BRAIN AMINES AND ELECTROSHOCK CONVULSIVE THRESHOLD[1]

By

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In order to avoid the disadvantages inherent to the supramaximal electroshock method in studying the influence of drugs on the convulsive threshold, a new electroshock method was developed, in which the minimal electrical energy required to provoke a typical convulsive seizure is determined on the basis of impedance measurements of the brain. (Delaunois *et al*, 1962).

According to this method, rectangular DC pulses, with a duration of 2 millisec. and a frequency of 125/sec., were applied for 0.5 sec. in unanesthetized rabbits with implanted electrodes. Application of these stimuli at an energy level of 0.2 W.sec. provokes in intact rabbits a typical convulsive seizure, characterized, after a latency period of 3.0 sec. $\pm$0.9 sec., by the occurrence of a flexion of the fore and hindlegs, an extension of both fore and hindlegs accompanied by a more or less pronounced hyperextension of the trunk, of a duration of 16.4 sec. $\pm$ 3.5 sec., and finally a shorter lasting and less pronounced clonic phase.

This method has been applied to the experimental study of pharmacological substances which are known to influence the level of brain amines. Control electroshocks were applied one week before administration of drugs.

Thus a decrease of the levels of brain amines was obtained by means of reserpine, dimenthylaminobenzoyl methylreserpate (Su-5171) (Brodie *et al* 1960) α-methyl-dihydroxyphenylalanine (Hess *et al.*, 1961) and α-methyl-m-tyrosine Brodie and Costa (1962).

A selective increase of brain serotonin and a combined increase of brain serotonin and noradrenaline, on the other hand, were provoked by pretreatment with 5-hydroxytryptophan or β-phenylisopropyl-hydrazine (JB-516) and by pretreatment with β-phenylisopropyl-hydrazine (JB-516) or β-phenylisobutyl-hydrazine (JB-835) respectively (Brodie, *et al.*, 1959). A selective increase in brain dopamine was obtained by means of a combined pretreatment with reserpine, iproniazid and l-dihydroxyphenylalanine (Carlsson, 1959).

As shown in Table I reserpine provokes a marked decrease of electroshock convulsive threshold. Since reserpine lowers brain serotonin as well as brain catecholamine levels, the question arises whether this decrease of electroshock threshold,

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which is also prevented by monoamine oxidase inhibitors, may be attributed more precisely to one or another of these amines.

TABLE I

Experimental conditions Drug (dose in mg/kg, route of administration, time of administration before electroshock)	Amine levels in % of normal (average values in groups of 8 animals)		% Increase (+) or Decrease(−) of electroshock threshold
	Serotonin	Noradrenaline	
Reserpine (1, i.v., 16 hrs)	10	9	−62
∝-Methyl-m-tyrosine (50, i.v., 13 hrs)	100	0	−50
Reserpine (1, i.v., a 23° C, 2 hrs)	25	20	−50
Reserpine (after 3 hrs a 4° C, 1, i.v., 2 hrs a 4° C)	65	25	−42
Su-5171 (2, i.v , 1 hr)	35	30	−35
Su-5171 (2, i.v., 6 hrs)	60	30	−30
∝-Methyl-dihydroxyphenylalanine (400. i.p., 4 hrs)	25	50	−32
∝-Methyl-dihydroxyphenylalanine 400, i.p., 18 hrs)	80	50	−30
Su-5171 (0.25, i.v., 4 hrs)	85	55	−25
5-Hydroxytryptophan (50, i.p., 1 hr)	270	100	0
JB-516 (2, i.v., 1 hr)	169	104	−10
JB-516 (2, i.v., 23 hrs)	183	140	0
JB-835 (10, daily, i.p. for 3 days	332	182	0

Using reserpine, the reserpine analogue Su-5171, ∝-methyl-dihydroxy phenylalanine and ∝-methyl-m-tyrosine, more or less selective decreases of either brain serotonin or brain noradrenaline levels may be obtained at well-defined periods of time after administration of these drugs.

It can be seen from Table I that there is no parallelism between the decrease of electroshock threshold and the decrease of brain serotonin, whereas a very good relationship holds between the decrease of electroshock threshold and the decrease of brain noradrenaline.

