From the metabolites identified in the urine of rats after oral administration of ^{14}C-prenylamine the following, still incomplete metabolic pathway of prenylamine may be assumed (Figure 3):

(1) Prenylamine is hydroxylated at the amphetamine moiety yielding *p*-hydroxy-prenylamine. This compound is more water soluble than prenylamine itself and therefore can be excreted by the kidneys to a certain extent as such and as a glucuronide.

(2) Presumably by oxidative cleavage of the propyl-chain, amphetamine is formed which is partially hydroxylated to *para*-hydroxy-amphetamine. This metabolite might also be formed from *para*-hydroxy-prenylamine.

(3) The β-hydroxylated metabolites norephedrine and *para*-hydroxy-norephedrine (α-methyloctopamine) are presumably formed in the sympathetic nerves – and may act there or in the central nervous system as false transmitters[10].

Since only the D-isomers of amphetamine or *para*-hydroxyamphetamine can be hydroxylated in the β-position[11] it is D-amphetamine, which – at least in part – originates from prenylamine.

Quantitative measurements of amphetamine and its derivatives in sympathetically innervated organs and in the brain after administration of prenylamine will further elucidate the mechanism underlying its pharmacological actions[12].

Zusammenfassung. Nach oraler Verabfolgung von ^{14}C-Prenylamin (Segontin®) an Ratten werden nur Spuren des unveränderten Pharmakons im Harn ausgeschieden. Folgende Metabolite (ca. 40% der ausgeschiedenen Radioaktivität) wurden identifiziert: *p*-Hydroxyprenylamin, Amphetamin, *p*-Hydroxy-amphetamin, Norephedrin und *p*-Hydroxy-norephedrin. Auch beim Menschen konnte nach zweitägiger Behandlung mit Segontin® in therapeutischer Dosierung das Auftreten geringer Mengen von Amphetamin im Harn nachgewiesen werden.

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Serotonin Metabolism and Kinin-Forming Activity of Plasma During Anaphylactic Shock in Guinea-Pigs and Their Modification After E-Aminocaproic Acid and Trasylol Administration

The role of serotonin (5-HT) and kinins as the mediators of anaphylaxis, responsible for some symptoms of anaphylactic shock, is not explained in a synonymous way.

Probably, in the release of these substances during anaphylaxis, an important role is played by the activation of some enzymatic systems (mainly the proteolytic enzymes).

In the present experiments, the behaviour of 5-HT metabolite-5-hydroxyindolacetic acid (5-HIAA) and blood amino-oxidase connected with metabolism of this amine, as well as kinin formation in plasma, were determined after induction of the anaphylactic shock. Simultaneously the behaviour of the fibrinolytic system was observed and the influence of fibrinolysis inhibitors (ε-aminocaproic acid, trasylol) on the 5-HT and kinin release during the shock was investigated.

Material and methods. Guinea-pigs of 280–300 g body weight and of both sexes were used. Acute or chronic anaphylactic shock was induced by intracardial or i.p. injection of horse serum to sensitized animals. After induction of shock, the following points were considered: (1) The metabolism of serotonin (excretion of 5-HIAA in urine[1], amino-oxidase activity in serum[2]). (2) Kinin formation of plasma (kinin-forming, esterase activity of plasma)[3]. (3) The activity of fibrinolytic system (time of fibrinolysis, fibrinogen level)[4].

Kinin-forming activity as the expression of kininogen supply in plasma was determined pharmacologically after activation of plasma by contact with glass and dilution with water. The level of released kinins was measured on the oestrus rat uterus in comparison with pure bradykinin[5].

In some groups of guinea-pigs production of shock was preceded by i.p. injection either of ε-aminocaproic acid (EACA) or trasylol and during the shock excretion of 5-HIAA and kinin-forming activity of plasma were determined. EACA and trasylol were administrated 30 min before induction of shock, in doses of 0.5 g and 5000 U/kg body weight respectively.

The determination of 5-HIAA excretion was made during chronic shock, all the rest was performed during acute shock. The blood samples were drawn from the heart of animals at the peak of shock symptoms: about 3 min from injection of serum.

