EFFECT OF ANTIDEPRESSANTS ON THE 11-HYDROXYCORTICOSTEROID CONCENTRATION IN RAT BLOOD PLASMA

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Tricyclic antidepressants imipramine (15 mg/kg), anafranil (2 mg/kg), and amitriptyline (2 mg/kg) lowered the concentration of 11-hydroxycorticosteroids (11-HC) in the blood plasma of intact rats by 35-40% 1 h after injection and had no effect on the hormone concentration 4 h after injection. Antidepressants of the monoamine oxidase (MAO) group – phenelzine (50 mg/kg), nialamide (100 mg/kg), iproniazid (100 mg/kg), and pargyline (100 mg/kg) – caused no significant change in the 11-HC level 1 h after injection. All the MAO inhibitors tested and imipramine diminished the increase in 11-HC concentration arising during stress induced by compelling the rats to swim in water at 20-22°C.

It was shown previously that imipramine-like tricyclic antidepressants inhibit the tryptophan-pyrrolase activity of the rat liver [6]. The absence of this effect in experiments in vitro as well as on adrenalectomized animals suggested that the inhibition of tryptophan-pyrrolase activity is not the result of a direct action on the enzyme, but is brought about through a decrease in the activating effect of the adrenocortical hormones, possibly through a decrease in the concentration of corticosteroids in the blood. To test this hypothesis experiments were carried out to determine the effect of tricyclic antidepressants on the concentration of 11-hydroxycorticosteroids (11-HC) in the blood plasma of rats under normal conditions and during stress.

Changes in the concentration of these hormones during the action of antidepressants of the monoamine oxidase (MAO) inhibitor group, which have no inhibitory effect on the tryptophan-pyrrolase activity of the liver [5], was studied in the investigation described below.

EXPERIMENTAL METHOD

Experiments were carried out on 220 noninbred male albino rats weighing 150-250 g. The tricyclic antidepressants were injected 1 and 4 h before decapitation in doses in which, as shown by data in the literature [2], the characteristic pharmacological effects of this group of preparations (synergism with amphetamine, antireserpine action, etc.) and also the inhibitory effect on the tryptophan-pyrrolase activity of the liver were most clearly manifested. Antidepressants of the MAO inhibitor group were injected 1 h before decapitation in doses completely inhibiting the MAO activity of the brain [3]. All the drugs were injected intraperitoneally. The animals of the control groups received distilled water. Stress was induced in the rats by compelling them to swim in water at 20-22°C for 30 sec. In this case decapitation was carried out 15 min after the end of swimming. The 11-HC concentration in the blood plasma was determined fluorimetrically [4].

EXPERIMENTAL RESULTS

The tricyclic antidepressants – imipramine (15 mg/kg), amitriptyline (2 mg/kg), and anafranil (2 mg/kg) – lowered the 11-HC concentration in the blood plasma of the intact animals by 35-40% (Table 1). The

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TABLE 1. Effect of Antidepressants on 11-HC Concentration in Blood Plasma of Rats Under Normal Conditions and During Stress (mean of five determinations; M± m)

Preparation	Gross (in mg/kg)	11-HC concentration (in μg %)			
		under normal conditions	P	during stress	P
1 h after injection					
Distilled water	—	35,41±3,75		63,38±5,49	
Imipramine	15	22,40±1,48	<0,01	34,40±3,03	<0,01
Anafranil	2	24,30±1,69	<0,02	59,60±6,60	NS
Amitriptyline	2	22,50±2,51	<0,05	67,20±4,57	NS
Distilled water	—	49,20±4,96		97,60±6,40	
Phenelzine	50	48,80±5,49	NS	73,60±6,22	<0,05
Iproniazid	100	57,60±6,94	NS	65,20±3,22	<0,02
Distilled water	—	36,50±6,39		74,00±5,51	
Nialamide	100	41,60±5,59	NS	56,80±4,86	<0,05
Pargyline	100	54,80±2,14	NS	56,40±2,34	<0,02
4 h after injection					
Distilled water	—	38,20±4,45		65,10±4,55	
Imipramine	15	47,50±3,70	NS	65,30±6,50	NS
Anafranil	2	43,50±4,60	NS	61,90±6,70	NS
Amitriptyline	2	46,20±4,99	NS	67,20±5,73	NS

Legend. ns) not significant compared with group of animals receiving distilled water.

effect of these substances appeared 1 h after injection, and at the time of their maximal inhibitory effect on the tryptophan-pyrrolase activity 4 h after injection the 11-HC concentration was indistinguishable from the control. The development of the inhibitory effect of the antidepressants on the tryptophan-pyrrolase activity after the decrease in the 11-HC level is evidence in support of the view that their inhibitory action on the enzyme takes place indirectly through a decrease in the activating effect of adrenocortical hormones on the enzyme.

Antidepressants of the MAO inhibitor group – phenelzine (50 mg/kg), iproniazid (100 mg/kg), pargyline (100 mg/kg), and nialamide (100 mg/kg) – had no significant effect on the 11-HC concentration in the blood plasma of the intact rats 1 h after injection.

In stress induced by brief swimming the 11-HC concentration was approximately doubled. Of the tricyclic antidepressants tested only imipramine, injected 45 min before swimming, prevented elevation of the 11-HC level under the influence of stress.

As Table 1 shows, all the antidepressants tested from the MAO inhibitor group diminished the increase in the 11-HC concentration induced by stress.

The effect of these two groups of antidepressants on the 11-HC concentration in the blood plasma of the rats thus differed to some extent. A more characteristic feature of the tricyclic antidepressants was a decrease in the initial 11-HC level, whereas the effect of MAO inhibitors was manifested during stress. However, this difference was not so great if it is remembered that the 11-HC concentration taken as initial (normal) in these experiments depended on many factors connected with the experimental conditions (transfer of the rats from the vivarium to the laboratory, the working noise in the laboratory, the weighing procedure, the injections, and so on, all capable of increasing corticosteroid secretion without any additional stress [8]) so that essentially all the antidepressants tested diminished the increase in 11-HC concentration induced by stress, although the effect of the tricyclic group of antidepressants was manifested in response to stress of lower intensity.

These results are in agreement with others showing that the tricyclic antidepressants, in doses close to those used in the present experiments, prevent the increase in the blood 11-HC concentration in rats during other types of stress [10].

Can the decrease in the corticosteroid concentration under the influence of antidepressants have any bearing on the therapeutic action of these substances? The answer is evidently yes, because the most common effect of antidepressants in depressed patients is in fact a decrease in the excretion of corticosteroids with elevation of their initial level [1]. During a prolonged therapeutic effect the adrenocortical function is also restored to normal.

Possibly as a result of the decrease in the corticosteroid level during administration of antidepressants to these patients, the tryptophan-pyrrolase activity of their liver is inhibited, leading to changes in tryptophan-metabolism and to activation of central serotoninergic processes, i.e., to changes linked with the genesis of depression [7] and with the thymoanaleptic action of antidepressants [9].

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