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Sympathoneuronal and Sympathoadrenal Activation During Ketamine Anesthesia*, **

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Summary. The effects of ketamine anesthesia (3 mg/kg i.v.) on cardiovascular parameters and noradrenaline, adrenaline and dopamine-β-hydroxylase (DBH) activity in plasma were studied in 12 patients. At 3, 6 and 10 min after induction of anesthesia, a pronounced increase in heart rate (+28%) and in systolic and diastolic blood pressure (+28% and 17% resp.) was observed. Concomitantly noradrenaline and adrenaline concentrations increased significantly from 187 to 415 ng/l and from 97 to 271 ng/l, respectively. DBH-activity in plasma remained almost unchanged. From these results it can be concluded that the well known cardiovascular stimulant effect of ketamine is due to greatly enhanced sympatho-neuronal and sympatho-adrenal activity, presumably brought about by a central mechanism of action of the drug. Furthermore, DBH-activity in plasma appeared not to be a reliable index of sympathetic activity in man.

Key words: ketamine, sympathoneuronal activity, sympathoadrenal activity; cardiovascular effects, plasma catecholamines

The cardiovascular stimulant action of ketamine is unique among general anesthetics. During the initial phase of anesthesia, ketamine elicits a pronounced rise in blood pressure and heart rate (for review see Gemperle et al., 1973; Lanning and Harmel, 1975; Rust et al., 1978). The increase in systolic and diastolic pressure in animals, as well as in man, is mainly due to enhanced cardiac output (Domino et al., 1965; Virtue et al., 1967; Schwartz and Horwitz, 1975), whereas the peripheral vascular resistance remains more or less unaltered (Virtue et al., 1967; Kreuscher and Gauch, 1967; Lanning and Harmel, 1975). The enhancement of cardiac output is brought about by a preferential increase in heart rate rather than in stroke volume (Dowdy and Kaya, 1968; Schwartz and Horwitz, 1975).

The cardiovascular stimulant effect of ketamine has been variously ascribed to an indirect sympathomimetic action, i.e., to a tyramine-like release of catecholamines from peripheral storage sites (Virtue et al., 1967; Chang et al., 1969), or to an imipramine-like inhibition of re-uptake of noradrenaline released from sympathetic nerve endings (Nedergaard, 1973; Montel et al., 1973; Miletich, 1973). On the other hand, Traber and coworkers (Traber and Wilson, 1969; Traber et al., 1970 a, b) postulated a central site of action of ketamine, by which sympathetic outflow from the central nervous system would be increased, leading to enhanced release of noradrenaline from sympathetic nerve endings.

However, the results of experiments were controversial in which attempts were made to demonstrate an increased concentration of catecholamines in peripheral blood after injection of ketamine. In dogs no alteration of circulating catecholamines was found (Peter et al., 1973; Hensel et al., 1973). Baraka et al. (1973) reported 3 patients in whom plasma noradrenaline and adrenaline rose significantly during ketamine anesthesia. On the other hand, Takki et al. (1972) found significantly enhanced adrenaline concentration in adults only when, in addition to ketamine, suxamethonium was

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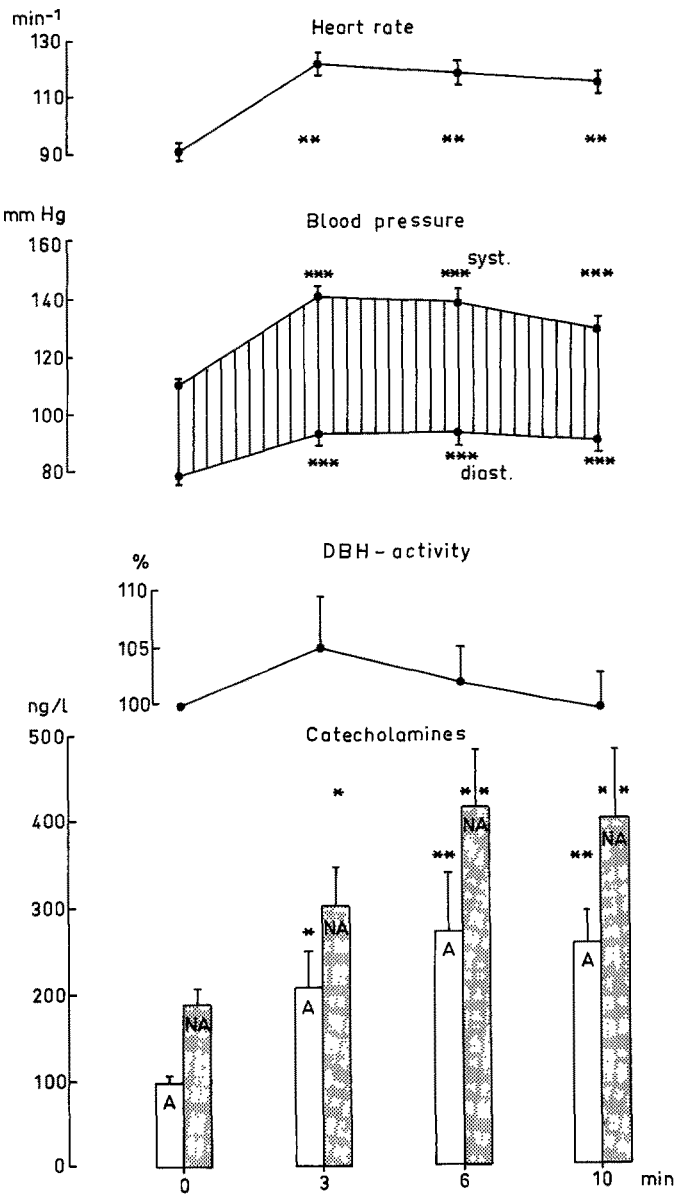

