Preliminary Communications

Modification of Hormonal Responses to Arginine by α -Adrenergic Blockade

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Summary: α -Adrenergic blockade with phentolamine significantly enhances the insulin response to arginine. In women phentolamine may inhibit the growth hormone response to arginine. It is suggested that adrenergic mechanisms may act as modulators in hormonal responses to infused amino-acid.

INTRODUCTION

Amino-acid infusions have been reported to produce a rise of plasma concentrations of insulin (Floyd *et al.*, 1966), glucagon (Assan *et al.*, 1967), and growth hormone (Merimee *et al.*, 1965). Since recent studies have indicated that intravenous arginine may also increase catecholamine secretion from the adrenal gland of the rat (Imms *et al.*, 1969), it is possible that adrenergic mechanisms may be involved as modulators in these hormonal responses to infused amino-acids.

We have investigated this possibility by studying the effect of the α -adrenergic blocking agent, phentolamine, on the response of plasma levels of growth hormone and insulin to arginine.

METHODS

Eight healthy subjects—five men aged 21 to 36 and three women aged 21 to 23—rested for 45 minutes after an overnight fast. A plastic cannula was then introduced into an antecubital vein for the sampling of blood and the administration of fluids. After a further 45 minutes an infusion of either 0.9% NaCl or phentolamine (1 mg./ml.) in 0.9% NaCl was begun, and was continued at 0.5 ml./min. for two hours. When this had been running for 30 minutes an additional infusion of 10% L-arginine mono-HCl (0.5 g./kg. body weight), buffered to pH 7.4 with sodium carbonate, was started and run for 30 minutes. A basal blood sample was taken for the estimation of growth hormone and insulin immediately before the first infusion. Subsequent samples were obtained immediately before the arginine, this being the 0 minute sample, and then at 30, 60, and 90 minutes. Two experiments were performed on each subject at intervals of at least three days, one with and one without phentolamine in varied sequence. All the subjects gave informed consent for this procedure.

Plasma growth hormone levels were performed as described by Jackson *et al.* (1968) and insulin by a modification of the technique of Pollard and Waldron (1966).

The effect of phentolamine was assessed by comparing the corresponding plasma insulin and growth hormone levels in the two experiments on each individual. The significance of the differences between paired values was tested against the null hypothesis, both tails of the *t* distribution being used.

RESULTS

Table I shows the effect of phentolamine on the 0 minute level of insulin and also on the post-arginine increments above the 0 minute concentration. It can be seen that phentolamine produces a significant increase in both the pre-arginine level of plasma insulin and in the insulin response to arginine. The basal level of insulin in the phentolamine experiment was 11.8 ± 2.8 μ U./ml., compared with 10.7 ± 2.1 μ U./ml. in the

saline control; thus there was no significant difference in the basal status of the subjects in the two experiments before starting the phentolamine or saline infusions.

TABLE I.—Plasma Insulin Concentrations (μ U./ml.) Means $\pm$ S.E.

	0 min.	Post-arginine Increments Above Values at 0 Min.		
		30 min.	60 min.	90 min.
Saline control	9.3 ± 1.7	47.5 ± 9.4	9.4 ± 4.0	3.1 ± 2.3
Phentolamine	17.5 ± 1.9	82.2 ± 25.8	26.8 ± 8.2	1.5 ± 4.2
Individual paired differences	8.3 ± 3.1	31.0 ± 14.0	17.5 ± 6.9	-6.4 ± 4.7
Phentolamine <i>v.</i> control (P)	< 0.05	$0.1 > P > 0.05$	< 0.05	0.3

Table II shows that phentolamine did not significantly affect either the pre-arginine growth hormone levels or the response of growth hormone in the eight subjects as a group.

It is, however, apparent (Table III) that in each of the three women studied phentolamine inhibited the rise in plasma growth hormone concentrations after arginine.

TABLE II.—Growth Hormone Levels ($m\mu$ g./ml.) Means $\pm$ S.E.

	0 min.	Maximal Increment After Arginine
Saline	5.4 ± 1.6	36.8 ± 8.8
Phentolamine	4.2 ± 1.5	17.9 ± 9.7
Individual paired differences	-2.1 ± 1.3	-22.0 ± 12.0
Phentolamine <i>v.</i> control (P)	0.2	0.1

TABLE III.—Growth Hormone Levels ($m\mu$ g./ml.) in the Three Women

Case No.	Age		0 min.	30 min.	60 min.	90 min.
1	23	Saline	11.0	5.6	25.3	31.1
		Phentolamine	14.0	5.3	7.7	5.1
2	22	Saline	4.4	32.4	92.8	52.8
		Phentolamine	4.2	3.8	15.4	12.4
3	21	Saline	3.8	11.0	68.0	36.8
		Phentolamine	4.4	2.8	23.8	22.4

DISCUSSION

The data indicate a pronounced effect of phentolamine on the insulin response to arginine. With growth hormone the result was not as clear-cut. Only the three women tested showed a consistent growth hormone rise with arginine and a suppression of the rise when the experiment was performed under adrenergic blockade.

