Catecholamine Uptake, Accumulation, and Release in Acute Porphyria

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ABSTRACT Hypertension and tachycardia are well known features of acute porphyria and have been shown to be related to increased circulating catecholamines. The mechanism by which circulating catecholamines are increased was studied using the isolated perfused rat heart and human platelets as a model of adrenergic neuronal function. It was found that neither δ-aminolevulinate (ALA) nor porphobilinogen (PBG) blocked uptake or caused release in the isolated perfused rat heart. Platelets from six patients with acute prophyria, three in remission and three latent, with matching normal controls were studied with regard to their uptake of [^{3}H]norepinephrine in the presence of ALA or PBG. It was found that ALA and PBG significantly reduced uptake and accumulation of [^{3}H]-norepinephrine in patients with acute porphyria; however, no similar reduction in uptake and accumulation was observed in the platelets of normal controls. Therefore, it appears that there is a latent defect in the catecholamine uptake and (or) accumulation of platelets of patients with acute prophyria which only manifests itself in the presence of ALA or PBG. If platelet uptake serves as a model of adrenergic neuron uptake, this suggests that elevated circulating catecholamine levels during acute attacks of acute porphyria are caused at least partially by blockade of re-uptake into the sympathetic neurons.

INTRODUCTION

The hepatic porphyrias consist of acute intermittent porphyria (AIP),[1] variegate porphyria, and hereditary coproporphyria (HC). These three diseases share many common characteristics; they are transmitted as autosomal dominants, clinical exacerbations manifest themselves as similar episodes of acute neurological dysfunction, and acute episodes are associated with increased urinary excretion of δ-aminolevulinate (ALA) and porphobilinogen (PBG) (1). The acute neurological exacerbations manifest themselves with tachycardia, hypertension, abdominal pain, constipation, vomiting, bladder symptoms, and ascending paralysis which may progress to quadriplegia and respiratory failure. The findings of tachycardia and hypertension have been frequently reported in AIP, and Waldenström considered the pulse rate to be a good indication of the activity of the disease (2–10).

The pathogenesis of the hypertension and tachycardia in AIP has been studied by Schley et al. (7), who studied four patients in the acute phase and in remission. They found significant correlations between blood pressure and pulse rate with the amount of catecholamine excretion. Atuk et al. confirmed these findings in three patients with acute porphyria (11). The etiology of increased catecholamines is unclear. There are several possibilities which could account for the abnormalities: (*a*) increased release of norepinephrine (NE) and epinephrine due to pathologic changes within the sympathetic nervous system itself; (*b*) impaired metabolism of catecholamines; (*c*) impaired re-uptake of NE by the adrenergic neurons, or (*d*) some combination of the above mechanisms.

The present study was designed to investigate whether ALA or PBG, the two porphyrin precursors known to be elevated during acute attacks of acute porphyria, could either block neuronal catecholamine uptake or cause release of catecholamines. The isolated perfused rat heart was chosen because of its convenience for in vitro studies to determine whether ALA and PBG have a direct toxic effect on catecholamine metabolism. Studies were also performed on normal human platelets and platelets of patients with acute porphyria, because platelets are able to accumulate and store catecholamines by a process which resembles that of adrenergic neurons (12–14).

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[1] *Abbreviations used in this paper*: AIP, acute intermittent porphyria; ALA, δ-aminolevulinate; DMI, desmethylimipramine; HC, hereditary coproporphyria; NE, norepinephrine; [^{3}H]NE, tritiated norepinephrine; PBG, porphobilinogen; URO-S, uroporphyrinogen I synthetase.

METHODS

Rat heart experiments. Hearts from 250-g rats were removed and immediately connected to an Anderson coronary perfusion apparatus (Metro Scientific, Inc., Farmingdale, N. Y.) via the aorta (15). The normal perfusion medium contained 119.8 mM NaCl, 5.63 mM KCl, 2.16 mM $CaCl_2$, 2.10 mM $MgCl_2$, 100 mM dextrose, and 25 mM $NaHCO_3$. The solution was bubbled with 95% O_2-5% CO_2, and the temperature was maintained at 38±1°C, pH 7.32–7.45. All hearts were perfused at a constant flow of 6.0±1.0 ml/min with a Harvard perfusion pump (Harvard Apparatus Co., Inc., Millis, Mass.).

To test the influence of ALA and PBG on the uptake of NE, all hearts were equilibrated with normal medium for 30 min and then switched to a medium containing [^{3}H]-norepinephrine ([^{3}H]NE) (1.0 ng/ml of *l*-[^{3}H]NE, 3.8 Ci/mM sp. act.) with or without different concentrations of the compound to be studied. Hearts were perfused with the [^{3}H]NE-containing medium for 10 min, followed by 3 min of drug-free medium to wash out the extracellular space. 10 ng/ml ascorbic acid and 10 ng/liter EDTA were added to the perfusion medium to prevent oxidation of NE. To inhibit monoamine oxidase, 0.125 mM pargyline was also added to the perfusion medium.

