by mescaline, 2,5 dimethoxy, -4 methylamphetamine and also by 3,4-

dimethoxy-phenylethylamine is caused by the direct serotonin agonistic action of these amines (Meltzer et al., 1978). The present finding of stimulation of PRL secretion by a single oral dose of mescaline sufficient to induce hallucinations in man seems to be the first data to support the view that mescaline may act on serotonin receptors in the human brain.

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References

Aden, N.-E., Corrodi, H., Fuxe, K., Hokfelt, T.: Evidence for a central 5-hydroxytryptamine receptor stimulation by lysergic acid diethylamide. Br. J. Pharmacol. **34**, 1–7 (1968)

Aden, N.-E., Corrodi, H., Fuxe, K., Meek, J. L.: Hallucinogenic phenylethylamines interactions with serotonergic turnover and receptors. Eur. J. Pharmacol. **25**, 176–184 (1974)

Aghajanian, G. K., Foote, W. E., Sheard, M. H.: Action of psychotomimetic drugs on single midbrain-raphe neurons. J. Pharmacol. Exp. Ther. **171**, 178–187 (1970)

Aghajanian, G. K.: Identifying indolamine hallucinogens by their preferential actions on serotonin autoreceptors. In: Animal models in psychiatry and neurology. Hanin, I., Usdin E., eds., pp. 83–89. Oxford, New York: Pergamon Press 1977

Boyd, A. D., Reichlin, S.: Neuronal control of prolactin in man. Psychoendocrinology **3**, 113–130 (1978)

Brown, R. G., Seegie, J. A., Chambers, J. W., Ettigi, P. G.: Psychoendocrinology and growth hormone: a review. Psychoendocrinology **3**, 131–153 (1978)

De Montigny, C., Aghajanian, G. K.: Preferential action of 5-methoxytryptamines on presynaptic serotonin receptors: a comparative iontophoretic study with LSD and serotonin. Neuropharmacology **16**, 811–818 (1977)

Freedman, D. X.: Effects of LSD-25 on brain serotonin. J. Pharmacol. Exp. Ther. **134**, 160–166 (1961)

Freedman, D. X., Gottlieb, R., Lovell, R. A.: Psychotomimetic drugs and brain 5-hydroxytryptamine metabolism. Biochem. Pharmacol. **19**, 1181–1188 (1970)

Gaddum, J. H.: Antagonism between lysergic acid diethylamide and 5-hydroxytryptamine. J. Physiol. (Lond.) **121**, 15P (1953)

Haigler, H. J., Aghajanian, G. K.: Mescaline and LSD: direct effects on serotonin containing neurons in the brain. Eur. J. Pharmacol. **21**, 53–60 (1973)

Kuhn, M. D., White, F. J., Apel, J. B.: The discriminative stimulus properties of LSD: mechanism of action. Neuropharmacology **17**, 257–263 (1978)

Meltzer, H. Y., Fessler, R. G., Simonovic, M., Fang, V. S.: The effect of mescaline, 3,4-dimethoxy-phenylethylamine, and 2,5-dimethoxy,4-methylamphetamine on rat plasma prolactin: evidence for serotonergic mediation. Life Sci. **23**, 1185–1192 (1978a)

Meltzer, H. Y., Fessler, R. G., Simonovic, M., Fang, V. S.: Stimulation of rat prolactin secretion by indolalkylamine hallucinogens. Psychopharmacology **50**, 255–259 (1978b)

Nakamura, M., Fukushima, L.: Effect of 5,6-dihydroxytryptamine on the head twitches induced by 5-HTP, 5-HT, mescaline and fludiazepam in mice. J. Pharm. Pharmacol. **30**, 56–63 (1978)

Schoenfeld, R. I.: Lysergic acid diethylamide- and mescaline-induced attenuation of the effect of punishment in the rat. Science **192**, 801–803 (1976)

Seiler, N., Demisch, L.: Oxidative metabolism of mescaline in the central nervous system-II. Oxidative deamination of mescaline and 2,3,4-trimethoxy-phenylethylamine by different mouse brain area in vitro. Biochem. Pharmacol. **20**, 2485–2493 (1971)

Seiler, N., Demisch, L.: Oxidative metabolism of mescaline in the central nervous system-IV. In vivo metabolism of mescaline and 2,3,4-trimethoxy-phenylamine. Biochem. Pharmacol. **23**, 273–287 (1974)

Winter, J. C.: Blockade of the stimulus properties of mescaline by a serotonin antagonist. Arch. Int. Pharmacodyn. **214**, 250–253 (1975)

Woolley, A. M., Shaw, E.: A biochemical and pharmacological suggestion about certain mental disorders. Proc. Natl. Acad. Sci. U.S.A. **40**, 228–231 (1954)

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