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5-AMINOLEVULINIC ACID SYNTHETASE INDUCTION: INHIBITORY EFFECT EXERTED BY ADMINISTRATION OF URIDINE DIPHOSPHATE GLUCOSE

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Abstract—Allylisopropylacetamide(AIA) administered subcutaneously to female Wistar rats increased 5-aminolevulinic acid(ALA) synthetase activity in liver. Uridine diphosphate glucose(UDPG) administered subcutaneously or intraperitoneally lowered ALA synthetase activity in AIA-treated rats, but related compounds such as uridine, glucose phosphate, UMP, UDP and UTP had no effect. The effect of UDPG is not attributable to its interaction with the porphyrogenic drug since ALA synthetase activity was depressed in animals treated with UDPG alone.

Allylisopropylacetamide (AIA) administration to rats not only increases 5-aminolevulinic acid (ALA) synthetase activity, but also raises ascorbic acid levels in urine [1]. High urine ascorbic acid values have been attributed to increased uridine diphosphate glucose (UDPG) dehydrogenase activity [1]. Barbital, which also stimulates ALA-synthetase activity and porphyrin excretion [2], has been reported to elevate UDPG dehydrogenase levels [3]. The observation that AIA and several other porphyrogenic drugs increase UDPG metabolism [1], prompted us to study the effects of UDPG administration in animals given a porphyrogenic chemical. This paper describes the effects of UDPG and related substances on ALA synthetase activity in the liver of intact and AIA treated rats.

MATERIAL AND METHODS

AIA was kindly supplied by Hoffman–La Roche (Basel). UDPG was obtained from Boehringer (Mannheim). Uridine, glucose-1-phosphate, uridine monophosphate (UMP), uridine diphosphate (UDP) and uridine triphosphate (UTP) were obtained from Biochemia (Milan). The reagents used in this experiment were from BDH (Milan).

Female Wistar rats weighing 100 ± 10 g were starved for 24 hr before injecting the porphyrogenic drug and were kept without food for the duration of the experiments. 4 groups of 6 animals were used in each experiment. One group of animals was kept as a control. Rats in the second group were injected subcutaneously with AIA (400 mg/kg) on two consecutive days. AIA at a concentration of 4%, was fully dissolved in water–polyethyleneglycol–ethanol (60:30:10). The third group of animals received either UDPG, uridine, glucose phosphate, UMP, UDP or UTP subcutaneously at a dose of 100 mg/kg. UDPG was also administered intraperitoneally. The fourth group of rats was treated with AIA and one of the compounds used in group three. All the animals were treated with the vehicle used for dissolving AIA.

Rats were sacrificed by decapitation 6 hr after the second AIA injection; livers were removed immediately and a portion was kept at 0° for immediate determination of ALA synthetase activity [4].

RESULTS AND DISCUSSION

AIA administration increased hepatic ALA synthetase activity in rats (Table 1, Fig. 1). UDPG, injected both subcutaneously and intraperitoneally lowered ALA synthetase activity in AIA treated animals (Table 1). The inhibitory effect of UDGP was also observed in intact animals, when the chemical was administered intraperitoneally, probably because it was more rapidly adsorbed and less hydrolized. The depressing effect of UDPG on ALA synthetase is not attributable to its interaction with the porphyrogenic drug, since it appears also in animals treated with UDPG alone. It is interesting to observe that compounds structurally related to UDPG, like uridine,

Table 1. Effects of AIA, UDPG and combined treatment on liver ALA synthetase activity

Treatment	ALA synthetase activity (ALA nM/g liver/hr ± S.E.)*	
Controls	36·50 ± 3·64	32 ± 5·73
AIA	274·49 ± 26·65	248·6 ± 60·3
UDPG	35·09 ± 3·42†	16·7 ± 2·61‡
AIA + UDPG	138·30 ± 13·81†	94·15 ± 10·25‡

* Each value is the mean ± S.E. of six animals.
† UDPG was injected subcutaneously.
‡ UDPG was administered intraperitoneally.

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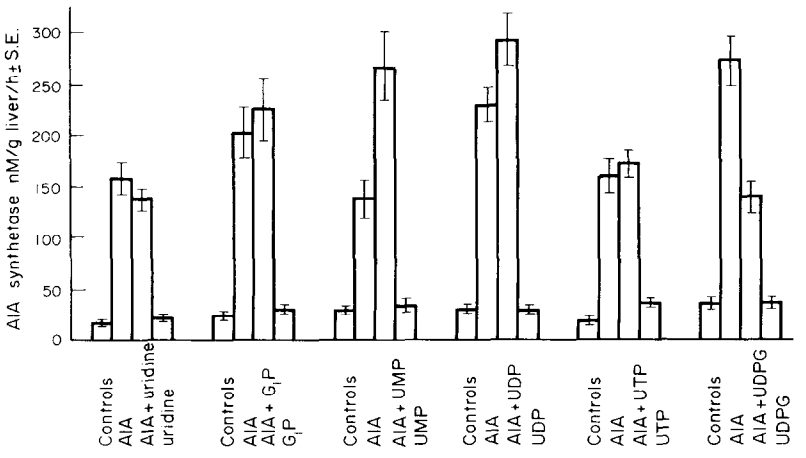

Fig. 1. Liver ALA synthetase activity in controls and in rats treated with AIA, uridine, glucose-1-phosphate, UMP, UDP, UTP or UDPG. Six different experiments are shown. Each column represents the mean ± S.E. for six animals. Uridine, glucose-1-phosphate, UMP, UDP, UTP did not depress ALA synthetase activity induced by AIA. Only UDPG markedly lowered ALA synthetase levels.

glucose-phosphate, UMP, UDP and UTP, are incapable of decreasing ALA synthetase activity in AIA treated rats (Fig. 1). A low dose of glucose linked to UDPG structure exerts an inhibitory action on ALA synthetase, while glucose alone is known to decrease ALA synthetase if administered at the high dose of 50 g/kg [5,6]. The inhibitory effect of glucose has been attributed to its ability of promoting the biosynthesis of compounds which lower ALA synthetase activity [5], like phosphorylated nucleotides [8–10].

The present results show that UDPG is a nucleotide which depresses ALA-synthetase activity similar to other phosphorylated compounds described by Gajdos [8–10], and is much more active than glucose administered alone [5]. Further experiments are needed to elucidate the mechanism of UDPG action.

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