Decreased Noradrenaline (Norepinephrine) Synthesis in Familial Dysautonomia

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ABSTRACT Noradrenaline synthesis and metabolism of dopamine was evaluated in three patients with familial dysautonomia and compared with that of six normal subjects. Each patient and subject was infused with 104.8 μCi of dopamine-2-^{14}C dissolved in 1000 ml of physiological saline. The urine was collected during the infusion period and at intervals thereafter. Using a specially designed flow monitor system, the various biosynthetic and metabolic products of dopamine were separated, identified, and their radioactivity measured. The results indicate that in familial dysautonomia the synthesis of noradrenaline is significantly decreased; this is reflected by a decrease in recovery of radioactive noradrenaline as well as various metabolic products of noradrenaline, i.e. 3-methoxy-4-hydroxymandelic acid (MOMA), normetadrenaline, and normetadrenaline conjugate. Concomitant with this decrease in noradrenaline synthesis, there was a shift towards dopamine metabolism as reflected by an increase in the recovery of primary and secondary dopamine metabolites; 3,4-dihydroxyphenylacetic acid (DOPAC), 3-methoxy-4-hydroxyphenylacetic acid (HVA), 3-methoxytyrosine, and respective conjugates, etc. Whereas all dysautonomic patients showed the same general metabolic pattern as was expected, they varied in degree.

INTRODUCTION

Since Riley, Day, Greeley, and Langford's original description of this syndrome (1), there have been many reports and reviews on this subject (2–7). Whereas the original describers felt that the pathogenesis was related to a central autonomic dysfunction, a number of investigators have since postulated involvement of the sympathetic system (8–15), to a lesser degree the parasympathetic system (1, 16, 17), and some have implicated other systems, i.e., central nervous system (18, 19), sensory nervous system (20), sensorium (18, 21), respiratory system (22, 23), gastrointestinal (18, 24, 25), skeleton (26), and the axon reflex (24, 27).

The most recent evidence appears to relate this syndrome principally to the sympathetic nervous system either by virtue of an alteration in the urinary output of noradrenaline (norepinephrine) or its metabolites. Smith, Taylor, and Wortis (11), showed that familial dysautonomic patients excreted subnormal amounts of 3-methoxy-4-hydroxymandelic acid (MOMA, VMA),[1] and increased amounts of 3-methoxy-4-hydroxyphenylacetic acid (homovanillic acid, HVA). Later, Moses et al. (28) confirmed the decrease in MOMA excretion and Gitlow, Bertani, Wilk, Li, and Dziedzic (10) demonstrated an elevated homovanillic acid, decreased MOMA, and 3-methoxy-4-hydroxyphenylglycol (MHPG), but a normal normetadrenaline; DeQuattro and Linde (29) did not observe these differences.

It is well established that noradrenaline is the neurohormone of the sympathetic nerves (30, 31) and that 3,4-dihydroxyphenylethylamine (dopamine, 3-hydroxytyramine) is its immediate precursor (32, 33). Further, it has been shown that the sympathetic nerves and ganglia synthesize noradrenaline but not adrenaline (epinephrine) (33). Therefore, the purpose of these studies is to evaluate the metabolic-precursor product relationship of dopamine to familial dysautonomia, and by so doing, determine if the synthesis and/or metabolism of endogenous noradrenaline is altered in this syndrome and in what manner.

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[1] *Abbreviations used in this paper:* DOMA, 3,4-dihydroxymandelic acid; DOPAC, 3,4-dihydroxyphenylacetic acid; HVA, 3-methoxy-4-hydroxyphenylacetic acid; MHPE, 3-methoxy-4-hydroxyphenylethanol; MPHG, 3-methoxy-4-hydroxyphenylglycol; MOMA, 3-methoxy-4-hydroxymandelic acid; 3-MT, 3-methoxytyramine.

