INFLUENCE OF ADRENERGIC STIMULANT AND BLOCKING DRUGS ON CEREBRAL ELECTRICAL ACTIVITY IN CURARIZED ANIMALS[1, 2]

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The effect of adrenergic drugs on the central nervous system has been of interest to numerous investigators, especially during the last 10 years (see review by Rothballer, 1959). In spite of extensive efforts, no clear-cut generalization has yet been formulated concerning the action of these drugs on the brain.

In the present study the main aspect of the central effect of these substances is that revealed by electroencephalography. It has most frequently been reported that epinephrine and norepinephrine produce an EEG "stimulation"[5]; that is, they induce an EEG pattern of high frequency, low voltage waves (Bonvallet *et al.*, 1954; Rothballer, 1956; Capon, 1960; Monnier, 1960; Savoldi *et al.*, 1960). Some authors, however, have been unable to see any change upon administration of catecholamines even when large doses were used (Gibbs *et al.*, 1937; Greenblatt *et al.*, 1947). Part of the contradictions in these results may be due to the method of analysis of the EEG which was used by the investigators. In unanesthetized animals the usual EEG pattern is one of periods of activation interspersed with periods of depression or drowsiness. By simple inspection of the records it is difficult to tell whether a short-acting drug may be responsible for an arousal pattern or whether the arousal may be spontaneous and a part of the highly variable EEG of unanesthetized animals.

For the past 2 years we have been using in our laboratory a method of analyzing voltage changes in the EEG first described by Drohocki (1948). This method allows us to evaluate, statistically, arousal or depression in the EEG. By using a sufficiently long control period in our measurements we were able to average out spontaneous fluctuations in the EEG and to determine the significance or lack of significance of the changes observed under drug effect. With this newer method of analysis we have undertaken to re-examine the influence on the EEG of adrenergic stimulant and blocking drugs. We have also attempted to find out, by such manipulations as spinal cord section and carotid sinus denervation, whether the effects on the EEG are predominantly central or peripheral.

METHODS. The experiments were performed on rabbits, cats and dogs. The rabbits were either albino or "California" adult males, weighing 2.5 to 4.0 kg. All the cats were adult females 2.5 to 4.0 kg in weight; the dogs were of both sexes, weighing 5.5 to 6.5 kg. A total of 101 animals were used in these studies.

The general experimental procedure was as follows. The animals were lightly anesthetized with ether and, after intubation of the trachea, they were curarized and subjected to artificial respiration. The dose of *d*-tubocurarine was 0.5 mg/kg given intravenously, followed immediately by 1.5 mg/kg subcutaneously. The same dose of 1.5 mg/kg was repeated subcutaneously every hour in order to maintain a stable paralysis. All

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[5] The term "stimulation" will be used in preference to the terms "arousal," "activation," or "waking reaction." It will be taken as being equivalent to them. Conversely the term "depression" will refer to the pattern called also "sedation," "drowsiness," or even "sleep."

subsequent surgical procedures were done under local anesthesia with procaine (2% solution). In the experiments involving carotid sinus denervation, care was taken to infiltrate the edges of the wound and all surrounding tissues with procaine. A constant supply of local anesthetic was provided in order to avoid pain. A dose of 1 mg/kg of heparin was administered intraarterially to prevent clotting of blood in the catheters. In rabbits, artificial respiration was provided at the rate of 40 to 60 per minute with a tidal volume of 40 to 50 ml, depending on the weight of the animal. In cats, the rate was 40 per minute with 50 ml as the tidal volume, and in dogs, 25 per minute, with a tidal volume of 100 ml. The artificial respirator used was driven directly by compressed, filtered air. Blood pressure was measured by a Statham P23AA transducer connected to the femoral artery, and recorded on an Offner oscillograph. The body temperature of the animals was monitored with a thermistor-thermometer and maintained between 37.5 and 38.5°C by radiant heat as needed.

