CCXIX. THE EFFECTS OF AMINES ON OXIDATIONS OF THE BRAIN.

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(Received August 29th, 1933.)

AN investigation into the effects of narcotics on the oxidative processes of the brain has shown [Quastel and Wheatley, 1932, 1, 2] that these substances exert specific inhibitions at low concentrations. The oxidations of glucose, sodium lactate and sodium pyruvate are markedly affected whilst those of sodium succinate and *p*-phenylenediamine are unimpaired. This generalisation holds for all narcotics investigated, the inhibitory power varying, among narcotics of the same chemical type, with the hypnotic activity. A view of the mechanism of narcosis, which fits the observed facts, is that the narcotic is adsorbed from the blood-stream at a specific area or centre of the nervous system. Here it diminishes the ability of the cells constituting the nervous centre to activate lactic or pyruvic acid and in this way inhibits the oxidation by these cells of glucose, lactic or pyruvic acid. The activation and access of oxygen remain unimpaired, but, in consequence of the inhibition of oxidative powers, a lowered amount of energy is available to the narcotised nervous centre for the accomplishment of its functional activity. Narcosis—or a depression of the normal activity of the centre in question—may then ensue. In spite therefore of the fact that oxygen is freely available, a state equivalent to partial anoxaemia exists at those areas of the nervous centre where the narcotic is adsorbed. The results of experiments carried out under anaerobic conditions (oxygen being replaced by methylene blue) show that the adsorption of the narcotic is reversible, a competition taking place between lactic acid and the narcotic for possession of the active surfaces in the nervous centre [Davies and Quastel, 1932].

A development of this work now shows that there exist substances, normally produced in the body, whose effects on the oxidative processes of the brain closely resemble those of the narcotics. This result is of particular significance in the study of mental disorder. Recent investigations [McFarland, 1932] have indicated that the psychological reactions following anoxaemia and light narcosis closely resemble those found in certain psychotic disorders. It is not unreasonable to consider that if substances normally produced in the body have effects similar to those of the narcotics and can induce an anoxaemia in the nervous system, they may be held, when present in the blood-stream in more than ordinary quantities, partially responsible for psychotic manifestations.

The substances in question have been found to be chiefly degradation products derived from tyrosine and tryptophan.

Experimental method.

The technique employed in this investigation has been described fully in previous papers by the writers [1932, 1, 2] in which all details are available. The method consists, briefly, in allowing mixed (whole) brain tissue, usually of the guinea-pig, to take up oxygen at 37° in a Barcroft respirometer until the rate of uptake has fallen to between 50 and 75 % of the initial value. After this period (about 2½ hours) glucose, sodium lactate or other metabolite under investigation is added to the tissue and the new rate of oxygen uptake determined. This rate is compared with that obtained by brain tissue exposed from the commencement of the experiment to the substances whose narcotic effects are the subject of this study.

The experiments are carried out on 0.5 g. tissue (made as homogeneous as possible by chopping with a scalpel) in a saline-phosphate (*M*/15) medium at an initial p_H of 7.4. The amines *etc.* are dissolved in saline and brought to neutrality before adding to the brain tissue. Measurements of O_2 uptake are made at 15 minute intervals, all the Barcroft vessels containing air. Experiments have been carried out with brain (cortex) slices in an atmosphere of oxygen, but, since it appears a characteristic feature of brain that mincing or chopping in the manner described does not appreciably affect its oxidative mechanisms (so far as the substances mentioned in this paper are concerned) and since the magnitude of the Q_{O_2} of brain slices (in oxygen) is much the same as that of minced brain (in air), the writers have confined themselves almost exclusively to work with the minced tissue. The results which have been obtained with brain slices are in agreement with those with the minced tissue.

Results.

The amounts of oxygen consumed by 0.5 g. guinea-pig (whole) brain tissue, normally and when exposed to various amines (usually at a final concentration of 0.12 %), in presence of glucose, sodium lactate, pyruvate, succinate and

Table I. *mm.³ O_2 taken up in 2 hours at 37° by 0.5 g. guinea-pig brain tissue, normally, and in the presence of various amines, after 2½ hours' oxidation prior to the addition of glucose, sodium lactate *etc.**

Amine 0.12 %	Metabolite.					
	Saline	Glucose 0.025 %	Sodium lactate 0.025 <i>M</i>	Sodium pyruvate 0.025 <i>M</i>	Sodium succinate 0.05 <i>M</i>	Sodium glutamate 0.05 <i>M</i>
None	287	615	721	785	1698	591
β -Phenylethylamine	303	462	594	520	1739	426
β -Phenyl- β -hydroxy-ethylamine	331	486	576	537	1808	482
β -3:4:5-Trimethoxy-phenylethylamine (Mescaline)	313	392	480	455	1744	436
Tyramine	242	285	296	293	540	275
Indole*	184	376	415	413	1558	221
isoAmylamine	208	287	302	342	1678	298
Neurine	290	672	848	788	1584	573
Cadaverine	317	570	686	613	1780	569
Putrescine	321	601	717	642	1660	540
Ethylamine	369	605	805	—	1585	—
Histamine†	315	670	813	877	1700	652

* 0.5 cc. of a saturated solution of indole in saline at 37° was added to the brain tissue in the saline-phosphate medium, the final volume being 4 cc.

† Present as 0.12 % histamine acid phosphate (neutralised).

glutamate are recorded in Table I. The amounts given are those found in typical experiments and afford a basis for comparison of the inhibitory effects of certain amines on brain oxidations. They are the values obtained after the brain tissue had been allowed largely to deplete itself of oxidisable material by shaking in air at 37° for 2½ hours prior to addition of the metabolites under investigation. The amines had been added to the brain at the commencement of the experiment so that exposure to these substances had occurred for 2½ hours before metabolites were added.

