CXLVI. THE EFFECTS OF ETHER ON BRAIN OXIDATIONS

By MAURICE JOWETT[1] and JUDA HIRSCH QUASTEL
From the Biochemical Laboratory, Cardiff City Mental Hospital

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The view has been advanced [Quastel & Wheatley, 1932] that narcotics exert their characteristic effects by depressing oxidations in the central nervous system. In a recent paper [Jowett & Quastel, 1937] the effects of certain narcotics (chloretone and two barbiturates) on brain oxidations have been examined.

In the present paper are presented experiments on the effects of ethyl ether on brain oxidations. The volatility of ether causes some experimental difficulties, but ether has advantages for our purpose over the non-volatile narcotics already studied. The volatility of ether has been utilized to determine its concentration in the manometric vessels, thereby eliminating possible uncertainties in its concentration in the medium due to its being taken up by the tissue. Another advantage of ether is that its anaesthetic concentration is known.

The results show that ether is like the other narcotics in some respects, unlike in others.

Experimental methods

The manometric methods of Warburg have been used, with slices of the grey matter of the cerebral cortex of the rat or guinea-pig. Usually 10–20 mg. dry weight of brain are used, in 3 ml. of medium, containing 0·001 *M* Ca^{++}, 0·0008 *M* Mg^{++} and 0·02 *M* phosphate of *p*H 7·2 or 7·4, in addition to NaCl and various constituents which are named. Carbon dioxide is absorbed in caustic soda.

The new feature of the work is the use of ethyl ether. Ether is transferred to the manometric vessels from wash-bottles containing a solution of ether in water. Oxygen is driven through a train of three narrow wash-bottles each containing about 120 ml. of ether solution and mounted in the thermostat. The circuit contains a wash-bottle in which the rate of bubbling can be counted and (by calibration) converted into gas volumes. The ether-oxygen mixture is passed into a manometer through the tap at the top, and leaves the vessel through a gas-tap. Frequently the mixture is passed through two manometer vessels in series. During the treatment with gas the vessels, containing tissue, are shaken at about 100 complete swings per min., and the manometer fluid is moved up and down a number of times.

If the gas treatment is too short, the vessels will contain a lower concentration of ether than the wash-bottles. If it is too long, the last wash-bottle in the circuit will lose some ether and again a low concentration will be found in the vessels. We have usually passed through about 300–600 ml. of oxygen during a period of 8 min. A method of estimating ether concentrations in the vessels has been devised [Jowett, 1937], by which it has been found that the technique described usually results in obtaining a calculated concentration of ether in the vessels equal to 80–95 % of that originally present in the wash-bottles. The low

[1] Beit Memorial Research Fellow.

and variable results are due to the rough way in which equilibration was carried out; finer regulation of gas flow and perhaps a longer train of wash-bottles would be desirable. When two manometric vessels were treated with gas in series, the second vessel showed an ether concentration about 6 % lower than the first.

The detailed application of the method of estimation is as follows. When respiration measurements are complete, excess acid (say, 0·1 ml. of 4N H_2SO_4) is tipped from a side-tube into the main compartment of the manometer vessels. After 20 min. shaking, manometer readings are made on the vessels containing ether and on at least one vessel containing none. The thermostat temperature is then altered (usually lowered) by 1·5–4·5°, and 15 min. later the manometers are read again. The temperature change is made as large as is compatible with keeping the readings within scale limits. The calculation of results is described elsewhere [Jowett, 1937]. The values calculated are considered to be accurate within a few per cent. The accuracy is sufficient for our purpose.

After etherizing manometer vessels, the readings of vessels containing no tissue become constant in a few minutes (as also do the readings of vessels containing tissue after acidification). This constancy is of course an almost indispensable condition of the experiments, and it allows us to use vessels containing oxygen only as thermo-barometer controls for ether-containing vessels.

When tissue is present, its respiration gives reasonable and consistent values if the first reading is made 10–12 min. after ceasing to etherize. It appears that the tissue reaches equilibrium with ether rapidly. This is convincingly shown in the experiments with succinate as substrate (Figs. 9 and 10), where the presence of ether has no apparent effect on the respiration of brain. If ether continued to be taken up by the tissue appreciably during the period of measurements, but at a decreasing rate, we should see superimposed on the true respiration an acceleration by ether which disappeared as time passed. It is unlikely that the true effect of ether at two different concentrations should be such as exactly to counterbalance the effect of an absorption of ether, and that the true effect should be an evanescent inhibition. Similar arguments, of varying force, can be applied to other curves, and the conclusion can safely be drawn that slow equilibration of tissue with ether does not appreciably affect our results. A possible exception exists with regard to loss of ether from tissues.