METHODS

General. Noradrenaline synthesis and metabolism of dopamine were evaluated in three patients with familial dysautonomia and compared with that of six normal, healthy male subjects between 21 and 35 yr. All patients as well as the normal subjects were maintained on bed rest during the infusion, for 24 hr postinfusion, and thereafter maintained in a sedentary state during the remaining collection periods. Each patient was carefully selected in order to obtain a typical case of familial dysautonomia.

Infusion of dopamine-2-^{14}C and collection of postinfusion urine. Each patient and normal subject was infused with 104.8 μCi (872 μg) of dopamine-2-^{14}C. The labeled dopamine was dissolved in 1000 ml of physiological saline and infused via the antecubital vein over a period of 4 hr and at a constant rate. Urine was collected during the infusion period and at 2-hr intervals for the first 4-hr postinfusion. After that, it was collected at the end of 8, 24, 48, 72, 96, and 120 hr. All samples were immediately frozen and stored at −20°C until assayed.

Isolation and quantitation of metabolic products of dopamine-2-^{14}C. The method for isolating and quantifying endogenous noradrenaline and the metabolic products of noradrenaline as well as the metabolic products of dopamine has been previously described (34, 35). In brief, the basic metabolites were separated on a column of Dowex-50-X4. They are adrenaline (epinephrine), noradrenaline (norepinephrine), normetadrenaline (3-*O*-methylnoradrenaline, normetanephrine), 3-hydroxytyramine (dopamine), and 3-methoxytyramine (3-MT).

The acidic metabolic products were separated on a column of Dowex-1-X2 acetate anion exchange resin. These metabolic products are MOMA, HVA, 3,4-dihydroxymandelic acid (DOMA), and 3,4-dihydroxyphenylacetic acid (DOPAC), 3-methoxy-4-hydroxyphenylethanol (MHPE), 3,4-dihydroxyphenylethanol, MHPG, 3,4-dihydroxyphenylglycol, vanillic acid (VA), and their respective conjugates as well as the conjugates of 3-MT, normetadrenaline, noradrenaline, and dopamine. The details of these procedures have been described in a previous paper (34, 35). All acidic and basic metabolites were compiled and compared with those of normal subjects similarly infused with dopamine-2-^{14}C.

The columns were first washed and then eluted with ammonium acetate of varying molarity and acidity. As the eluate passes from the Dowex-50-X4 or the Dowex-1-X2 column, it is passed through a quartz flow cell (1.0 ml vol) of the UV Spectrophotometer and the optical density measured at 279 mμ and recorded on one channel of a dual recorder. From there it is passed through a 10 ml flow cell and the radioactivity counted with a specially designed flow system. This output was recorded on the other channel of the dual recorder and from the fraction collector the impulse was relayed to an event marker on the recorder so as to indicate the precise fraction which was counted. Further, the amount of radioactivity counted in each fraction is printed out and punch taped. The punch tape is fed into a NOVA 8 K Computer (Data General Corporation, Southboro, Mass.) which was programmed to print out the percentage of radioactivity of each fraction (metabolite) in terms of the amount infused and in terms of each collection period, see Table I. This information is then compared with those of normal subjects similarly infused with dopamine-2-^{14}C, see Table I.

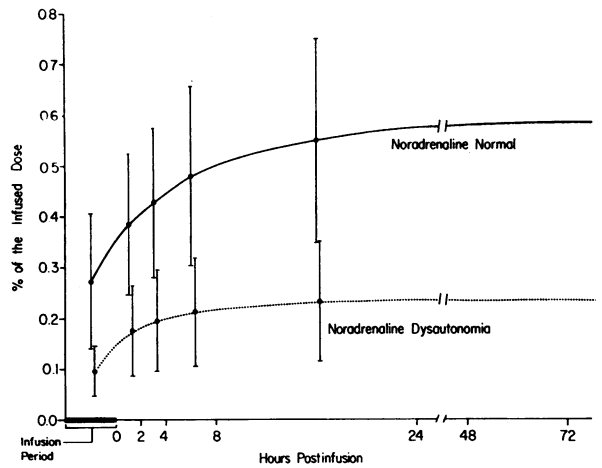

FIGURE 1 The accumulative recovery of the infused radioactivity as noradrenaline (norepinephrine) from the beginning of the infusion of dopamine-2-^{14}C (3-hydroxytyramine) for 72 hr after infusion. A comparison between normal subjects and three patients with familial dysautonomia.