Normally under these experimental conditions constant and reproducible results may be obtained [Quastel and Wheatley, 1932, 1]. The values of the amounts of oxygen taken up by untreated guinea-pig brain in presence of various metabolites are shown on the first line of Table I. The rest of this table shows the effects of exposure of the brain tissue to various amines on the amounts of oxygen consumed. Calculations of the percentage inhibitions effected by these amines on the extra oxygen uptakes due to the addition of metabolites are shown in Table II. Included in Table II, for purposes of comparison, are

Table II. *Percentage inhibition by amines of extra oxygen uptakes due to various metabolites.*

Amine 0.12 %	Glucose	Sodium lactate	Sodium pyruvate	Sodium succinate	Sodium glutamate
β -Phenylethylamine	52	33	44	0	60
β -Phenyl- β -hydroxyethylamine	53	44	54	0	50
Mescaline	76	62	72	0	59
Tyramine	87	88	88	79	89
Indole*	41	47	54	3	87
<i>iso</i> Amylamine	76	79	73	0	70
Neurine	0	0	0	8	7
Cadaverine	26	15	41	0	17
Putrescine	15	9	36	5	28
Histamine	0	0	0	2	0
Narcotic 0.12 %					
Allyl <i>iso</i> propylbarbituric acid	73	71	67	2	28
Phenylethylbarbituric acid	94	79	85	0	50
Hyoscine	79	73	71	0	60
Chloral	66	90	90	0	62

* See footnote, p. 1610.

the percentage inhibitions of oxygen uptakes effected by typical narcotics—allyl*iso*propyl- and phenylethyl-barbituric acids, hyoscine and chloral—the experiments being carried out in the same manner as for the amines.

A characteristic feature of narcotic activity is the large inhibitory effect on the oxidations of glucose, sodium lactate and pyruvate, and little or none, at the concentrations used, on that of sodium succinate. It will be observed from Tables I and II that there exists a similar behaviour on the part of a number of amines.

Whilst cadaverine, putrescine, neurine and ethylamine have relatively little action on the oxidation of glucose or sodium lactate at the concentrations used, tyramine, β -phenylethylamine and β -phenyl- β -hydroxyethylamine have relatively large inhibitory effects. Mescaline (β -3 : 4 : 5-trimethoxyphenylethylamine), well known for its production of visual hallucinations and used of late in psychiatric studies, has similar large effects. Indole¹ and *iso*amylamine also have considerable inhibitory actions, but histamine is without effect.

¹ Skatole is also highly effective in diminishing the oxidation of glucose by brain.

A notable feature is the exceptionally toxic action of tyramine. Whilst the other derivatives of tyrosine exert specific effects similar to the narcotics, tyramine has a considerable inhibitory action on the oxidation of sodium succinate. This would indicate a more widespread inhibition of the oxidative changes of the brain by tyramine than by the basic amines and narcotics so far investigated. Another point of some interest is the inhibitory action of cadaverine and putrescine on the oxidation of sodium pyruvate with relatively little effect on that of glucose and sodium lactate.

The results as a whole show clearly that amines of the aromatic type, together with *isoamylamine*, exert effects upon brain oxidations which resemble those of the narcotics. There is the same relatively large inhibitory action¹ on the oxidation of glucose and sodium lactate and, except in the case of tyramine, a lack of effect on the oxidation of sodium succinate. The oxidation of sodium glutamate is also considerably affected by the amines and by narcotics. The magnitude of the effects is of the same order as that of the narcotics at the concentrations used.

Whilst the explanation of this behaviour of the amines is probably similar to that of the narcotics, *i.e.* a competition with lactic acid *etc.* for the active surfaces involved, the practical result is of some importance.

Many of the substances studied are normally produced in the bacterial breakdown of amino-acids. Their passage into the liver after absorption into the blood from the intestine is followed by their detoxication—either conjugation as in the case of indole or oxidation as in the case of tyramine. A disturbance in the hepatic detoxicating mechanisms might lead to the circulation in the blood of more than the ordinary quantities of these bases, and this would be expected to lead ultimately to the production of psychological reactions similar to those met in anoxaemia or in the early stages of narcosis. It is not unreasonable therefore to suspect a disturbance in hepatic function as a causative element in certain types of mental disorder. Investigations of the metabolic events in the liver and their possible variations in certain psychotic conditions are clearly necessary and such work is now in progress.

SUMMARY.

1. An investigation has been made of the effects of a number of amines on the oxidations of brain tissue.

2. β -Phenylethylamine, β -phenyl- β -hydroxyethylamine, tyramine, indole, *isoamylamine* and mescaline inhibit strongly the oxidation of glucose, sodium lactate and sodium pyruvate by the brain. They also inhibit the oxidation of sodium glutamate but, with the exception of tyramine, they have little or no effect on the oxidation of sodium succinate. Tyramine presents the only instance so far of an amine or narcotic affecting succinate oxidation at the concentration used. The effects of these amines are similar to, and are of the same order of magnitude as, those of typical narcotics (*e.g.* luminal, hyoscine, chloral).

3. Neurine, cadaverine, putrescine, ethylamine and histamine have relatively little effect on the oxidation by the brain of glucose, sodium lactate or sodium succinate.

¹ The inhibition decreases with decrease in concentration of amine (or of narcotic), definite inhibitions being observed at concentrations considerably lower than 0.12 %. The latter concentration was chosen to give results quite outside experimental error and clearly to indicate the specificity of behaviour.

4. The bearing of these results on the study of certain types of mental disorder is considered.

We are much indebted to the Medical Research Council for a grant to this laboratory in aid of equipment and for a whole time grant to one of us (A. H. M. W.)

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