Fig. 1. Changes in heart rate, systolic and diastolic blood pressure, and adrenaline (A) and noradrenaline (NA) concentration, and in dopamine-β-hydroxylase (DBH) activity in plasma, 3, 6 and 10 min after induction of anesthesia with ketamine 3 mg/kg i.v. Mean values ± SEM of 12 patients. Significance of differences between pre-anesthetic and anesthetic values: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

used as a muscle relaxant. In contrast, Zsigmond et al. (1972) demonstrated a consistent and significant rise in circulating noradrenaline during ketamine anesthesia alone; and this effect was suppressed when pancuronium was used as a muscle relaxant (Zsigmond et al., 1972; Zsigmond and Kelsch, 1973; Matsuki et al., 1974).

It was the aim of the present study to reinvestigate the mechanism of the cardiovascular stimulatory action of ketamine. In contrast to the authors mentioned above, we replaced the fluorimetric method by a highly sensitive and specific radioenzymatic method for determination of catecholamine concentration in peripheral blood. In addition, the activity of dopamine-β-hydroxylase (DBH) in plasma was measured; this enzyme is assumed to be released from sympathetic nerve endings together with the neurotransmitter noradrenaline (for review, see Geffen, 1974).

Methods and Materials

The investigations were performed in 12 patients with good general condition and normal cardiovascular function, who were undergoing minor surgical procedures; 9 males: age 15.9 ± 5.1 years; height 162 ± 11 cm; weight 50 ± 12 kg; and 3 females: age 20 ± 4 years; height 167 ± 4 cm; weight 57 ± 4 kg.

All patients were given preanesthetic medication of i.m. atropine 0.5 mg, pethidine 1 mg/kg and promethazine 1 mg/kg 45 min before induction of anesthesia. All measurements were performed in the induction room. No intubation, no change in position and no surgical preparation was allowed.

A catheter was inserted in the cubital vein under local anesthesia. After stabilisation of blood pressure and heart rate, a control blood sample was taken (about 5 ml). Anesthesia was then induced by slow i.v. injection of ketamine 3 mg/kg over a period of 60 s; 3, 6 and 10 min later blood pressure and heart rate were measured, and serial blood samples were collected for determination of plasma catecholamine concentration and DBH-activity.

The heparinized blood samples were immediately chilled in ice and centrifuged in glutathione-SH containing tubes. Noradrenaline and adrenaline concentrations in plasma were determined by the radioenzymatic method of Passon and Peuler (1973). For the thin layer chromatographic separation of the labelled metanephrines, the solvent system n-butanol/formic acid water = 75/12.5/7.5 (V/V/V) and cellulose plates F (Merck, Darmstadt) was used. In this system it is an advantage that metanephrine has a R_f-value greater than normetanephrine, as it permits avoidance of contamination of the metanephrine fraction due to tailing of the several-fold higher concentration of noradrenaline. The fractions scraped from the plates were eluted with 4N NH_4OH and oxidised directly in counting vials. C^3H_3-S-Adenosylmethionine (spec. act. 6–8 Ci/mmol) was obtained from NEN (Dreieich). COMT was prepared from rat liver as described by Axelrod and Tomchick (1958), except that the last purification step was omitted.

DBH activity in plasma was determined radiometrically according to Weinshilboum and

Axelrod (1971), using tyramine as a substrate, as described previously (Planz and Palm 1973). $^{14}CH_3$-S-Adenosylmethionine (spec. act. 60 mCi/mmol) was purchased from NEN (Dreieich).

All results are expressed as mean ± SEM from N individual experiments. The significance of differences was calculated by the unpaired t-test.

Results

Mean values for heart rate, systolic and diastolic blood pressure, DBH activity and the concentrations of adrenaline and noradrenaline in plasma during the first 10 min of ketamine anesthesia are shown in Figure 1.