The electrical activity of the cortex was recorded in bipolar arrangement with a Model T Offner EEG, from the anterior and posterior area of the fronto-parietal cortex, 10 mm in front and in rear of the coronal suture, at equal distances of 2 mm from the sagittal suture. The electrodes were small (1.25 x 2.00 mm) stainless steel wood screws. These were lightly engaged in the outer table of the calvarium, above the chosen regions of the cortex, where they were firmly held in place and insulated with dental plastic cement. The EEG from the anterior part of the fronto-parietal cortex was quantified by means of the Electronic Integrator of Drohocki (1948) of which a complete description has been recently published (Goldstein and Aldunate, 1960). Briefly stated, this device measures the surface under the successive rectified waves of the EEG and transforms this information into signals which are recorded on the Offner oscillograph together with the primary pattern. For any given time period the number of signals is directly proportional to the cumulative voltage output. In these studies the sensitivity of the integrator was adjusted so that 5 integration signals were recorded for a cumulative output of 100 μV in a 1-second period. The voltage output thus calculated will be termed hereafter "electrogenesis."

In this type of quantitative transformation of the EEG it is the voltage output which is measured. Therefore the shift from a state of wakefulness to a state of sedation is reflected in an *increase* in the number of integration signals. The shift from a sedated to a wakeful state, on the other hand, is accompanied by a *decrease* in the number of integration signals. This change in the number of integration signals is not completely specific for stimulation and depression since very high degrees of stimulation, such as a major seizure, will produce increases in electrogenesis as will deep depression. However, the pattern of the distribution of the signals under either of these states would be entirely different from that seen in our experiments and easy to recognize either in the integrated or nonintegrated patterns.

In each experiment the statistical significance or nonsignificance of the changes produced by the drugs was determined by comparing, on the basis of the standard t test, the mean number of signals before, during and after administration of the adrenergic drugs or antagonists. With control periods of sufficient duration, the spontaneous changes, mentioned above, were taken into account in the calculation of the statistical parameters of the means. For the presentation of the data, the EEG responses of the animals were converted into "yes" or "no" answers on the basis of the significance or lack of significance of the changes (see in table 1 how these classifications were performed). These results have been compiled in chi-square type tables. In most experiments the injection of the adrenergic drugs was preceded by test-injections of 0.85% saline solution.

Except for reserpine which was used in ready-made solution (Serpasil) the drugs were freshly dissolved or diluted in saline solution and injected into the femoral vein through polyethylene tubing. The catecholamines were administered rapidly, over an 8- to 10-second period, while the adrenergic blocking drugs and reserpine were injected slowly, over a 3- to 5-minute period.

The following drugs were used: *l*-epinephrine bitartrate; *l*-norepinephrine bitartrate hydrate; methoxamine hydrochloride; isoproterenol hydrochloride; dihydroergotamine methanesulfonate; phentolamine hydrochloride; azapetine phosphate; phenoxybenzamine hydrochloride; chlorpromazine hydrochloride; dichloroisoproterenol; reserpine; pentobarbital sodium; *d*-tubocurarine sodium. All the doses are expressed as salt weight.

For reasons which will become apparent later it is convenient here to separate the amines into two groups, one comprised of epinephrine, norepinephrine and methoxamine (the so-called "alpha type"), and the other isoproterenol (the so-called "beta type"). The drugs belonging to the first group, whenever spoken of together, will be abbreviated as E, N, and M, while those of the second group will retain their generic names in full.

RESULTS. *Effects of epinephrine.* The effects of

TABLE 1

Examples of the effects of catecholamines on cortical electrogenesis and on blood pressure, given alone, or after adrenergic blocking drugs, or after carotid sinus denervation (curarized rabbits)