Two methods of experiment have been employed: (1) before etherizing one of two experimental vessels, measurement of the respiration in both is made for a period, and subsequent effects of ether in one vessel are calculated with reference to these initial measurements as a basis; or (2) one of the vessels is etherized at once on placing in the thermostat, and the effect of ether, relative to the behaviour of the other, is calculated from tissue weights and vessel constants.

The effect of ether on brain oxidations

A general result which has been found to apply to all our observations is that when ether affects oxidation in brain slices the action is an inhibitory one which develops gradually and progressively as time passes.

When the curves for the effect are extrapolated to the time at which the exposure to ether began, there is at that time no effect on the respiration. This result has been obtained so generally that in a few experiments where the curves do not lead to this result we have felt justified in applying a correction of not more than ± 10 % to the position of the curve. The necessity for such a correction arises from the fact that the effects of ether on respiration are calculated by allowing by means of a "control" vessel for changes in respiration which occur in the absence of ether. Two sets of tissue slices from the same brain examined at

the same time under the same conditions may show differences in their Q_{O_2} values up to 10%, although the course of the respiration in a relative sense usually agrees much better.

In the curves which follow, the respiration in absence of ether is always set equal to 100, and that in presence of ether is stated relatively to this standard. Experimental points are usually indicated, except in smoothed curves which generalize the results. Few numerical values are given, since curves express the data more conveniently. Times are stated in minutes, and the zero point is the time at which ether was first admitted, although several minutes pass before the final ether concentration is approximately attained. Typical results are given in the curves.

The effects of various concentrations of ether on respiration of rat and guinea-pig brains in presence of glucose

As is shown in Figs. 1 and 2, ether causes a progressive inhibition of the respiration at 37°. The inhibition is, within experimental error, nil when ether is

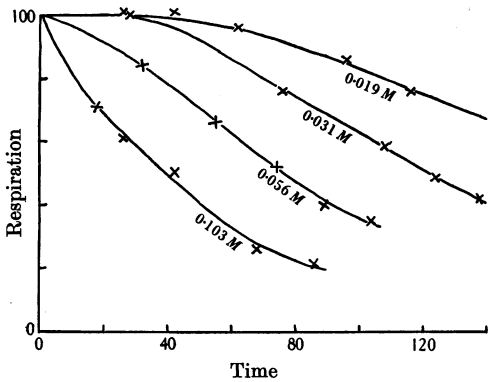

Fig. 1.

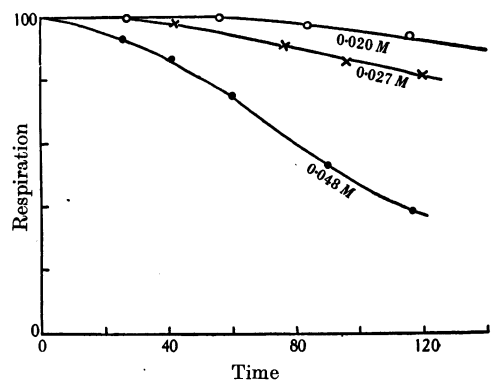

Fig. 2.

Fig. 1. Effect of ether on respiration of rat brain in presence of glucose. 37°, K^+ 0·002*M*.

Fig. 2. Effect of ether on respiration of guinea-pig brain in presence of glucose. 37°, K^+ 0·002*M*.

first added, and develops in a regular manner with time. At the lower concentrations of ether (0·02–0·03 *M*) there is an apparent time-lag before the inhibition begins to appear. At the higher concentrations (0·05 *M* upwards) the inhibition begins to appear at once. At sufficiently high concentrations (0·1 *M*) the inhibition of respiration proceeds roughly as if the respiratory system were attacked by ether according to the law of mass action, so that the respiration follows approximately an equation of the type $R = R_0 . e^{-\alpha c t}$, in which c and t are concentration and time. In the experiments of Figs. 1 and 2 the potassium ion concentration in the medium is 0·002 *M*, a rather low value.

The effect of potassium ion concentration on the inhibitory action of ether

It has already been found [Jowett & Quastel, 1937] that the potassium ion concentration in the medium influences the inhibitory action of certain narcotics on brain respiration. At a low potassium ion concentration the inhibitory action of narcotics becomes progressively greater with time, while at higher potassium ion concentrations the inhibition reaches, or tends to reach, a steady level.

With ether also the level of the potassium ion concentration influences the inhibitions. In Figs. 3 and 4 are shown the effects of ether on the respiration of guinea-pig brain in presence of glucose at 39° at high and low potassium ion concentrations (0·0128 and 0·002 *M*), the experiments being carried out in parallel.