Hearts were removed at the end of the perfusion, weighed, and homogenized in 5% trichloroacetic acid. The homogenates were then filtered under suction, and a 1-ml aliquot was taken for analysis by liquid scintillation spectrometry. 5 ml of the remaining filtrate was taken for isolation of [^{3}H]NE according to the technique described by Cheramy et al. (16) with some modifications. The perfusate samples were adjusted to pH 6.6–6.9 with a NaH_2PO_4-K_2HPO_4 buffer (0.01 M, pH 7.2) and then passed on an Amberlite column (Amberlite CG50 H^+ Type II, 200–400 mesh, Rohn & Haas Co., Philadelphia; purified and buffered with a NaH_2PO_4-K_2HPO_4 solution 0.2 M, pH 6.1; 2.5 cm high, 0.5 cm diameter) to separate [^{3}H]NE and [^{3}H]normetanephrine from [^{3}H]NE acid metabolites which were present in the Amberlite effluent. 1 ml of effluent was taken for analysis by liquid scintillation spectrometry. The Amberlite column was washed with 5 ml of 3:5 ethanol-H_2O and with 5 ml of water containing 1% Triton X-100 (Rohm & Haas Co.) [^{3}H]NE and [^{3}H]normetanephrine were eluted with 5 ml of 0.2 N acetic acid in tubes containing 500 μl of a protective solution (EDTA 2%-thioglycolic acid 0.6%).

Finally, [^{3}H]NE was separated from the [^{3}H]O-methylated amine by adsorption on alumina columns (15). Each Amberlite eluate was adjusted to pH 8.4 with a 0.5-ml Tris buffer and passed over a 100-mg, 0.5-cm diameter, alumina column. The alumina columns were washed with 5 ml of 0.2 M sodium acetate, pH 8.4, and then with 5 ml of water containing 1% Triton X-100. [^{3}H]NE was eluted with 1 ml of 0.2 N HCl. Eluates were collected directly into scintillation vials. For liquid scintillation counting, the 1-ml samples were placed in 10 ml of Triton-based solution containing 5.5 g of 2,5 diphenyloxazole, 150 mg of 1,4-bis-2-(5-phenyloxazolyl) benzene, and a 2:1 mixture of toluene and Triton X-100. The samples were then counted in a Packard Tri-carb liquid scintillation spectrophotometer (Packard Instrument Co., Inc., Downers Grove, Ill.). NE recoveries by Amberlite column were checked by passing known amounts of [^{3}H]NE through parallel columns and found to be 81% with a range of 75–85%. Therefore, no correction for recovery has been made.

Release of [^{3}H]NE. In these experiments, hearts from rats were connected to the perfusion apparatus as described above and perfused for 10 min with normal perfusion medium, and then for 20 min with 1.0 ng/ml of *l*-[^{3}H]NE, 3.8 Ci/mM sp act, in the perfusion medium to label the endogenous store. It was assumed that the release of [^{3}H]NE from the heart reflects release from adrenergic terminals because procedures which cause degeneration of the nerve terminals, such as the use of 6-hydroxydopamine, are known to prevent drug-induced release of [^{3}H]NE from the heart (17). After labeling with [^{3}H]NE, the hearts were switched to a NE-free medium for 12 min. They were then perfused for 2 min with normal medium containing the compound to be tested via a side arm cannula and then switched back to a drug-free medium for another 10 min. The perfusate effluents from the hearts were continuously collected and analyzed for [^{3}H]NE by liquid scintillation analysis after the suitable preparative procedures described above.

Platelet experiments. Six acute porphyria patients (three in remission and three latent) and six age-matched normotensive normal controls were selected for the study. Patients were characterized further by the determination of erythrocyte uroporphyrinogen I synthetase (URO-S) levels, as were the normal controls (18). Platelet-rich plasma was prepared by collecting blood by venipuncture into plastic syringes containing 0.8 ml 19% wt/vol sodium citrate per each 10 ml of blood, to give a final concentration of 12.9 mM sodium citrate. Citrate was used as an anticoagulant, because Hughes and Brodie (19) have shown that EDTA impairs platelet uptake of serotonin and catecholamines. The citrated blood was then centrifuged three times for 10 min at 3000 rpm at room temperature with the platelet-rich plasma being pipetted off and pooled after each successive centrifugation. All glassware with which the platelets came into contact was made of plastic. Platelet counts were made by a light absorption particle analyzer. The platelet-rich plasma was then pipetted in 1.8-ml aliquots into 15-ml conical plastic centrifuge tubes closed with a cap, through which a tube was thrust, and was gassed with 95% O_2-5% CO_2 mixture. The tubes were held in a water bath at 37°C and rocked gently to-and-fro mechanically. 28 tubes could be incubated simultaneously. After a 10-min incubation, 0.2 ml of a solution of NE in 0.9% sodium chloride solution with or without the drug being tested was added to each tube. The tubes were incubated for 90 min, then cooled in ice, and centrifuged at 10,000 rpm in a Sorvall #2 centrifuge (Du Pont Co., Instrument Products Div., Sorvall Biomedical Div., Wilmington, Del.) at 4°C for 10 min. The supernate was then poured off from the platelet pellet, and the tubes were left to drain for a few minutes. All adhering drops of plasma in the tubes were removed with filter paper. The pellets were then resuspended in 1 ml 5% TCA, frozen and thawed once to liberate the catecholamines, and recentrifuged for 10 min at 15,000 rpm. Following centrifugation, 0.8 ml of the supernate was added to 6 ml of liquid scintillator, and the radioactivity was counted in a Packard Tri-carb scintillation spectrometer. Inasmuch as the platelets were not washed after centrifugation, [^{3}H]NE caught in the interstices of the platelet pellet was included in the estimation. Born and Bricknell (20) estimated that the volume of trapped solution was 0.352 μl/10^8 platelets. It was calculated that this volume of radioactivity would make a negligible contribution to the total uptake radioactivity; therefore, no correction has been made for it.