It has been proposed that insulin release may be mediated through stimulation of β -adrenergic receptor sites (Porte, 1967a) and inhibited by α -adrenergic stimulation (Porte, 1967b). With growth hormone the converse occurs (Blackard and Heidingsfelder, 1968; Imura *et al.*, 1968). If arginine induces catecholamine release in man, as in the rat (Imms *et al.*, 1969), α -adrenergic blockade would be expected to increase insulin response as was observed in these experiments.

Although it is apparent that the insulin response to arginine may be modulated through adrenergic receptors, further work is necessary to ascertain whether the catecholamine was of adrenal origin or was released locally in the pancreas.

More experiments are also required in order to define fully the pattern of α -adrenergic blockade on growth hormone release induced by arginine. Since women may show a more sensitive growth hormone response to arginine (Merimee *et al.*, 1966; Hembree and Ross, 1969) it is possible that the sex difference suggested by this study may be of significance.

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Medical Memoranda

Acute Iatrogenic Hypothyroid Psychosis

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It has been known for many years that hypothyroidism can cause psychosis. Sir William Gull (1873) noted mental changes in his hypothyroid patients, and Asher (1949) drew attention to the prevalence of "myxoedema madness." The kind of mental illness shown is variable, and of a group of 18 patients described by Tonks (1964) five showed essentially organic features, and five schizophrenic, six affective, and two mixed pictures. The duration of mental symptoms in this group varied from a few days to eight years.

We describe here a very acute psychotic illness of mixed organic/schizophrenic type, apparently precipitated by carbimazole-induced hypothyroidism in a young thyrotoxic woman.

CASE HISTORY

A 22-year-old married woman was referred to the medical outpatient department at West Middlesex Hospital with obvious clinical thyrotoxicosis. She had a large goitre, pronounced exophthalmos and lid lag, and a tachycardia of 130. Her protein-bound iodine was 12.9 µg./100 ml.

She was treated with carbimazole 45 mg./day, and when she was seen in the outpatient department two months later she was noted to be clinically euthyroid.

Three weeks after this visit she was admitted as an emergency to Springfield Hospital. On admission she was very disturbed and presented a rather bizarre mental state in that her level of consciousness varied between semi-stupor and wild excitement. She had auditory hallucinations and thought that she had killed her baby and was being spied on by the police. On the day after admission she cut both her wrists with broken glass, and for a while showed *flexibilitas cerea*.

On physical examination she had a dry skin with a rounded facies and malar flushing. Exophthalmos (but no lid lag) was still present, and she had a large goitre with an easily heard bruit. Her pulse varied widely between 70 and 110, and there was obvious slowing of relaxation of ankle and knee jerks.

Investigations showed a protein-bound iodine of 1.8 µg./100 ml., serum cholesterol 191 mg./100 ml., haemoglobin 14.8 g./100 ml., and an E.S.R. of 7. Wassermann reaction and Kahn test were negative.

There was no family history of mental illness. Her premorbid personality was good, and, apart from a short episode of depression after the birth of her baby 14 months previously that had rapidly

responded to imipramine given by her general practitioner, she had no previous psychiatric history.

Treatment consisted of stopping carbimazole, and no thyroid replacement therapy was given. She received trifluoperazine 30 mg./day and orphenadrine 300 mg./day, and was twice given electric convulsion therapy in view of her severe clouding of consciousness.

Within 10 days her mental state had returned to normal, she was clinically euthyroid, and her protein-bound iodine had risen to 4.6 µg./100 ml. After a month she again showed clinical signs of hyperthyroidism, so that carbimazole in a dose of 15 mg./day was restarted. Follow-up for nine months showed no recurrence of psychiatric symptoms, and she has remained euthyroid on the small dose of carbimazole.

COMMENT

In most cases of psychosis associated with hypothyroidism, the latter condition has been present for some time (Asher, 1949). Psychotic reactions are uncommon in thyrotoxicosis (Greer and Parsons, 1968), and the above patient had shown no real evidence of disturbance in her thyrotoxic phase. It is true that she received specific "antipsychotic" treatment with trifluoperazine and electric convulsion therapy and did not receive thyroid replacement therapy, thereby not fulfilling Tonks's (1964) criteria for defining hypothyroid psychosis. Also, she had a relatively rapid pulse throughout her acute illness, though bradycardia is by no means invariable in hypothyroidism (Cecil and Loeb, 1959). Nevertheless, she became acutely psychotic when her thyroid function fell below normal, and her rapid recovery and continued psychiatric normality without specific treatment indicates that this was a psychotic illness of mixed organic/schizophrenic type precipitated by a very short period of drug-induced hypothyroidism.

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