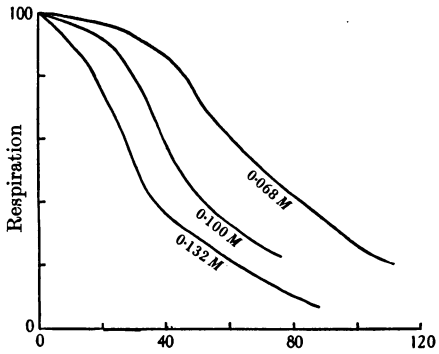

Fig. 3.

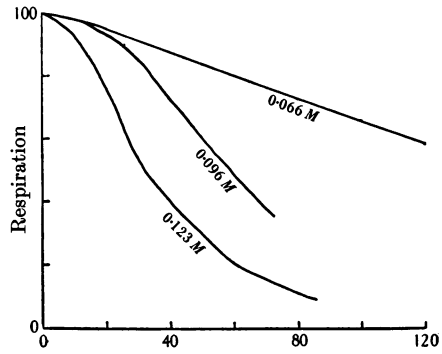

Fig. 4.

Fig. 3. Effect of ether on respiration of guinea-pig brain in presence of glucose. 39°, K^+ 0·002*M* (low potassium).

Fig. 4. Effect of ether on respiration of guinea-pig brain in presence of glucose. 39°, K^+ 0·0128*M* (high potassium).

At the lowest ether concentration shown (0·067 *M*), there is a considerable effect of potassium ion concentration on the inhibitory action of ether. The inhibition is considerably smaller at the higher potassium ion concentration, an effect which shows a parallelism with other narcotics.

On the other hand, at higher ether concentrations (about 0·13 *M*) the level of the potassium ion concentration does not appreciably affect the inhibitory action of ether.

Is the action of ether in vitro *reversible?*

As has been shown by Quastel & Wheatley [1934], the effects of a number of narcotics on the respiration of brain are reversible, that is, on removing the brain slices to media containing no narcotic, the original respiration is nearly restored.

Experiments have been made on analogous lines with ether. After exposing rat brain slices to ether in the presence of glucose for some time, the ether was swept out of the manometer vessels with a stream of oxygen which was passed through for 8 min., and the respiration was subsequently measured. The removal of ether from the vessels was effective, for as determined by the manometric method the ether tension in the vessels (after acidifying the tissue) was only 3–5 % of that originally introduced.

In the exposure to ether both concentration and time of exposure must be taken into account. In Table I the time of exposure is reckoned as the interval between first beginning to admit ether and first beginning to remove it. After the ether has been removed the respiration is lower (relative to the control) than it was before ether was admitted, and the magnitude of the lowering (as far as the data go) increases with the concentration of ether originally present and the time of exposure to it. With the shorter exposures, the observed respiration is

not strictly constant. The apparent partial recovery in respiration seen with the shorter exposures is perhaps unreal; it may be that for some time after sweeping out ether the tissue is continuing to give up small quantities of ether and thereby vitiating for some time the respiration values, which may be initially too low. It is nevertheless clear that when ether has brought about a large inhibition of respiration this does not disappear on removing ether. The last column of Table I shows, from experiments in which ether is present throughout (and in which the respiration falls continuously), the approximate time of exposure to

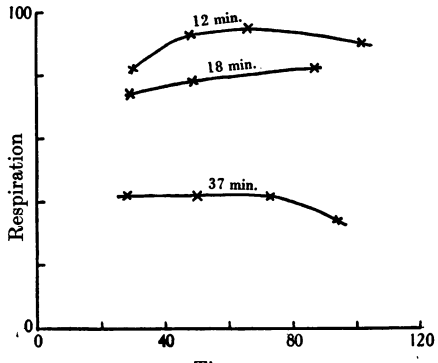

Fig. 5.

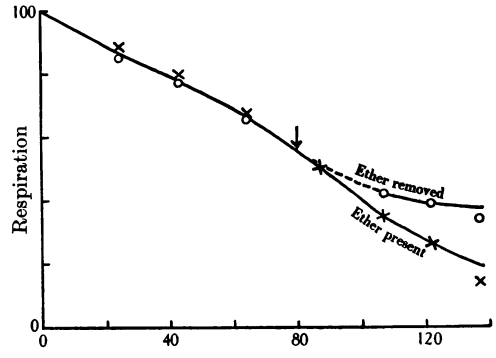

Fig. 6.

Fig. 5. Respiration of rat brain in presence of glucose after exposure to 0·051*M* ether for various times and removal of ether. 37°, K^+ 0·002*M*. (Cf Table I.)