RESULTS

From the results it appears that the most important change occurs in the synthesis of noradrenaline. The synthesis of noradrenaline is significantly decreased and this was reflected, not only by a decrease in the recovery of the radioactive noradrenaline throughout the collection periods (see Table I and Fig. 1), but also reflected by a decrease in the various metabolic products of noradrenaline, i.e., MOMA, normetadrenaline, and the conjugate of normetadrenaline (see Table I and Fig. 2).

Concomitant with the decrease in the synthesis of noradrenaline and decreased formation of noradrenaline metabolic products, there was a shift toward dopamine metabolism as reflected by an increase in the metabolic products of dopamine. DOPAC, the primary metabolite of dopamine, and homovanillic acid, the largest metabolite of dopamine, were both significantly increased, (see Table I and Fig. 3); DOPAC is rapidly *O*-methylated to homovanillic acid, which explains the larger quantity of homovanillic acid. Further, there was a marked increase in the recovery of secondary dopamine metabolites, 3-MT conjugate and homovanillic acid conjugate as well as the unknown peak 17.

Whereas all dysautonomic patients showed the same general metabolic pattern, as was expected, they varied in degree one from the other.

DISCUSSION

It is well established that noradrenaline is the sympathetic neurohormone (30, 31) and that the sympathetic

TABLE 1

Excretion Pattern of the Basic Metabolites, Acidic Metabolites, and Biosynthetic Products of Dopamine after a 4-Hr