The time-course of catecholamine uptake and accumulation in the platelets was linear over 90 min. Similarly, incubation with [^{3}H]NE concentration (10 mM) was also linear over the same period (Fig. 1), indicating that we were studying initial uptake. Using column chromatography, our studies on the metabolism of NE demonstrated that 70.5% of the total activity was represented by free [^{3}H]NE. The

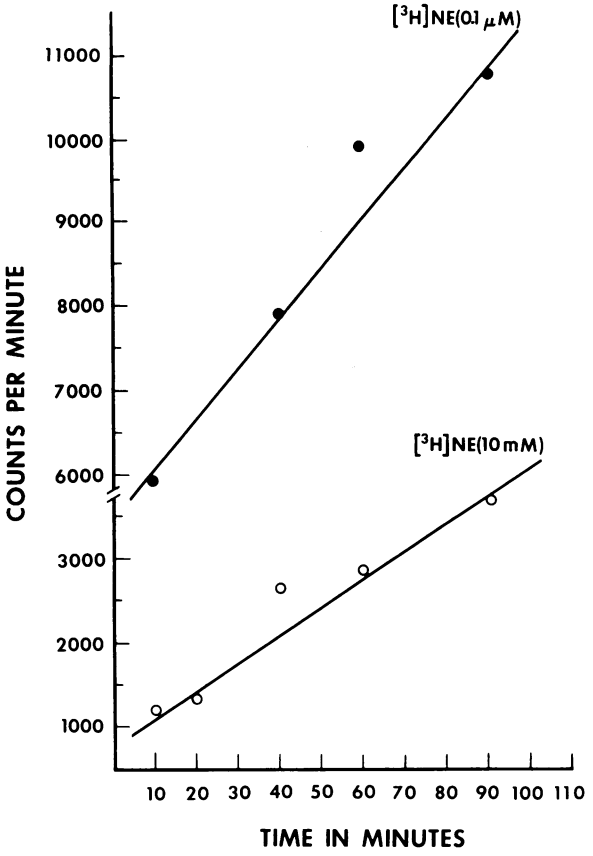

FIGURE 1 The time-course of [^{3}H]NE uptake and accumulation in normal platelets, at high and low [^{3}H]NE concentrations.

remaining 29.5% was represented by ^{3}H metabolites. This finding is consistent with that of Abrams and Solomon (12), showing that most of the NE taken up by platelets is not metabolized.

For these experiments, 1 μg of *l*-[^{3}H]NE (*l*-NE-7-H^3, sp act 3.8 Ci/mM, Amersham/Searle Corp., Des Plaines, Ill.) was diluted with cold *l*-NE in a ratio of 1:1,500 to make a solution of 100 μg *l*-NE/ml. When added to the platelet-rich plasma, the final concentration of *l*-NE was 10 μg/ml. ALA and PBG were obtained from Sigma Chemical Co., St. Louis, Mo.

Statistical analysis. Data in the test, tables and figures are given as mean±SEM. Statistical significance was determined by Student's one-tailed or pair *t* test whenever applicable.

RESULTS

Fig. 2 depicts the uptake of [^{3}H]NE into rat hearts in the presence of variance concentrations of ALA and PBG. Guanethidine, which is well known to block NE uptake into adrenergic nerve terminals, was used as a control. As can be seen, there was a significant reduction of NE uptake in the presence of 0.1 mM guanethidine as compared to normals ($P < 0.01$); however, a similar reduction in the uptake of [^{3}H]NE in the presence of various concentrations of ALA and PBG was not observed.

The possibility that ALA and PBG might increase the release of NE from adrenergic neurons was examined next. Fig. 3 shows the effect of a 2-min application of KCl with ALA or PBG on the efflux of [^{3}H]NE from rat hearts previously labeled with ^{3}H-amine. KCl produced a marked increase in the release of [^{3}H]NE (107% of the 6-min value). Neither ALA (A) nor PBG (B) in varying concentrations had any effect on the release of [^{3}H]NE.