Results. The results are presented in the Table. The significant rise in 5-HIAA excretion and decrease of plasma kinin-forming activity is accompanied by an increase of plasma enzymatic activity. The rise in amino-oxidase activity connected with 5-HT metabolism and esterase activity known as a factor which releases the kinins[6] was observed simultaneously with the fibrinolytic

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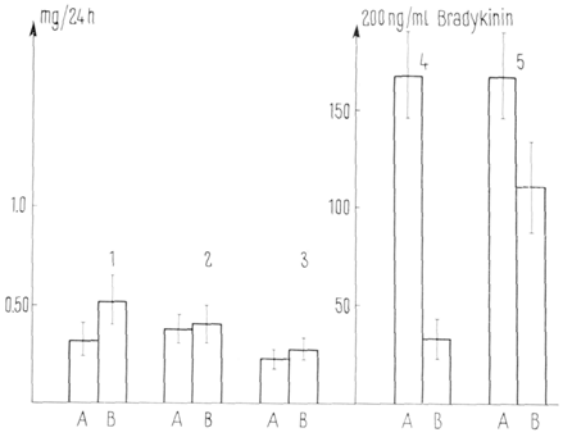
The excretion of 5-HIAA in urine, kinin-forming activity (KFA) of plasma, and activity of some enzymes and fibrinolytic system in blood of guinea-pigs during anaphylactic shock

	Control group	Shock	Index of significance
5-HIAA (mg/24 h)	0.33 ± 0.15 (18)	0.53 ± 0.25 (18)	$p < 0.01$
Amino-oxidase (O.D. × 1000)	57 ± 45 (12)	120 ± 76 (20)	$p < 0.02$
K.F.A. (ng bradykinin)	165 ± 45 (11)	32.5 ± 20 (10)	$p < 0.001$
Esterase activity (μM T.A.M.E.)	11.8 ± 1.25 (6)	14.25 ± 4.1 (12)	$p < 0.01$
Fibrinolysis activity (time of fibrinolysis)	12′ 26″ ± 1′ 18″ (15)	8′ 27″ ± 1′ 23″ (15)	$p < 0.01$
Fibrinogen (mg %)	244 ± 38 (15)	86 ± 22 (15)	$p < 0.01$

Mean values ± standard deviations. Number of animals in parentheses.



Influence of EACA and trasylol on the excretion of 5-HIAA in urine (1, 2, 3) and kinin-forming activity of plasma (4, 5) during anaphylactic shock in guinea-pigs. (A) control group; (B) shock. Excretion of 5-HIAA: (1) during the shock, (2) during the shock preceded by EACA administration, (3) during the shock preceded by trasylol administration. Kinin-forming activity: (4) during the shock, (5) during the shock preceded by trasylol administration.

system activation (Table). The results of amino-oxidase determinations show very great deviations. Some values in shock were the same as or smaller than in the control group. The rise of 5-HIAA excretion and the fall in kinin-forming activity of plasma were limited by EACA or trasylol administration (Figure).

Discussion. The role of 5-HT and kinins in anaphylaxis is not finally recognized but it has been noted that during anaphylaxis the 5-HT metabolism[7,8] and kinin system[9–11] are activated. In our investigation the rise in 5-HIAA excretion and fall in blood kininogen supply were accompanied by increase in amino-oxidase and esterase activity of the plasma, although the behaviour of serum amino-oxidase was not characteristic. However, it is necessary to remember that the blood amino-oxidase is different from the tissue one[2], which plays the most important role in 5-HT metabolism.

The observed fall in kinin-forming activity of plasma can be the result either of the release and degradation of many kinins in the first seconds of shock, or direct kininogen destruction by proteolytic enzymes.

The release of 5-HT and kinins depends on the activation of proteolytic and fibrinolytic enzymes, which supposition was supported by the fact that it can be limited by EACA or trasylol administration. On the other hand, it has been known that EACA is able to protect the life of animals in anaphylaxis[12–14] or alleviate the symptoms in the acute human allergy[15].

The protective action of EACA and trasylol is performed by enzymatic system inhibition, and our results show that in this way it is possible to obtain a decrease in the release of 5-HT, kinins and probably other mediators of anaphylaxis.

Résumé. Le choc anaphylactique provoque une augmentation du métabolisme de la sérotonine et une activation des kinines sanguines. Ces phénomènes sont causés par l'activation de certains systèmes enzymatiques, et ils peuvent être antagonisés par l'administration d'inhibiteurs de la fibrinolyse et de la protéolyse (acide ε-aminocaproïque, trasylol) avant l'induction du choc.

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