Experimental Conditions	Control Values			Values Obtained 1 min Following Drug Injection			
	N		Mean ± S.E.	N		Mean ± S.E.	P‡
Epinephrine (2 μg/kg)	57	E*	4.70 ± 0.12	30	E	4.40 ± 0.13	0.10
		BP†	105 ± 0.2 / 68 ± 0.2		BP	150 ± 5.5 / 101 ± 3.7	
Epinephrine (2 μg/kg) after DCI (4 mg/kg) in same experiment as above	14	E	2.93 ± 0.17	30	E	0.80 ± 0.15	0.001
		BP	91 ± 0.4 / 48 ± 0.2		BP	163 ± 8.8 / 133 ± 8.0	
Epinephrine (5 μg/kg) after phentolamine (5 mg/kg)	20	E	5.05 ± 0.31	30	E	3.53 ± 0.12	0.001
		BP	94 ± 1.3 / 62 ± 1.4		BP	91 ± 1.6 / 62 ± 0.7	
Epinephrine (5 μg/kg) after DCI (4 mg/kg) and phenoxybenzamine (2 mg/kg)	14	E	4.94 ± 0.24	28	E	4.74 ± 0.65	0.50
		BP	118 ± 1.8 / 52 ± 0.9		BP	132 ± 1.1 / 63 ± 0.9	
Epinephrine (10 μg/kg) after phenoxybenzamine (2 mg/kg)	39	E	9.69 ± 0.47	30	E	14.10 ± 0.62	0.001
		BP	104 ± 1.0 / 43 ± 0.3		BP	84 ± 1.0 / 56 ± 0.3	
Norepinephrine (20 μg/kg) after phenoxybenzamine (2 mg/kg)	20	E	8.50 ± 0.54	30	E	8.30 ± 0.40	0.60
		BP	72 ± 0.0 / 44 ± 0.0		BP	70 ± 0.3 / 43 ± 0.3	
Isoproterenol (2 μg/kg)	28	E	6.71 ± 0.39	30	E	2.83 ± 0.69	0.02
		BP	89 ± 0.0 / 44 ± 0.0		BP	61 ± 2.5 / 21 ± 5.6	
Isoproterenol (4 μg/kg) after bilateral denervation of carotid sinuses	25	E	4.88 ± 0.39	30	E	6.33 ± 0.36	0.01
		BP	90 ± 1.4 / 47 ± 0.9		BP	65 ± 1.7 / 23 ± 1.2	

* Electrogenesis (mean number of integration signals/2 sec time periods, calculated on the number N of these periods. The number of animals involved in each type of experiment can be found in tables 2 and 3.)

† Blood pressure. Upper value: systolic; lower value: diastolic. Means calculated from the number N of measurements.

‡ Calculation from the *t* test performed on the comparison of the means during control period and 1 min following injection of the drug.

i.v. injections of epinephrine, 1 to 5 μg/kg, were studied in 54 experiments, of which 7 were on cats, 2 on dogs, and 45 on rabbits. In 37 experiments performed on rabbits no significant change in cortical electrogenesis was found, *i.e.*, the mean level of electrogenesis during control period prior to the injection was not significantly changed for any measurable time interval during or 3 to 5 minutes after the effect of epinephrine on blood pressure (table 1). In 8 rabbits a short-lasting but significant decrease in electrogenesis was observed. This consisted of the typical clear-cut shift of the EEG to a high frequency, low voltage pattern, corresponding to the stimulated state.

Since it is possible to show stimulation clearly only by testing drug effects on animals whose EEG pattern is one of depression, we were careful to inject epinephrine only in animals attaining this state either spontaneously or in response to a small dose of pentobarbital, 1.5 to 3.0 mg/kg. The relative proportion of animals responding to epinephrine was found to be the same in spontaneously depressed animals and in those receiving pentobarbital. Roughly the same proportion was found also in intact cats (of which 2 displayed a waking reaction and 5 did not), in rabbits and cats whose spinal cord was sectioned at C_2, and in rabbits whose carotid sinuses were denervated, with or without bilateral vagotomy.

The presence or absence of the stimulating effect of epinephrine appeared to be independent of the influence on blood pressure which was of the same order of magnitude in presence or absence of an EEG stimulant effect (table 1).

Effects of norepinephrine and methoxamine. The same general effects were obtained with 1 to 5 μg/kg of norepinephrine and with 200 to 500 μg/kg of methoxamine. Whenever a stimulant effect was found after one of the amines in a given animal, it was also observed with the other two. No significant differences were found in the duration of the stimulant action of epinephrine, norepinephrine or methoxamine. However, it will be seen later that a difference in the type of action of epinephrine and norepinephrine could be demonstrated after pretreatment with certain agents.