Table I depicts the results of erythrocyte URO-S determinations. Five patients with AIP had low URO-S levels, a characteristic abnormality in this disease (21), whereas all controls had normal values. The one patient with HC manifested a level of urinary coproporphyrin diagnostic of this disease during an acute exacerbation (22), and confirmed by the normal URO-S level. The results of [^{3}H]NE uptake studies in the platelets of patients and normal subjects are shown in Table II. Absolute values for the uptake of [^{3}H]NE are 2.645±0.41 for the patients with acute porphyria as compared to 1.654±0.13 for the normal controls. When the platelets of patients with porphyria were incubated in the presence of ALA or PBG, there was a significant reduction in uptake of [^{3}H]NE which did not occur with the platelets from normal controls. With concentration of 0.1 mM PBG, there was a minimal loss of inhibition of [^{3}H]NE uptake in the patient group and a slight increase in uptake of NE in normal controls. To test the specificity of [^{3}H]NE uptake into platelets, desmethylimipramine (DMI) was used (12) and found to produce a significant inhibition of [^{3}H]NE uptake into platelets obtained from both groups.

DISCUSSION

The basic defect of AIP is a genetically determined partial lack of URO-S activity (21). Thus, when ALA synthetase (the rate- controlling enzyme in the porphyrin pathway) is induced, the porphyrin precursors (ALA and PBG) build up to high levels in the blood. In HC, the enzymatic defect has recently been shown to be decreased activity of coproporphyrinogen oxidase. Substrate compensation for this defect is not possible, however, because the activity of URO-S becomes rate-limiting with consequent accumulation of PBG and ALA (22). Since hematin feedback inhibits ALA synthetase, infusions of this compound have recently been used to treat acute attacks of AIP with successful clinical remission (23). The elevated plasma levels of both ALA and PBG were shown to return to normal with clinical remission. This implies a possible direct toxic effect of ALA or PBG in the pathogenesis of acute attacks of AIP. Other evidence in

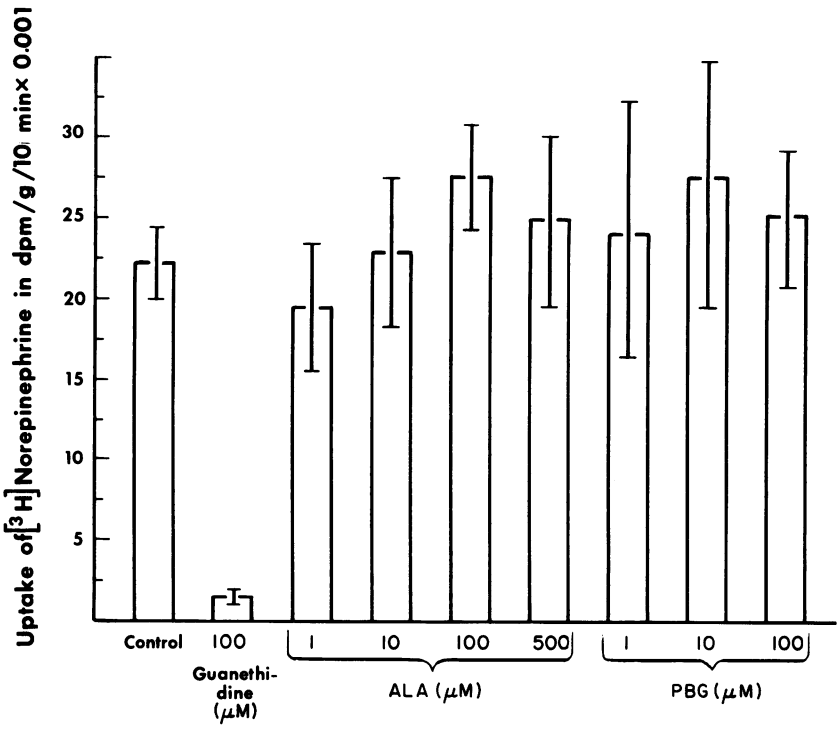

FIGURE 2 The uptake of [^{3}H]NE by the perfused rat heart in the absence (control) or presence of guanethidine, ALA, or PBG. All hearts were perfused with normal medium for 30 min and then switched for 10 min to medium containing 1.0 ng/ml of [^{3}H]NE with or without the compound being tested for its ability to block uptake, followed by a 3-min perfusion with NE and drug-free medium. The hearts were then removed and homogenized in 5% trichloroacetic acid, and the ^{3}H-NE content was analyzed as described in Methods. Data are plotted as uptake of [^{3}H]NE in disintegrations per minute per gram/10 min × 0.001. Each bar represents the mean±SEM of four to six hearts.

support of this view has recently been summarized (24).