During the first 3 min of anesthesia a sharp rise in heart rate (+28%), in systolic blood pressure (+28%) and in diastolic blood pressure (+17%) was observed. All the changes were highly significant as compared to the respective pre-anesthetic values. As might have been expected, there was a tendency for all cardiovascular parameters to decrease during the succeeding 7 min.

Concomitantly, there was a significant simultaneous increase in adrenaline and noradrenaline concentration in plasma. Maximum values were reached within 6 min, the increase in adrenaline concentration being from 97 ± 9 ng/l to 271 ± 62 ng/l, and that of noradrenaline from 187 ± ng/l to 415 ± 67 ng/l.

No significant difference was found in the mean values of DBH-activity during ketamine anesthesia. Only in 4 out of 12 patients was an increase in DBH activity of 9 to 28% observed after 3 and 6 min, respectively.

Discussion

The results strongly suggest that the cardiovascular stimulant effect of ketamine results from a pronounced and sudden activation of both the sympatho-neuronal and the sympatho-adrenal systems. This was clearly demonstrated by the highly significant increase in noradrenaline *and* adrenaline concentration in the peripheral circulation. These results in part confirm and further extend data obtained by others (see 'Introduction'). Apparent discrepancies are probably due to methodological differences; for example, whereas by fluorimetric measurement adrenaline and noradrenaline can be differentially determined only with difficulty, the highly sensitive and specific radioenzymatic method of Passon and Peuler (1973) detects even a small change in the concentration of either catecholamine in plasma. In addition, and in contrast to the fluorimetric method, there is no interference by other fluorescent compounds which may be present in plasma after premedication and/or anesthesia.

The present results from man confirm the conclusions drawn indirectly from animal experiments, i. e. after application of ganglionic blocking, antiadrenergic and anticholinergic drugs (Traber et al., 1970 a, b; Constantin et al., 1972; Tanaka and Pettinger, 1974; Campbell, 1978): Ketamine acts via a central mechanism, i. e., by sympathetic activation, and by a simultaneous vagal release; when central sympathetic outflow is increased, there is a rise both in circulating noradrenaline and adrenaline (Frankenhäuser et al., 1976; Badian et al., 1978). In contrast, physical stress (Planz et al., 1975) leads almost exclusively to enhancement of sympatho-neuronal activation, i. e., to an increase only in circulating noradrenaline.

It is in accord with this conclusion that ketamine is devoid of any cardiovascular stimulant effect in decerebrate animals (Hagenau et al., 1976). Thus, the *inhibition of neuronal uptake* of noradrenaline observed in isolated organs at high concentrations of ketamine (Nedergaard, 1973; Miletich et al., 1973; Montel et al., 1973) is of no importance for its cardiovascular effects. Also, Chang (1973) could not demonstrate release of noradrenaline from isolated heart preparations. A *tyramine-like action* of ketamine (as might be predicted from its chemical constitution) would not lead to a pronounced rise in circulating adrenaline either, as such agents have no effect in vivo on the adrenal medulla (for review, see Holtz and Palm, 1966).

The observation that ketamine induces only a minor alteration in peripheral vascular resistance might be explained by the β_2-adrenoceptor stimulating effect of enhanced adrenaline secretion from the adrenal medulla. This effect, in addition to the smooth muscle relaxing effect of ketamine itself (Lundy et al., 1975; Clanachan and McGrath, 1976), antagonizes the α-sympathomimetic vasoconstrictor effect of noradrenaline released from the sympathetic nerve endings. Similarly, greater release of noradrenaline from nerve endings in the heart might induce only an increase in heart rate, whereas the anticipated increase in contractility would be antagonised by the cardiodepressant action of the drug (Dowdy and Kaya, 1968; Chang, 1973). Thus, cardiac output rather than stroke volume is preferentially increased (Tweed and Mymin, 1974; Schwartz and Horwitz, 1975).

Surprisingly, the mean value of DBH activity was not altered during ketamine anesthesia (see Fig. 1). Previous results from man have shown that during

physical exercise there is a highly significant correlation between an increase in sympathetic activity and increased DBH-activity in plasma (Planz et al., 1975). Under other experimental conditions this correlations has not been confirmed (Palm et al., 1975; for review see Grzanna and Coyle, 1978). The reason for the discrepancy as yet remains unclear. According to Grzanna and Coyle the primary and main source of DBH-activity in plasma is continous "shedding" of DBH bound to vesicular membranes; however, the relase of DBH together with noradrenaline following sympathetic stimulation might make only a negligible amount of the soluble enzyme available for exocytosis. This might in part also explain our negative result. In any case, it is apparent that DBH-activity in plasma is not a reliable index of changes in sympathetic activity in man.

Based upon the marked increase in sympathoneuronal and sympatho-adrenal activity induced by ketamine, it must be concluded that this anesthetic agent should be used cautiously, or after adequate premedication, in patients with cardiovascular disease, or with signs of adrenergic hypersensitivity, e. g. in the hyperthyroid state.

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