Period of urine collection	Subject	% of the infused dose recovered	Basic metabolites—Dowex-50 fractions						Acidic metabolites—Dowex 1 fractions				
			Adr	Noradr	NM	3-HT	3-MT	Unk.	Dowex-1 effluent	P2 unk.	3-MT conj.	NM conj.	Noradr conj.
During infusion	K. E.	48.0	—	0.3	0.2	6.2	1.2	Trace	8.6	0.6	3.4	3.1	2.6
	B. R.	49.5	—	0.1	0.1	9.3	1.8	0.1	18.5	1.0	5.2	2.7	1.3
	S. H.	46.1	—	Trace	Trace	11.9	3.1	Trace	17.0	3.9	5.8	2.7	3.4
	Normal	38.8 ±7.5	—	0.7 ±0.3	0.8 ±0.4	8.5 ±2.4	4.4 ±0.5	0.1 ±0.1	14.5 ±4.1	0.4 ±0.3	3.3 ±0.4	3.5 ±0.8	2.5 ±0.7
0–2 hr postinfusion	K. E.	22.7	—	0.6	0.5	0.6	0.3	Trace	1.3	0.4	6.6	3.6	5.2
	B. R.	20.2	—	0.3	0.1	2.0	0.6	Trace	3.3	0.4	7.2	5.3	2.4
	S. H.	17.5	—	0.2	Trace	0.5	0.4	Trace	2.2	0.7	7.6	7.8	3.2
	Normal	19.1 ±1.7	—	0.6 ±0.1	0.3 ±0.1	1.9 ±0.8	1.3 ±0.2	Trace	4.1 ±1.4	0.8 ±0.3	6.9 ±0.6	6.3 ±1.3	4.8 ±0.6
2–4 hr	K. E.	10.3	—	0.1	0.1	0.1	0.4	Trace	1.4	1.2	8.4	4.0	3.8
	B. R.	6.8	—	0.2	0.3	0.3	0.4	1.8	2.1	1.0	10.9	5.2	3.4
	S. H.	9.0	—	0.2	0.1	0.3	0.3	2.4	2.1	1.6	11.0	7.4	4.9
	Normal	7.9 ±0.6	—	0.5 ±0.2	0.3 ±0.1	0.2 ±0.1	0.4 ±0.1	Trace	1.4 ±0.5	0.9 ±0.4	10.0 ±0.7	9.8 ±3.5	5.2 ±1.9
4–8 hr	K. E.	9.5	—	0.1	Trace	0.1	0.2	Trace	1.6	0.2	11.1	5.9	7.1
	B. R.	11.4	—	0.2	0.2	0.1	0.3	0.8	3.0	1.7	11.3	5.1	3.9
	S. H.	10.2	—	0.3	0.5	0.4	0.6	0.7	1.6	0.4	9.5	7.2	4.9
	Normal	9.2 ±0.9	—	0.6 ±0.3	0.4 ±0.1	0.5 ±0.3	0.3 ±0.1	Trace	1.8 ±0.8	1.0 ±0.4	9.7 ±0.9	9.0 ±1.0	5.7 ±1.6
8–24 hr	K. E.	6.5	—	Trace	Trace	0.1	0.1	0.4	1.5	0.6	12.1	7.8	3.9
	B. R.	9.5	—	0.1	0.1	0.2	0.2	Trace	2.0	0.4	15.7	6.6	3.9
	S. H.	9.1	—	0.5	0.4	0.6	0.9	Trace	1.5	0.4	8.0	5.6	2.4
	Normal	12.6 ±2.1	—	0.5 ±0.2	0.3 ±0.1	0.2 ±0.1	Trace	Trace	1.0 ±0.4	0.8 ±0.2	6.8 ±0.3	6.9 ±0.6	3.4 ±1.6
24–48 hr	K. E.	2.0	—	—	—	—	—	—	2.4	0.7	13.0	6.9	4.6
	B. R.	1.9	—	—	—	—	—	—	3.1	1.1	9.7	4.9	2.1
	S. H.	3.0	—	—	—	—	—	—	1.9	0.6	7.5	6.8	3.4
	Normal	7.4 ±1.9	—	0.5 ±0.1	0.3 ±0.2	0.1 ±0.1	Trace	Trace	0.9 ±0.4	1.0 ±0.3	3.1 ±1.0	4.6 ±0.9	2.2 ±0.9
48–72 hr	K. E.	0.5	—	—	—	—	—	—	—	—	—	—	—
	B. R.	0.3	—	—	—	—	—	—	—	—	—	—	—
	S. H.	0.6	—	—	—	—	—	—	—	—	—	—	—
	Normal	2.4 ±0.2	—	—	—	—	—	—	3.2 ±0.2	1.1 ±0.1	1.5 ±0.4	4.3 ±0.4	1.1 ±0.7
72–96 hr	K. E.	0.1	—	—	—	—	—	—	—	—	—	—	—
	B. R.	0.1	—	—	—	—	—	—	—	—	—	—	—
	S. H.	0.3	—	—	—	—	—	—	—	—	—	—	—
	Normal	1.3 ±0.1	—	—	—	—	—	—	3.5 ±1.3	1.4 ±0.5	0.9 ±0.6	3.6 ±0.9	1.8 ±1.0
96–120 hr	K. E.	0.2	—	—	—	—	—	—	—	—	—	—	—
	B. R.	0.2	—	—	—	—	—	—	—	—	—	—	—
	S. H.	0.1	—	—	—	—	—	—	—	—	—	—	—
	Normal	0.5 ±0.2	—	—	—	—	—	—	—	—	—	—	—
			% of infused dose										
Infusion to 24 hr	K. E.	97.0	—	0.3	0.2	3.1	0.7	Trace	4.8	0.5	5.8	3.8	3.7
	B. R.	97.4	—	0.2	0.1	5.1	1.1	Trace	11.0	1.0	6.3	4.0	2.2
	S. H.	91.9	—	0.1	0.1	5.7	1.7	Trace	9.0	2.0	6.0	4.0	3.0
	Normal	88.1 ±1.8	—	0.5 ±0.2	0.5 ±0.2	3.7 ±0.7	2.5 ±0.4	Trace	9.0 ±2.5	0.6 ±0.2	5.1 ±0.3	3.3 ±0.2	3.3 ±0.2
Infusion to 120 hr	K. E.	99.8	—	0.3	0.2	3.1	0.7	Trace	4.9	0.6	6.1	3.9	3.8
	B. R.	99.9	—	0.2	0.1	5.1	1.1	Trace	11.0	1.0	7.0	4.0	2.0
	S. H.	95.9	—	0.1	0.1	5.7	1.7	Trace	9.0	2.0	6.0	4.0	3.0
	Normal	99.2 ±2.8	—	0.6 ±0.2	0.6 ±0.2	3.7 ±0.6	2.5 ±0.4	Trace	11.1 ±3.5	0.8 ±0.2	5.3 ±0.5	2.0 ±0.2	3.5 ±0.2