The findings of tachycardia and hypertension are among the most frequent manifestations of attacks of AIP and HC. Ridley found persistent tachycardia in 24 of 25 patients, and hypertension in 15 of 25 during acute attacks (6). The hypertension and tachycardia were found to correlate with the amount of catecholamine excretion (7, 11). The etiology of elevated catecholamines has not been elucidated. Inasmuch as ALA and PBG are elevated during acute attacks and may be toxic, our studies were designed to examine whether either ALA or PGE could block uptake or cause release of catecholamines from adrenergic neurons.

The uptake of NE into isolated perfused rat hearts was studied first because this preparation has been well delineated as a model of sympathetic neuronal function (25). Previous studies had demonstrated no tachycardia or hypertension in the presence of these compounds in experimental animals, but their effects on catecholamine metabolism had not been studied. The results demonstrate that neither ALA nor PBG in concentrations from 1 μM to 0.1 mM block uptake or cause release of [^{3}H]NE from sympathetic neurons in this system. Concentrations of ALA and PBG in this range are found in the plasma during acute attacks of AIP (23).

Intact human platelets can be employed to test uptake mechanisms for NE (12). The platelets are capable of functioning in appropriate conditions and actively taking up NE from the medium in concentrations up to 10 μg/liter (26). Our uptake experiments using this test system revealed that neither ALA nor PBG blocked uptake or [^{3}H]NE in the platelets of normal controls. In contrast, both ALA and PBG significantly blocked the uptake of [^{3}H]NE into the platelets of patients with acute porphyria. The patients' platelets were not deficient in uptake capacity, in that their control uptake of [^{3}H]NE was actually greater than that of platelets from normal controls. The fact that PBG did not block uptake as well at the higher concentrations may have been due to its ability to polymerize in vitro to form porphyrins (5). There would be more of a tendency to polymerize at higher concentrations, and the products formed may have artifactually elevated [^{3}H]NE uptake by causing membrane damage. Hematoporphyrin has been shown to be toxic to platelet membranes in vitro (27).

Our experiments reveal that neither ALA nor PBG affect uptake or release of [^{3}H]NE in normal rat

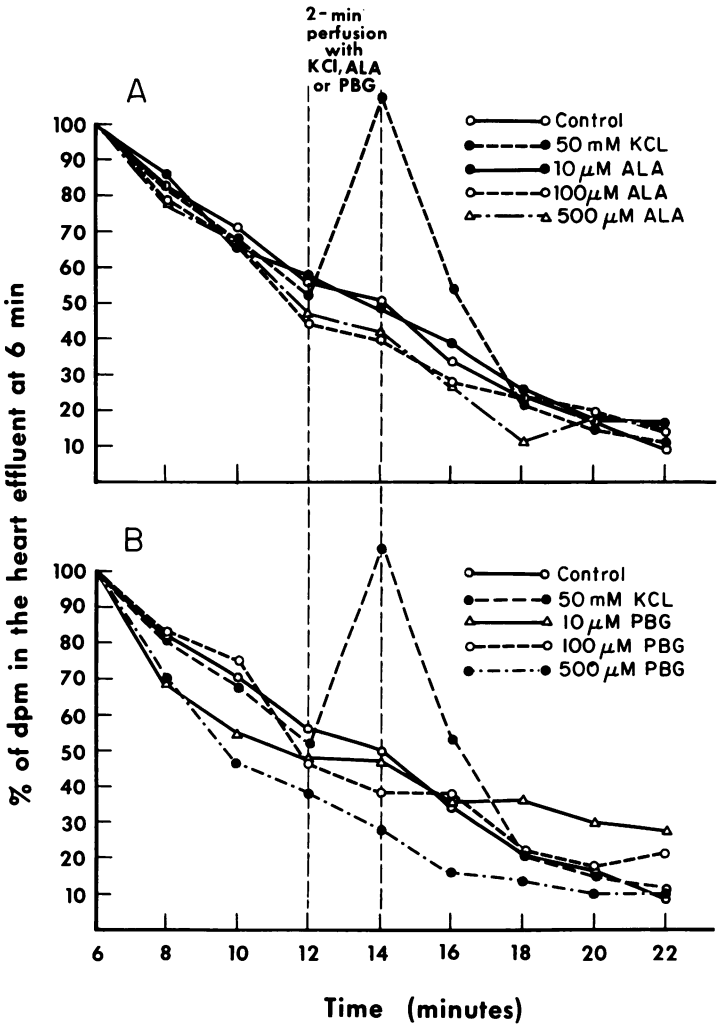

FIGURE 3 The efflux of [^{3}H]NE from perfused rat hearts perviously labeled for 20 min with [^{3}H]NE (1.0 ng/ml). Between 12 and 14 min after switching to a NE-free medium, the hearts were challenged with 50 mM KCl and ALA in varying concentrations (A), or KCl and PBG (B). Each curve represents data obtained from four to six hearts and is plotted as percentage of the disintegrations per minute in the heart effluent at 6 min vs. time in minutes.