Effect of dichloroisoproterenol (DCI). In order to find out why E, N, and M showed an EEG stimulant effect in only a small proportion of the animals, the adrenergic blocking drugs were studied for their effect on the E, N, and M activity. The first of these to be employed was DCI, a drug that blocks the vascular and cardiac effects of isoproterenol (Powell and Slater, 1958), and thus a "beta adrenergic blocking drug" following Ahlquist's terminology (Ahlquist, 1948).

As can be seen in table 1, the effect of DCI was very clear. Before the administration of that drug only 20% of the 54 animals used responded to E, N, or M, and these with a stimulant effect of 15.4 ± 2.6 (standard error) seconds' duration. Ten minutes after a slow injection of 4 mg/kg of DCI, E, N, and M produced, at doses ranging from 1 to 5 μg/kg for epinephrine and norepinephrine, and from 200 to 500 μg/kg for methoxamine, a definite stimulant action in all 37 animals in which such experiments were performed. The mean duration of the stimulant effect was 45.3 ± 3.3 seconds; thus it was increased 3-fold in comparison to the mean value obtained in animals not treated with DCI.

An attempt to determine dose-response relationships for the interaction of E, N, and M with DCI was thwarted by the finding that DCI itself exerted a significant stimulant action. This prevented tests for the significance by the usual procedures. Although dose-effect curves could not be established for rendering manifest responses of E, N, and M after DCI, the threshold dose of DCI for this effect was determined to be between 0.5 and 2.0 mg/kg. In all the experiments performed on animals treated with DCI where stimulant effects of either E, N, or M were to be tested, caution was taken to administer small doses of pentobarbital (1.5 to 3.0 mg/kg) in order to obtain EEG patterns which allowed the stimulant effect to be detected.

In order to rule out possible reflex effects, E, N, and M were tested before and after DCI in animals with spinal cord section at C_2 (2 rabbits), bilateral vagotomy (8 rabbits), and after bilateral denervation of carotid sinuses (8 rabbits). None of these procedures changed the initial response to E, N, and M, or the modification of these responses by DCI. The same results were found in cats after spinal cord section at C_2 (2 animals) and bilateral vagotomy (2 animals).

Effect of alpha-adrenergic blocking drugs. The action of the so-called "alpha-blocking drugs"

on the effect of E, N, and M was studied next. In these series of experiments, alpha-blocking agents were administered only to those animals which showed initially consistent EEG stimulation after E, N, and M. If the animals did not respond initially to these three agents they were pretreated with DCI.

We found that the alpha-blocking drugs were of two kinds. After the administration of the drugs belonging to the first kind, comprised of phenoxybenzamine and chlorpromazine, the EEG effect of E, N, and M was entirely blocked. This was true in 14 out of 16 experiments performed on rabbits, whether the animals responded to E, N, and M without DCI or whether it was necessary to inject DCI to render their effect manifest. The minimum active doses were found to be 0.25 mg/kg for phenoxybenzamine, and 0.5 mg/kg for chlorpromazine. In these experiments the usual delay of 10 minutes for the development of the blocking action was allowed before injection of E, N, or M. The EEG action of epinephrine could be blocked at doses of phenoxybenzamine which had no measurable effect on blood pressure. With larger doses of phenoxybenzamine (1 to 2 mg/kg) both EEG and blood pressure effects of E, N, and M were blocked.

In 5 experiments, after 2 to 4 mg/kg of phenoxybenzamine, large doses of epinephrine (10 μg/kg) were administered. No EEG stimulant effect was produced, but in 3 of these animals a significant deepening of the depressant state was induced after a latency of 1 to 2 minutes. This corresponded to increases of cortical electrogenesis of 45% and more (table 1); at the same time the pressor effect was blocked and only the depressor action of epinephrine, manifested by a fall in blood pressure, remained. There was no apparent correlation between the decrease in blood pressure and the presence or absence of increased depression in the EEG. Under the same conditions it was observed that norepinephrine, even at a higher dose (20 μg/kg), did not change electrogenesis (table 1).

The second group of alpha-blocking drugs was composed of phentolamine, dihydroergotamine and azapetine. With none of these drugs, even at relatively large doses (respectively, 10 mg/kg, 0.5 mg/kg and 10 mg/kg), was the central effect of E, N, and M changed in any significant way. The pattern of stimulation appearing in animals pretreated with phentolamine (table 1), azapetine or dihydroergotamine, upon administration of E, N, or M was indistinguishable from that observed in absence of these adrenergic blocking drugs. The effect appeared in spite of the complete blockade of the action of E, N, and M on blood pressure.