Adr, adrenaline; Noradr, noradrenaline; NM, normetadrenaline; 3-HT, 3-hydroxytyramine (dopamine); 3-MT, 3-methoxytyramine; Unk., unknown; Conj., conjugate; MOMA, 3-methoxy-4-hydroxymandelic acid; HVA, 3-methoxy-4-hydroxyphenylacetic acid; DOMA, 3,4-dihydroxymandelic acid; DOPAC, 3,4-dihydroxyphenylacetic acid; MHPG Conj., 3-methoxy-4-hydroxyphenylglycol conjugate; MHPE Conj., 3-methoxy-4-hydroxyphenylethanol conjugate; (ages of patients, K. E., 27 yr, B. R., 6 yr, S. H., 12 yr.

All figures express per cent of the radioactivity recovered in each collection period.

Infusion of Dopamine-2-^{14}C; Comparison of Normal Subjects ±SD and Three Patients with Familial Dysautonomia

Acidic metabolites—Dowex 1 fractions												
3-HT conj.	P 6 unk.	MOMA	HVA	DOMA	P 11 unk.	DOPAC	P 12 unk.	MHPE and MHPG conj.	DOPAC conj.	MOMA conj.	HVA conj.	P 17 unk.
1.6	1.0	3.1	43.5	0.7	Trace	10.6	Trace	2.8	2.9	0.5	8.2	6.6
1.5	1.2	1.3	37.6	0.6	Trace	11.7	Trace	1.7	3.6	1.5	5.7	4.9
4.0	1.2	1.7	31.9	Trace	Trace	10.1	Trace	1.0	3.0	0.6	6.3	7.9
2.5 ±0.9	1.2 ±0.8	2.4 ±0.5	37.5 ±3.3	0.6 ±0.4	0.6 ±0.5	10.1 ±2.7	Trace	3.3 ±0.9	6.8 ±1.7	0.2 ±0.2	5.4 ±0.6	5.6 ±1.3
2.6	1.3	6.4	35.8	0.9	1.3	2.0	Trace	4.1	5.1	1.0	13.2	10.8
1.6	1.3	3.0	36.6	1.1	Trace	7.1	0.3	3.3	7.1	3.1	9.9	7.0
2.6	2.0	6.1	24.0	Trace	2.3	2.2	Trace	3.4	8.4	2.2	12.0	12.6
3.1 ±0.4	2.5 ±0.3	5.3 ±1.1	29.4 ±2.9	0.6 ±0.5	1.3 ±1.0	5.0 ±1.7	0.9 ±0.5	4.5 ±1.9	8.7 ±1.1	1.9 ±1.1	6.4 ±0.6	5.9 ±1.2
3.7	2.0	6.2	20.7	1.2	1.2	1.7	1.1	5.5	7.2	1.7	11.0	16.9
2.7	2.8	5.9	19.0	1.0	1.0	2.3	1.4	5.0	9.3	3.2	9.7	12.9
2.9	2.6	9.2	9.3	Trace	Trace	2.8	Trace	6.8	11.2	3.8	10.1	13.2
4.5 ±0.9	4.6 ±0.7	11.5 ±1.3	12.4 ±2.6	1.0 ±0.5	2.2 ±0.6	0.6 ±0.4	1.0 ±0.4	6.9 ±0.7	12.2 ±0.6	2.8 ±0.9	5.3 ±1.1	6.9 ±0.4
4.3	2.7	7.9	14.1	1.0	1.0	1.3	1.4	6.4	10.1	2.4	10.0	12.5