TABLE I
Erythrocyte URO-S Activity in Patients with AIP and HC

Subject	Age	Sex	State of illness	URO-S	Diagnosis
	yr			*nmol/g Hb per h*	
B. D.	27	F	Remission	51.0	AIP
D. D.	46	F	Latent	62.4	AIP
S. D.	23	M	Latent	43.3	AIP
J. D.	18	F	Latent	44.9	AIP
G. S.	56	M	Remission	44.8	AIP
S. S.*	23	F	Remission	132.7	HC
Normal	26–55	—	—	99.9±5.5	—

Normal values are mean±SEM.
* Urinary coproporphyrin during the acute attack was 9,245 μg/24 h (normal = 75–225 μg/24 h).

hearts. Similarly, ALA or PBG has no effect on uptake of [^{3}H]NE into normal human platelets. In contrast, however, both compounds inhibit uptake of ^{3}H-NE into platelets of patients with acute porphyria. Inasmuch as there is significantly greater [^{3}H]NE uptake in the absence of ALA and PBG in patients' platelets, our findings suggest the possibility that there must be an overt defect in the uptake mechanisms of porphyria patients' platelets. The studies of Born and Smith (26) indicate that there are two different uptake systems, one of which is inhibited by alpha and beta adrenergic blocking agents. Using DMI in concentrations from 1 μM to 0.1 mM, we have examined uptake in both high and low concentrations of NE. There is a maximum inhibition of uptake of 50%, regardless of concentrations of either DMI or NE. Therefore, there are DMI-sensitive and DMI-insensitive uptake mech-

TABLE II

Effects of ALA and PBG on [^3H]NE Uptake of Acute Porphyria Patients and Normal Controls

Groups	Patients	Control NE uptake	DMI 1	ALA 1	ALA 10	ALA 100	PBG 1	PBG 100
					μM			
Porphyria	B. D.	2.585	1.312	1.691	1.561	1.666	1.604	2.083
	D. D.	4.137	2.616	2.881	2.885	3.789	3.241	3.363
	S. D.	1.340	0.369	1.186	1.425	1.092	1.171	1.509
	J. D.	3.210	2.528	2.198	2.990	2.396	2.574	3.550
	G. S.	1.695	0.939	1.407	1.584	2.056	1.628	2.459
	S. S.	2.903	1.316	1.115	1.033	0.990	1.196	1.674
		2.645±0.41	1.513±0.36	1.746±0.27	1.913±0.33	1.998±0.42	1.902±0.33	2.439±0.34
Significance, *P*			0.004	0.008	0.030	0.051	0.001	0.290
Normal	S. T.	1.786	1.277	1.882	1.817	1.912	1.753	2.270
	N. A.	1.156	0.599	1.169	1.151	1.112	1.273	1.181
	J. L.	1.823	1.077	1.582	2.048	1.938	1.942	1.933
	F. B.	1.976	1.267	1.678	1.836	2.127	1.544	2.213
	B. O.	1.317	0.343	1.300	1.213	1.056	1.511	1.423
	J. G.	1.865	1.418	1.972	1.968	2.081	1.985	1.986
		1.654±0.13	0.997±0.17	1.597±0.12	1.672±0.20	1.704±0.19	1.668±0.11	1.834±0.17
Significance, *P*			0.0005	0.230	0.380	0.250	0.450	0.022

Data are given as mean±SEM. All mean values represent four experiments and are expressed as uptake of [^{3}H]NE in disintegrations per minute × 0.001/90 min per 10^5 per mm^3 platelets (actual number added to the incubation ranged from 3 to 6 × 10^8 platelets in 1.8 ml platelet-rich plasma). *P* values are derived from Student's one-tailed *t* test.

anisms. At this point, our data would not permit us to differentiate which uptake system is being antagonized by ALA.

Previous experimental results have demonstrated that neither ALA nor PBG in intravenous doses of 100 mg/kg caused any alteration in heart rate or blood pressure in normal anesthetized cats. There was also neither potentiation nor inhibition of cardiovascular responses to epinephrine and NE (28, 29). In nephrectomized rats receiving ALA or PBG intravenously, plasma concentrations of >5 mg/100 ml have been achieved without any alteration in blood pressure or symptoms of nervous system toxicity (23, 30). Also, no alterations in blood pressure or heart rate have been observed in allylisopropylacetamide-induced experimental porphyria in rats (31–33). The ingestion of 1 g ALA by a normal man was not associated with alteration of blood pressure or heart rate (34). All these observations are in accord with our findings that neither ALA nor PBG block uptake of [^{3}H]NE in normal rat hearts and normal human platelets.