Selective or combined increases of brain serotonin and noradrenaline, on the other hand, provoked by pretreatment with 5-hydroxytryptophan and JB-516 or JB-835 respectively, were not found to significantly modify the electroshock threshold.

The selective increase (4.7 mcg/g vs. 0.28 mcg/g in controls) of brain dopamine, however, provoked by pretreatment with reserpine (1mg/kg, i.v., 21 hrs. before electroshock), iproniazid (100 mg./kg., i.p., 13 hrs. before electroshock), and 1-dihydroxyphenylalanine (75 or 25 mg/kg, i.p., 1 hr. before electroshock) *was followed by a very pronounced increase of electroshock* threshold, which appeared to be dose-dependent for 1-dihydroxyphenylalanine *(300% increase for 75 mg/kg of 1-dihydroxyphenylalanine* vs. 100% increase for 25 mg/kg of 1-dihydroxyphenylalanine).

These experimental observations suggest that brain dopamine levels are of importance in determining the sensitivity to electroshock.

Another series of experiments corroborated this point of view. In these experiments a very pronounced increase of electroshock convulsive threshold was found to occur after administration of amphetamine or imipramine. (Table II). This increase

TABLE II

Experimental conditions: Drug (dose in mg/kg, route of administration, time of administration before electroshock)	% Increase (+) or decrease (−) of electroshock threshold (average values in groups of 10 animals)
Amphetamine (20, i.v., 5 min)	+ 900
Reserpine (I, i.v., 24 hrs) + Amphetamine (20, i.v., 5 min)	0
Iproniazid (100, i.p., 24 hrs) + Amphetamine (20, i,v., 5 min)	+ 1300
Reserpine (I, i.v., 21 hrs) + Iproniazid (100, i.p., 13 hrs) + l-Dihydroxyphenylalanine (25, i.p., 1 hr) + Amphetamine (20, i.v., 5 min)	+ 2500
Imipramine (5, i.v., 5 min)	+ 5900
Reserpine (I, i.v., 24 hrs) + Imipramine (5, i.v., 5 min)	+ 75
Iproniazid (100, i.p., 24 hrs) + Imipramine (5, i.v., 5 min)	+13.750
Reserpine (I, i.v., 21 hrs) + Iproniazid (100, i.p., 13 hrs) + l-Dihydroxyphenylalanine (50, i.p., 1 hr) + Imipramine (5, i.v., 5 min)	+15.000
∝-Methyl-n-tyrosine (50, i.v., 13 hrs) + Imipramine (5, i.v., 5 min)	+15.000

did not occur in reserpinized animals. Since reserpine decreases serotonin as well as noradrenaline and dopamine levels in the brain, the question arises again whether one or another of these substances may be regarded to be specifically operative in the mechanism of action of this effect of amphetamine and imipramine.

Our experimental observations show that this effect is more marked in presence of a combined increase of brain serotonin and catecholamine levels, i.e. after pretreatment with iproniazid, whereas a very pronounced potentiation occurs in presence of selectively increased brain dopamine levels, i. e. after combined

pretreatment with reserpine, iproniazid and l-dihydroxyphenylalanine. These observations produce additional evidence for a dopamine-mediated mechanism in determining the electroshock convulsive threshold.

It is noteworthy that the imipramine-induced increase in electroshock threshold still occurs in case the brain noradrenaline stores have been completely depleted by pretreatment with ∝-methyl-m-tyrosine.

In conclusion, our experimental observations point to a relationship between the level of brain dopamine and the electroshock convulsive threshold and suggest that amphetamine and imipramine induce an increase in electroshock threshold through the same dopamine-mediated mechanism, e.g. by provoking a sensitization towards dopamine. This would also explain why imipramine facilitated the effect of amphetamine on spontaneous motor activity. (Vernier, *et al.*, 1962)

The present findings on the influence of drugs and brain dopamine levels on the convulsive threshold may also have clinical implications. First, the possibility of reducing this threshold and thus the total electroshock energy required may perhaps allow the application of therapeutically effective electroshocks with less danger of unwanted cerebral complications, such as permanent memory damage. Second, these experimental observations may be of importance with regard to both the pathogenesis and the pharmacotherapy of Parkinsonism, (Bernheimer, *et al.*, 1963, and Friedhoff, *et al.*, 1963).

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