2.4	3.0	5.9	10.0	Trace	0.7	2.0	0.8	6.3	11.6	5.4	10.7	17.8
3.1	4.3	11.8	6.2	0.7	2.4	Trace	1.2	8.6	13.2	4.5	7.6	12.9
3.9 ±1.2	6.2 ±0.7	16.3 ±1.7	5.7 ±0.8	1.2 ±0.6	1.5 ±0.6	0.3 ±0.3	1.9 ±0.6	8.9 ±1.2	13.7 ±0.6	2.5 ±0.7	3.9 ±0.4	5.9 ±0.6
2.8	2.9	5.9	8.1	1.3	Trace	1.5	0.7	8.2	11.9	3.0	10.3	17.1
1.4	3.2	7.4	8.0	Trace	Trace	2.1	0.6	8.7	15.0	2.3	10.9	12.2
3.4	5.0	13.9	3.9	1.2	3.5	Trace	1.4	10.9	16.0	3.9	8.7	10.3
3.1 ±0.9	8.6 ±0.7	22.4 ±3.2	2.9 ±1.4	1.6 ±0.4	2.2 ±0.4	Trace	1.6 ±0.4	10.6 ±0.8	14.9 ±1.3	4.1 ±0.6	2.9 ±0.6	4.7 ±1.1
1.2	1.6	11.2	4.6	Trace	Trace	Trace	Trace	8.9	18.5	2.9	10.1	11.3
1.9	3.3	8.5	3.5	0.4	3.2	0.3	0.3	8.8	13.6	6.2	13.7	14.7
4.3	7.2	2.5	4.6	Trace	6.1	Trace	2.7	13.2	18.9	0.4	6.0	14.0
2.9 ±0.5	11.1 ±1.5	29.9 ±3.5	1.4 ±0.3	1.9 ±1.1	1.9 ±0.3	—	2.2 ±0.6	11.9 ±1.0	12.0 ±1.1	3.8 ±0.8	2.9 ±0.4	3.1 ±0.7
—	—	—	—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	—	—	—	—
2.2 ±0.4	12.6 ±2.1	34.9 ±4.0	—	0.9 ±0.8	1.9 ±0.7	—	2.6 ±0.7	7.0 ±2.4	10.8 ±2.4	3.3 ±1.4	2.8 ±0.9	1.9 ±0.8
—	—	—	—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	—	—	—	—
0.6 ±0.5	12.8 ±2.3	39.0 ±4.3	—	0.6 ±0.4	1.3 ±0.4	—	2.2 ±1.0	13.8 ±1.9	11.5 ±3.0	2.0 ±0.8	1.7 ±0.6	2.4 ±0.8
—	—	—	—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	—	—	—	—
% of infused dose												
2.3	1.4	4.7	33.0	0.8	0.5	5.9	0.3	4.0	5.0	1.1	9.7	9.6
1.7	2.0	2.4	29.2	1.0	0.2	8.0	0.3	3.4	7.0	2.4	8.0	8.0
3.0	2.0	4.4	21.0	0.2	1.0	5.0	0.3	3.0	6.0	2.0	7.0	8.2
2.7 ±0.2	3.0 ±0.6	7.1 ±0.4	22.3 ±2.6	0.3 ±0.3	1.0 ±0.5	5.0 ±0.9	0.5 ±0.2	4.8 ±0.3	8.4 ±1.0	1.3 ±0.3	4.6 ±0.4	4.1 ±1.4
2.4	1.5	4.9	33.1	0.8	0.5	5.9	0.3	4.2	5.4	1.1	9.9	9.9
2.0	2.0	3.0	29.3	1.0	0.2	8.0	0.3	4.0	7.0	3.0	8.0	8.2
3.0	2.0	4.4	21.0	0.2	1.0	5.0	0.3	3.0	6.0	2.0	7.0	8.3
3.0 ±0.2	4.4 ±0.8	10.8 ±0.4	22.4 ±2.7	0.8 ±0.8	1.2 ±0.5	5.0 ±0.9	0.8 ±0.2	6.2 ±0.4	9.7 ±1.1	1.8 ±0.3	4.9 ±0.5	5.4 ±1.5