In the past, both autonomic neuropathy and denervation of the baroreceptors have been proposed as underlying mechanisms for the tachycardia and hypertension seen during acute attacks of porphyria. Pathologic changes consisting primarily of demyelination have been described in the autonomic nervous system at autopsy (35, 36). These changes, however, are probably secondary to a primary axonal metabolic disturbance as evidenced by normal nerve conduction velocities during acute attacks. The baroreceptor reflexes in one case of AIP were shown to be unresponsive to carotid sinus massage and procaine block (37). This suggests a deafferentation of the baroreceptors which, in experimental situations, is known to lead to increased sympathetic tone by central neurogenic mechanisms (38). The tachycardia and hypertension during acute attacks of porphyria may therefore be caused by several mechanisms. The finding of elevated catecholamines during acute attacks of porphyria has recently been brought to light. We found this to be the case in all of our patients.

The uptake of NE into human platelets has been proposed as a model of uptake into adrenergic neurons. The uptake mechanisms are similar in that they are temperature-dependent, saturable, and able to concentrate NE about five-fold. In addition, they are inhibited by the same drugs (12–14, 26, 39–41). Because ALA and PBG block uptake of NE into the platelets of patients with acute porphyria, it is tempting to speculate that a similar mechanism occurs in their adrenergic neurons. Re-uptake is the predominant means of terminating the physiologic action of neuro-

transmitter NE in vivo (41). Therefore, if there is decreased re-uptake of NE during acute attacks of porphyria, this must contribute to elevated levels of circulating catecholamines. It is therefore suggested that adrenergic-receptor blocking agents are the drugs of choice in managing the hypertension and tachycardia associated with acute porphyria. These have previously been shown to be effective, and they do not induce ALA synthetase in vitro (7, 11, 42).

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REFERENCES

1. Marver, H. S., and R. Schmid. 1972. The prophyrias. *In* The Metabolic Basis of Inherited Disease. J. B. Stanbury, J. B. Wyngaarden, and D. S. Frederickson, editors. McGraw-Hill Book Company, New York. 3rd edition. 1087–1140.
2. Waldenström, J. 1937. Studien über porphyria. *Acta Med. Scand. Suppl.* **82:** 1–254.
3. Goldberg, A. 1959. Acute intermittent porphyria. *Q. J. Med.* **110:** 183–204.
4. Nesbitt, S. 1944. Acute porphyria. *JAMA (J. Am. Med. Assoc.)* **124:** 286–294.
5. Tschudy, D. P., M. Valsamis, and C. Magnussen. 1975. Acute intermittent porphyria: clinical and selected research aspects. *Ann. Intern. Med.* **83:** 851–864.
6. Ridley, A. 1969. Neuropathy of acute intermittent porphyria. *Q. J. Med.* **38:** 307–333.
7. Schley, G., K. D. Bock, V. Hocevan, P. Merguet, J-G. Rausch-Stroomann, E. Schröder, and H. J. Schümann. 1970. Hypertension and tachycardia in AIP. *Klin. Wochenschr.* **48:** 36–42.
8. Goldberg, A., C. Rimington, and A. Lockhead. 1967. Hereditary coproporphyria. *Lancet.* **I:** 632–636.
9. Haeger-Aronsen, B., G. Stathers, and G. Swahn. 1968. Hereditary coproporphryria. *Ann. Intern. Med.* **69:** 221–229.
10. Lomholt, J. C., and T. K. With. 1969. Hereditary coproporphyria. *Acta. Med. Scand.* **186:** 83–85.
11. Atuk, N. O., J. A. Owen, Jr., and T. C. Westfall. 1975. Acute intermittent porphyria: altered catecholamine metabolism and response to propranolol. *J. Clin. Pharmacol.* **15:** 552–553. (Abstr.)
12. Abrams, W. B., and H. H. Solomon. 1969. The human platelet as a pharmacologic model for the adrenergic neuron. *Clin. Pharmacol. Ther.* **10:** 702–709.
13. Paasonen, M. K. 1973. Blood platelets as a model for aminergic neurons. *In* Pharmacology and the Future of Man. S. Karger, editor. Basal. Switzerland. 4:328–342.
14. Barbeau, A., G. Campanella, R. F. Butterworth, and K. Yamada. 1975. Uptake and efflux of ^{14}C-dopamine in platelets: evidence for a generalized defect in Parkinson's disease. Neurology. **25:** 1–9.
15. Westfall, T. C., and M. Brasteel. 1972. The mechanism of action of nicotine on adrenergic neurons in the perfused guinea-pig heart. *J. Pharmacol. Exp. Ther.* **182:** 409–418.
16. Cheramy, A., M. J. Besson, and J. Glowinski. 1970. Increased release of dopamine from striatal dopaminergic terminals in the rat after treatment with a neuroleptic: thioproperazine. *Eur. J. Pharmacol.* **10:** 206–214.
17. Thoenen, H., and J. P. Tranzer. 1968. Clinical sympathectomy by selective degeneration of sympathetic nerve endings with 6-hydroxydopamine. *Naunyn-Schmeidebergs Arch. Pharmakol. Exp. Pathol.* **261:** 271–288.
18. Sassa, S., S. Granick, D. R. Bickers, H. L. Bradlow, and A. Kappas. 1974. A microassay for uroporphyrinogen I synthetase, one of three abnormal enzyme activities in acute intermittent porphyria, and its application to the study of the genetics of this disease. *Proc. Natl. Acad. Sci. U.S.A.* **71:** 732–736.
19. Hughes, F. B., and B. B. Brodie. 1959. The mechanism of serotonin and catecholamine uptake by platelets. *J. Pharmacol. Exp. Ther.* **127:** 96–102.
20. Born, G. V. R., and J. Bricknell. 1959. The uptake of 5-hydroxy-tryptamine by blood platelets. *J. Physiol. (Lond.).* **147:** 153–161.
21. Meyer, U. A., L. J. Strand, M. Doss, A. C. Rees, and H. S. Marver. 1972. Intermittent acute porphyria. Demonstration of a genetic defect in porphyrin metabolism. *N. Engl. J. Med.* **286:** 1277–1282.
22. Elder, G. H., J. O. Evans, and N. Thomas. 1976. The primary enzyme defect in hereditary coproporphyria. *Lancet.* **II:** 1217–1219.
23. Dhar, G., B. Bossenmaier, Z. Petryka, R. Cardinal, and C. J. Watson. 1975. Effects of hematin in hepatic porphyria. *Ann. Intern. Med.* **83:** 20–30.
24. Kramer, S., D. Becker, and D. Viljoen. 1973. Significance of the porphyrin precursors ALA and PBG in the acute attack of porphyria. *S. Afr. Med. J.* **47:** 1735–1738.
25. Iversen, L. L. 1963. The uptake of noradrenaline by the isolated perfused rat heart. *Br. J. Pharmacol.* **21:** 523–537.
26. Born, G. V. R., and J. B. Smith. 1970. Uptake, metabolism, and release of ^{3}H-adrenaline by human platelets. *Br. J. Pharmacol.* **39:** 765–778.
27. Zieve, P. D., H. M. Solomon, and J. R. Krevans. 1966. The effect of hematoporphyrin and light on human platelets. I. Morphologic, functional and biochemical changes. *J. Cell. Physiol.* **67:** 271–280.
28. Jarret, A., C. Rimington, and D. A. Willoughby. 1956. Delta-aminolevulic acid and porphyria. *Lancet.* **I:** 125–127.
29. Goldberg, A., W. D. M. Paton, and J. W. Thompson. 1954. Pharmacology of the porphyrins and porphobilinogen. *Br. J. Pharmacol.* **9:** 91–94.
30. Watson, C. J. 1975. Hematin and porphyria. *N. Engl. J. Med.* **293:** 605–067.
31. Goldberg, A., and C. Rimington. 1964. Diseases of porphyrin metabolism. Charles C Thomas, Publisher, Springfield, Ill., 180–181, 72–75.
32. Tschudy, D. P., and H. L. Bonkowsky. 1972. Experimental porphyria. *Fed. Proc.* **31:** 147–159.
33. Shanley, B. C., J. J. Taljaard, W. M. Deppe, and S. M. Joubert. 1972. Delta-aminolevulinic acid in acute porphyria. *S. Afr. Med. J.* **46:** 84. (Corresp.)