It should be emphasized at this point that the two alpha-blocking agents which suppressed the EEG stimulant effect of E, N, and M, namely phenoxybenzamine and chlorpromazine, produced by themselves, at doses of 0.5 and 1.0 mg/kg, respectively, a depressant effect on the EEG patterns. On the other hand the three blocking drugs which had no action on the EEG response to E, N, and M, namely phentolamine, dihydroergotamine and azapetine, did not by themselves change the brain waves.

All the results obtained with epinephrine and norepinephrine, with or without pretreatment with blocking drugs, are summarized in table 2.

Effect of reserpine. In 7 rabbits reserpinized by i.v. injection of 1 mg/kg of reserpine 4 hours prior to the experiment, thus at a point where according to Brodie *et al.* (1957) the level of brain catecholamines is at a minimum, the effect of E, N, and M, of DCI and of the alpha-blocking drugs was studied. All of the foregoing that concerns nonreserpinized animals applies as well to reserpine-treated animals, except that the EEG and vascular effects of E, N, and M were found to be markedly increased in intensity and duration.

Effect of isoproterenol. Isoproterenol, a so-called beta-stimulant drug, was administered i.v. to 27 rabbits in doses ranging from 1 to 5 μg/kg. In 20 of these isoproterenol elicited a short-lasting but significant stimulating effect, very similar to the one observed with E, N, and M (table 1). In 7 rabbits there was no significant change in EEG pattern after injection of isoproterenol. This stimulant effect produced by isoproterenol was also observed in 7 cats and 2 dogs, while it was absent in 5 cats and 2 dogs.

The EEG effect of isoproterenol was blocked by DCI and by all of the alpha-blocking drugs used in these studies. In the case of DCI the suppression of the EEG stimulant effect of isoproterenol was accompanied also by blockade of its vascular action. After treatment with the alpha-blocking agents, the EEG effect of isoproterenol was suppressed without any significant

TABLE 2

EEG effects obtained with small and large doses of catecholamines, with or without pretreatment with adrenergic blocking drugs in curarized rabbits

Pretreatment	Epinephrine 2–5 μg/kg	Norepinephrine 2–5 μg/kg	Epinephrine 10 μg/kg	Norepinephrine 20 μg/kg
None	No effect (35/43)*	No effect (35/43)	No effect (5/7)	No effect (3/4)
DCI	Stimulant effect (26/26)	Stimulant effect (26/26)	Stimulant effect (3/3)	Stimulant effect (3/3)
Phenoxybenzamine or chlorpromazine†	No effect (14/16)	No effect (14/16)	Depression (3/5)	No effect (3/3)
Phentolamine, or dihydroergotamine or azapetine†	Stimulant effect (18/18)	Stimulant effect (18/18)	—	—

* Proportion of animals in which the reported effect was observed (and calculated as being significant by the method exemplified in table 1) to the total number of animals used.

† DCI (4 mg/kg) was injected 10 minutes before administration of the blocking drugs in those animals which did not respond initially to the catecholamines.

change in its effects on blood pressure and on heart rate.

These findings suggested that the EEG stimulant effect of isoproterenol might be different from the EEG stimulant effect of the other amines, E, N, and M. As with the effects of E, N, and M, the stimulant action of isoproterenol persisted after spinal cord section at C_2 and bilateral vagotomy, but it was completely blocked after bilateral denervation of the carotid sinuses. As a matter of fact, large doses of isoproterenol (4 to 10 μg/kg) administered to rabbits whose carotid sinuses were denervated produced, in 2 out of 3 such experiments, an increase in EEG depression, corresponding to increases of 30% and more of cortical electrogenesis. This same observation was made in 3 out of 5 animals whose carotid sinuses were intact and to which large doses of isoproterenol were administered following 2 mg/kg of phenoxybenzamine. For instance, over and above the depressant effect resulting from the alpha-blocking drug by itself, isoproterenol at a dose of 10 μg/kg produced 30 to 50% increases in cortical electrogenesis in 2 animals.

