found to induce the liberation of Ca^{2+} ions bound by the mitochondrial membrane. Characteristically, on the addition of the nucleotide to loaded mitochondria, their ability to accumulate Ca^{2+} persisted for another 10 min. This suggests the absence of an effect on the binding process. This conclusion is also supported by the absence of any action of cyclic AMP on the Ca-accumulating activity of the mitochondria. It was shown previously that cyclic AMP can liberate Ca^{2+} also from the matrix of unloaded mitochondria without injury to the mechanisms of uptake [3].

Cardiac mitochondria in vitro can thus take up Ca^{2+} into the inner membrane and cyclic AMP can cause the outflow of the cation from the loaded organelles.

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EFFECT OF 3-ACETYLPYRIDINE ON ADRENOCORTICAL FUNCTION

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The corticosteroid concentration in the blood of rats was found to be lowered after injection of 3-acetylpyridine. In rats previously given 3-acetylpyridine, ACTH reduced the fall in the corticosteroid level in the blood and adrenal tissue compared with that in intact animals. Glucose-6-phosphate dehydrogenase activity in the adrenals was reduced after administration of 3-acetylpyridine. It is suggested that 3-acetylpyridine exerts its action at the adrenal level by inhibiting NADPH generation in dehydrogenase systems.

KEY WORDS: *3-acetylpyridine*; *corticosteroids*; *adrenals*.

The use of antivitamins in order to reproduce hypo- or avitaminosis is now being increasingly adopted as an experimental procedure. It does away with the need for keeping the animals on a special diet, and so rules out any effect of an unbalanced diet and abolishes the added stressor effect of starvation. The use of antivitamins is particularly promising in species of animals which are capable of endogenous synthesis of the corresponding vitamin. In particular, for the production of hypovitaminosis PP in rats, which can actively synthesize the coenzyme forms of the vitamin from tryptophan [8], more and more often nowadays 3-acetylpyridine (3-AP), an antivitamin PP, is being used [2, 5, 9].

Considering that, when interpreting the changes he has found, the investigator has often to differentiate between the effect of the vitamin deficiency itself and of the accompanying stress, it was interesting to examine how 3-AP affects adrenal function.

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TABLE 1. Effect of 3-Acetylpyridine on Corticosteroid Concentration in Blood and Adrenals (in μg %) of Intact Rats and Rats Receiving ACTH (M ± m)

Test object	Control	3-AP	ACTH	3-AP + ACTH
Blood	22.4±1.2	17.5±1.6	43.9±2.4	34.8±1.8
P_1		<0.05	<0.001	<0.001
P_2				<0.01
Adrenals	2592±202.8	2186.8±177.6	5115.5±186.5	2928.7±101.4
P_1		>0.1	<0.001	>0.1
P_2				<0.001

Note. P_1) Criterion of significance of differences from control; P_2) ditto, from previous experimental group.

EXPERIMENTAL METHOD

Experiments were carried out on male albino rats weighing 150-180 g and kept on an ordinary diet. 3-AP was injected subcutaneously (in a dose of 8 mg/kg daily for 7 days) into the rats of one group, the second group received a single dose of ACTH (5 units/100 g body weight 1 h before sacrifice), and the rats of the third group received ACTH in the same dose but after preliminary administration of 3-AP for 1 week. Intact animals served as the control. Each group consisted of eight rats. The corticosteroid concentration was determined fluorometrically [10] in the blood and adrenals. In addition, activity of glucose-6-phosphate dehydrogenase (EC 1.1.1.49) [1] was determined in the adrenals.

EXPERIMENTAL RESULTS AND DISCUSSION

The corticosteroid level in the blood of the intact animals was lowered by 3-AP (Table 1). Although the fall in the hormone concentration in the adrenal tissue under these circumstances did not reach statistical significance, it can be postulated that the antivitamin on the whole depressed adrenal function and, consequently, the production of PP insufficiency with the aid of 3-AP is not complicated by undesirable side effects of stress. This conclusion is also confirmed by the experiments in which ACTH was given. After preliminary administration of 3-AP, ACTH caused a much smaller rise in the corticosteroid concentration in the blood and adrenal tissues than in intact animals. The depression of the functional response of the adrenals to exogenous ACTH by 3-AP may indicate that this substance can limit the development of the state of stress. Since the inhibitory effect of 3-AP can be reproduced not only in intact animals, but also after ACTH loading, it can be assumed that it exerts its action at the level of the adrenals themselves.