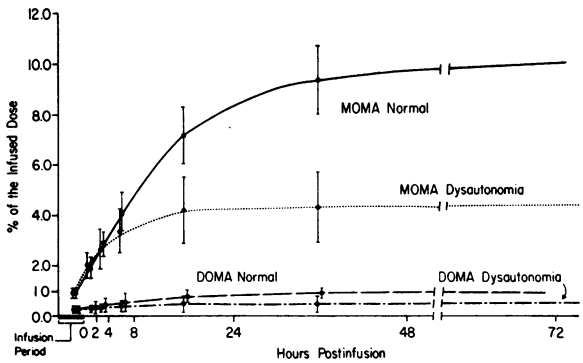

FIGURE 2 The accumulative recovery of the infused radioactivity as MOMA and DOMA from the beginning of the infusion of dopamine-2-^{14}C (3-hydroxytyramine) for 72 hr after infusion. A comparison between normal subjects and three patients with familial dysautonomia.

nerves synthesize noradrenaline from dopamine (33). Further, it has been postulated that the sympathetic nervous system is implicated in the pathogenesis of familial dysautonomia (1, 8–15), however, the mechanisms of involvement have not hitherto been elucidated. Albeit, it has been shown that in familial dysautonomia there is a decrease in certain urinary metabolites of noradrenaline, i.e. MOMA (10, 11), MHPG (10), and an elevation in one of the metabolites of dopamine, i.e., homovanillic acid (10, 11, 28). Whereas these findings clearly implicate the sympathetic nervous system they nevertheless do not indicate the extent or position of the defect.

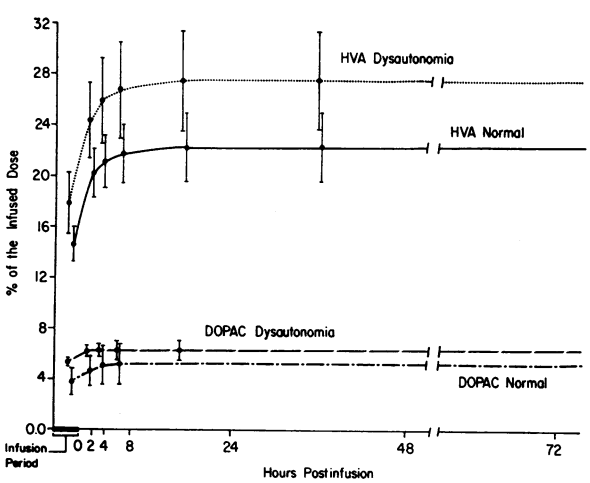

FIGURE 3 The accumulative recovery of the infused radioactivity as HVA (homovanillic acid) and DOPAC from the beginning of the infusion of dopamine-2-^{14}C (3-hydroxytyramine) for 72 hr after infusion. A comparison between normal subjects and three patients with familial dysautonomia.