All the results obtained with isoproterenol, with or without pretreatment or manipulation, are summarized in table 3.

TABLE 3

EEG effects obtained with small and large doses of isoproterenol with or without drug pretreatment or carotid sinus denervation in curarized rabbits

Pretreatment	Isoproterenol	
	2–5 μg/kg	10 μg/kg
None	Stimulant effect (20/27)*	— —
DCI	No effect (9/9)	No effect (2/2)
Phenoxybenzamine	No effect (16/19)	Depressant effect (3/5)
Phentolamine, dihydroergotamine or azapetine	No effect (15/19)	Depressant effect (4/6)
Carotid sinus denervation	No effect (7/7)	Depressant effect (2/3)

* Proportion of animals in which the reported effect was observed (and calculated as being significant by the method exemplified in table 1) to the total number of animals used.

Discussion. The experimental findings presented in this study can be examined first from the standpoint of the relationships between the effects of amines on the EEG and on blood pressure. It was suggested recently by Capon (1960) that the EEG effects of epinephrine are only due to the pressor action of that drug. If one compares the three kinds of EEG patterns defined in these studies, stimulation, depression, no change, with the status of blood pressure during their occurrence, one can see that the

same effect, a shift from a depression to a stimulation, was observed under normotensive, hypotensive and hypertensive states. The alternate shift, that from a stimulation to a depression pattern, was found in both normotensive and hypotensive animals. Furthermore under both a change from normotension to hypertension or from normotension to hypotension, no EEG alterations were observed. The only condition which was never found was that of EEG depression under hypertension. From this the conclusion of independence between the two variables, EEG and blood pressure levels, appears difficult to avoid. However, the possibility remains that a correlation does exist but with parameters not measured in these studies, especially blood flow. If such were the case, one would have to assume that DCI is capable of modifying blood flow responses to epinephrine, norepinephrine and methoxamine without affecting in any apparent way the directly measurable pressor effect of these amines.

Contrary to what was reported by Bonvallet *et al.* (1954) from experiments performed on cats, it has been our constant finding that pentobarbital does not abolish the stimulant effect of the amines in either rabbits, cats or dogs, provided the dose of barbiturate administered is small (1.5 to 3.0 mg/kg) and the animals are able to respond to the amines (which is realized, as previously pointed out, in only 20% of them). In all the animals pretreated with DCI the EEG stimulant effect of E, N, and M was obtained, even when pentobarbital at the above stated doses was injected in order to induce an EEG pattern permitting detection of stimulant actions.

The next question concerns the mode of action of adrenergic blocking drugs, either by themselves or as affecting the action of the amines. Insofar as DCI is concerned, the existence of a threshold dose for its action in rendering manifest the effect of E, N, and M on the EEG could indicate that DCI being rapidly destroyed or bound at small doses cannot reach its reactive sites within the usual delay of 10 minutes observed in these studies. It could also indicate that the action of that drug is of an unmasking nature. Whatever may be the case, the finding that for a dose of 4 mg/kg DCI could produce conditions under which the effects of E, N, and M became significant in all the animals argues in favor of the action of DCI on some important mechanism involved in the reactivity of the EEG to E, N, and M.

On the question of the effect of alpha-blocking drugs, we do not have any explanation at present for the difference in the activity of phenoxybenzamine and chlorpromazine, on the one hand, and of phentolamine, dihydroergotamine and azapetine, on the other hand. Two assumptions could be made, either the existence of a difference in the affinity or access of these agents to the sites of action of E, N, and M on the EEG, or possibly a dosage level problem. It remains to be seen if with higher doses of phentolamine, dihydroergotamine and azapetine the blockade of the effect of E, N, and M on the EEG could be obtained. If such were the case it would mean that the blockade of the EEG effects is not proportionate in these agents to the blockade of the peripheral effects, as is the case with phenoxybenzamine and chlorpromazine. In fact, as has been shown, it was possible with these last two blocking agents to suppress the EEG effects of E, N, and M at doses below the level producing a blockade of the pressor effects.