When the activity of oxidative reactions of the pentose phosphate pathway, the main supplier of reduced NADP for corticosteroid biosynthesis in the adrenals [3, 4, 6], was investigated, a decrease in glucose-6-phosphate dehydrogenase activity was observed (684 ± 12.2 μmoles/g/h compared with 720 ± 10.4 μmoles/g/h in the control; $P < 0.05$). The inhibition of glucose-6-phosphate dehydrogenase can evidently be explained by the ability of the antivitamin to be incorporated into nicotinamide coenzymes instead of nicotinamide itself, with the formation of false coenzymes [9], blocking NADP-dependent dehydrogenases [7].

The results thus indicate that 3-AP depresses adrenal function and restricts the response of the adrenal glands to ACTH. In all probability the antivitamin exerts its action at the level of the adrenals themselves, where it inhibits NADPH generation in dehydrogenase systems.

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ROLE OF NONSPECIFIC OXIDASES OF RAT LIVER MICROSOMES IN THE BREAKDOWN OF N_1-FURANIDYLPYRIMIDINES

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N_1-(3¹-Butyrolactono)-5-fluorouracil, N_1-(2¹-furanidyl)-5-trifluoromethyluracil, and N_1-(2¹-furanidyl)-5-fluorouracil are broken down in the rat in vivo with the liberation of free 5-fluorouracil. Rupture of the C–N bond in the molecule of N_1-(2¹-furanidyl)-5-fluorouracil takes place in the liver microsomes. This process is stimulated in the presence of NADPH and is inhibited by SKF-525A. All three furanidylpyrimidines studied induce differential spectra of type I in the suspension of liver microsomes, evidence of interaction of these substances with cytochrome P-450.

KEY WORDS: *N_1-furanidylpyrimidines; metabolism; nonspecific oxidases of microsomes.*

A number of N_1-furanidylpyrimidines, with antitumor properties, have been synthesized recently at the Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR [3]. The question of the stability of the pseudoglycoside C–N bond in their molecule is of vital importance to the understanding of the biological properties of the N_1-furanidylpyrimidines. Depending on this factor, they may act as structural analogs of the pyrimidine nucleosides or as the corresponding pyrimidine bases. It has been shown that N_1-(2¹-furanidyl)-5-fluorouracil (Ftorafur) is not hydrolyzed by pyrimidine-nucleoside phosphorylases, which rupture the C–N bonds of natural nucleosides and of some of their closely related structural analogs [6]. These compounds are characterized by the possession of a hydroxyl group in the sugar residue of the nucleosides and the third carbon atom, necessary for binding with the enzymes [7]. In this respect, the N_1-furanidylpyrimidines differ significantly from the natural pyrimidine nucleosides.

In this investigation the possibility of rupture of the C–N bonds in the molecule of these compounds by nonspecific oxidases of the liver microsomes was studied with particular reference to three derivatives of N_1-furanidylpyrimidine.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred male albino rats weighing 150-200 g. Separation of the N_1-furanidylpyrimidines from their metabolites in the samples of urine was carried out by paper chromatography [1].

Microsomes were isolated from liver homogenate (2 g tissue in 4 volumes of 0.02 M Tris-HCl buffer, pH 7.4, containing 0.15 M KCl) by the method of Cinti et al. [9]. To isolate other subcellular fractions from the liver homogenate, differential centrifugation was used [8]. The biological material was standardized in relation to a definite quantity of tissue or in relation to protein content [4].

The incubation medium for studying the mechanisms of breakdown of Ftorafur contains the following ingredients depending on the aims of the experiment (in a total volume of 1 ml):

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