The results herein described indicate that there is a decrease in the synthesis of noradrenaline and a shift toward dopamine metabolism, (see Figs. 1 and 3 and Table I). In normal subjects, approximately 25% of the infused dopamine is synthesized to noradrenaline and noradrenaline metabolic products and 75% to dopamine and dopamine metabolic products (34). In familial dysautonomia, approximately 15–20% is synthesized into noradrenaline and noradrenaline metabolic products and 80–85% into dopamine and dopamine metabolic products, thereby indicating a decrease in noradrenaline synthesis and a shift toward dopamine metabolism, (see Table I, Figs. 1–3). This decrease in noradrenaline synthesis is reflected not only by a decrease in the recovery of radioactive noradrenaline but also a decrease in radioactive noradrenaline metabolites, i.e. MOMA, the largest single (secondary) metabolite of noradrenaline, normetadrenaline, and a slight decrease in normetadrenaline conjugates (0–24 hr).

The amount of radioactivity recovered in the dysautonomic averaged 95.5% in 24 hr vs. 88.1 ±1.8 in the normal and 98.5% in 120 hr vs. 99.2 ±2.8. This would indicate that in the dysautonomic the turnover rate was within normal limits or possibly slightly elevated in the 24 hr period. The fact that 100% of the radioactivity was accounted for, or that is recovered, in the urine within a normal period of time means that the radioactive endogenous noradrenaline that was synthesized was also released and recovered in the urine. Therefore, from these results, it would seem reasonable to conclude that there was no defect in the release mechanisms per se but rather some aberration in synthesis; and too, the fact that the dysautonomic patient shows a diurnal variation in noradrenaline output (release) argues in favor of such a conclusion. The decrease in noradrenaline synthesis could be related to a decrease in dopamine uptake by the vesicles, changes within the neuron or a decrease in the number of viable adrenergic neurons all of which are compatible and/or commensurate with the sympathetic nerve degeneration.

A somewhat similar decrease in noradrenaline synthesis and a shift towards dopamine metabolism has also been noted in idiopathic postural hypotension (neurogenic postural hypotension) (35); also hypotension and supersensitivity to infused noradrenaline (9) are common to both syndromes. Whereas in neurogenic postural hypotension, the pathogenesis has been shown to be the result of degenerative changes in the sympathetic nerves (35), such has not been demonstrated in familial dysautonomia.

In stressful situations a decreased recovery of radioactive noradrenaline is observed (36), but in this instance the decrease is related to an increase in the metabolism of noradrenaline rather than a decrease in

synthesis. This increased metabolism of noradrenaline is not only reflected by a decrease in recovery of radioactive noradrenaline but by a concomitant increase in noradrenaline metabolic products and a shift away from dopamine metabolism (36). As noted from the experiments herein described, the opposite occurs in familial dysautonomia, i.e. there is a decrease in noradrenaline synthesis, a decrease in the noradrenaline metabolic products, and a shift toward dopamine metabolism.

The question naturally arises as to whether one is justified in comparing dopamine metabolism and noradrenaline synthesis of normal subjects (21–35 yr) with that of patients with familial dysautonomia, most of whom were younger and all of whom were in some degree debilitated. Such a comparison seems acceptable in view of Gitlow et al. (10) "age-size" study of 52 dysautonomic patients. Gitlow et al. (10) collected urine samples from dysautonomic patients and assayed for the metabolites MOMA, normetadrenaline, and MHPG. The studies herein described infused dysautonomic patients with dopamine-2-^{14}C, the immediate precursor to noradrenaline, and monitored the urine for all of the metabolic products of dopamine and noradrenaline as well as monitored the synthesis of endogenous noradrenaline.

To recapitulate, from these results it appears that in familial dysautonomia there is a decrease in the synthesis of the sympathetic neurohormone, noradrenaline. The pathogenesis of this defect in noradrenaline synthesis can not, from these studies, be precisely delineated. However, evidence seems to indicate that the defect could be the result of a degenerate change in the sympathtic system as is seen in idiopathic postural hypotension (35) or the result of an inborn error in the enzymatic system involved in the synthesis of noradrenaline from phenylalanine. The latter seems more plausible in view of this syndrome's autosomal recessive inheritance (28, 37, 38).

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