The last, and perhaps most controversial question, concerns the very nature of the action of the amines on the EEG. The evidence presented suggests an independence between the effect of these drugs on blood pressure and on the EEG. In addition, it was found in these studies that section of the spinal cord at C_2 did not change EEG effect of the amines; a similar conclusion was reached by Bonvallet *et al.* (1954) and by Rothballer (1956) for the effect of these drugs on the "encéphale isolé" preparation. From this, one could conclude that the amines probably exert a direct action on the brain. However, it must be kept in mind that neither in spinal animals nor in those with midpontine transection is the innervation of the head destroyed; therefore, what are usually considered as formal conditions for detecting purely central actions may be open to question. If one accepts the existence of a central action of the amines, however, all the data presented in this paper could be explained on the basis of either of the following hypotheses.

The first postulate is that there are two kinds of adrenergic receptors in the brain, stimulant and depressant receptors, somehow resembling but not identical with the alpha and beta pe-

ripheral adrenergic receptors. The reactivity of an animal to the amines at any one moment would depend on the relative state of these receptors. Thus if the depressant receptors are actively functioning, any "activation" of the stimulant receptors will be counteracted and no change will ensue. If the depressant receptors are blocked, either spontaneously or after administration of DCI, no such counteracting will be possible and a definite stimulant effect will be obtained on activating the stimulant receptors. Conversely when the stimulant receptors are blocked, the activation of the depressant receptors will lead to a depression. This is what occurs when isoproterenol is administered after phenoxybenzamine, and also when a large dose of epinephrine is injected to animals under the same pretreatment. A further indication of the possibility of existence of such a dual mechanism is provided by the lack of depressant action of pure alpha stimulant drugs, such as norepinephrine, under the same conditions. If this hypothesis were accepted it would introduce a new concept concerning "central" adrenergic mechanisms, which are most often considered as purely stimulant, "ergotropic" in Hess's terminology (Hess, 1954). It would indicate that these mechanisms could be responsible for certain phenomena of depression as well as stimulant actions.

But this explanation of a central effect, which can account for all our experimental findings (and must be therefore considered as an "operational hypothesis") is not the only possible one. As previously mentioned, DCI exerts by itself a stimulant effect on the EEG. This could be interpreted not as the suppression of the action of hypothetical depressant receptors, but as an effect on stimulant receptors. The action of E, N, and M after DCI would not result from the blockade of supposed depressant receptors but from the combined action of DCI and of E, N, and M on the same receptors, which would be only stimulant. One would be back to Hess's conception that, at the level of the brain, the adrenergic system is entirely stimulant in nature.

We do not have at present any decisive fact which would allow us to choose between these two concepts. Further work along these lines, especially recordings from the reticular formation, which are now in progress, may provide more facts on which to decide in favor of one or the other.

SUMMARY

A quantitative EEG study was made of the action of adrenergic stimulant and blocking drugs. It was found that:

At doses of 1 to 5 μg/kg, epinephrine or norepinephrine exerted an EEG stimulant action in only 20% of the animals. The same was true for methoxamine at 200 to 500 μg/kg.

This effect could be obtained in all the animals when epinephrine, norepinephrine and methoxamine were administered after a pretreatment with 4 mg/kg of DCI. The EEG effect appeared to be independent of the vascular action of epinephrine, norepinephrine and methoxamine.

Alpha-blocking drugs were found to belong to 2 groups: either they blocked entirely the EEG stimulant action of epinephrine, norepinephrine and methoxamine (phenoxybenzamine and chlorpromazine), or they did not change their effect in any way (dihydroergotamine, phentolamine and azapetine).

Isoproterenol exerted an EEG stimulant action which could be blocked by DCI, by all the alpha-blocking drugs used, and by denervation of the carotid sinuses.

When the indirectly determined stimulant EEG action of isoproterenol was suppressed one could demonstrate an EEG depressant effect with large doses of this catecholamine.

When alpha-blocking drugs capable of suppressing the stimulant effect of the amines on the EEG, such as phenoxybenzamine, were administered, one could obtain depressant EEG actions with epinephrine, but not with norepinephrine.

Assuming a direct central effect of the amines, these experimental findings are discussed. Two hypotheses are presented of which one involves the existence of adrenergic stimulant and depressant receptors in the brain.

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