34. Berlin, W. I., C. H. Gray, A. Neuberger, and J. J. Scot. 1954. The metabolism of the porphyrin precursor delta-aminolevulic acid in normal man and in the rat. *Biochem. J.* **58:** XXX. (Commun.)
35. Gibson, J. B., and A. Goldberg. 1956. The neuropathology of acute porphyria. *J. Pathol. Bacteriol.* **71:** 495–509.
36. TenEyck, F. W., W. J. Martin, and J. W. Kernohan. 1961. Acute porphyria: necropsy studies in nine cases. *Mayo Clin. Proc.* **36:** 409–422.
37. Kezdi, P. 1954. Neurogenic hypertension in man in porphyria. *Arch. Int. Med.* **94:** 122–130.
38. Doba, N., and D. J. Reiss. 1974. Role of central peripheral adrenergic mechanisms in neurogenic hypertension produced by brainstem lesions in rats. *Circ. Res.* **34:** 293–301.
39. Dengler, H. J., I. A. Michaelson, H. E. Spiegel, and E. O. Titus. 1962. The uptake of labeled norepinephrine by isolated brain and other tissues of the cat. *Int. J. Neuropharmacol.* **1:** 23–38.
40. Bygdeman, S., and O. Johnsen. 1969. Studies on the effect of adrenergic blocking drugs on catecholamine induced platelet aggregation and uptake of norepinephrine and 5-hydroxytryptamine. *Acta Physiol. Scand.* **75:** 129–138.
41. Molinoff, P., and J. Axelrod. 1971. The biochemistry of catecholamines. *Ann. Rev. Biochem.* **40:** 465–500.
42. Beattie, A. D., M. R. Moore, A. Goldberg, and R. L. Ward. 1973. Acute intermittent porphyria: response of tachycardia and hypertension to propranolol. *Br. Med. J.* **3:** 257–260.