Fig. 6. The effect of 0·077*M* ether on respiration of rat brain in presence of glucose, 39°, K^+ 0·0128*M*. Ether is present initially in two vessels, and is removed from one after 80 min.

ether required to inhibit respiration to an extent equal to that observed subsequently in the experiments in which ether has been present and has been removed. The data suggest that respiration continues to fall for some time after ether is removed from the vessels. The suggestion is supported by an experiment at the higher potassium ion concentration (Fig. 6). Perhaps ether leaves the tissue slowly, or alternatively the progressive changes induced by ether may not be arrested at once. Removal of 95–97 % of the ether from the vessels will not necessarily result in removing quickly a corresponding proportion of ether from the tissue. An impression exists that ether leaves tissues only with difficulty. In the organism, according to the work of Haggard [1924], the limiting factor in the elimination of most of the ether is the ventilation; *in vitro*, where ventilation can be made very rapid, slow release of ether from tissue may be a limiting factor.

Table I. *The respiration of rat brain after exposure to and removal of ether*

Glucose. 37°. K^+ 0·002 *M*

Exp.	Approx. conc. ether (*M*)	Time of exposure min.	Approx. subsequent respiration %	Time of continuous exposure to ether for equivalent effect
1	0·030	34	86	65
2	0·051	12	93	20
3	0·051	18	78	40
4	0·051	37	42	90

From these experiments it may be concluded that if reversibility of the inhibitions of respiration is found *in vitro*, it will be found only when the exposure to ether is slight and the inhibitions small.

The action of ether at various temperatures

The steady inhibition of respiration caused by chloretone does not change appreciably with temperature [Jowett & Quastel, 1937].

The behaviour of ether is different. The progressive inhibitory action of ether on the respiration of guinea-pig brain in presence of glucose falls off very rapidly when the temperature is decreased (Fig. 7). The curves at 42° and 37° are similar in shape, and it is deduced from them that the time required to produce a given inhibition at 37° is about two and a half times as great as at 42°. Hence the temperature coefficient of the rate of inhibition is about 6 for 10°. The inhibitions at 32° are very small, and those at 27° are not measurable.

The respiration in presence of lactate likewise has a considerable temperature coefficient for its rate of inhibition by ether (Fig. 8), the coefficient being perhaps smaller than with glucose.

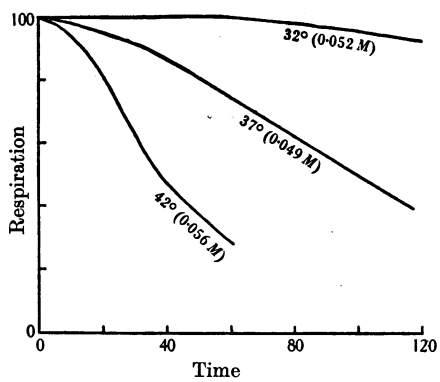

Fig. 7.

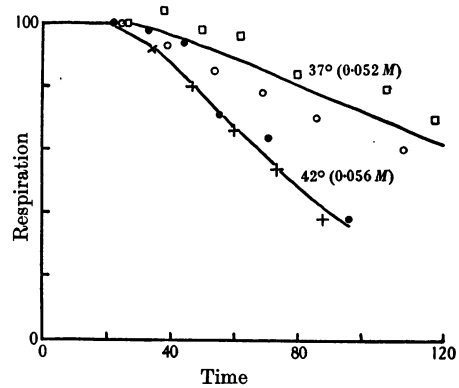

Fig. 8.

Fig. 7. Effect of ether on respiration of guinea-pig brain in presence of glucose at different temperatures. K^+ 0·002*M*.

Fig. 8. Effect of ether at different temperatures on respiration of guinea-pig brain in presence of lactate. K^+ 0·002*M*.

The difference in behaviour between chloretone and ether is due to the fact that with the former we measure the effect of temperature on an equilibrium, with the latter its effect on the rate of a process.

The effect of ether on brain respiration in presence of various substrates

The inhibitory action of ether on respiration has been found to depend on the substrate that the brain is oxidizing. When an inhibition is brought about by ether, the inhibition follows the same type of curve as that already found with glucose as substrate (Figs. 9–12).

The magnitude of the inhibitions may be seen in Figs. 9–12 and Table II.

The results may be summed up by placing the substrates examined in four

classes, the oxidation of the substrates decreasing in sensitivity to ether from the first class onwards:

(1) Glucose.
(2) Lactate, pyruvate and fructose.
(3) Glutamate.
(4) Galactose, α-glycerophosphate, hexosediphosphate and succinate.

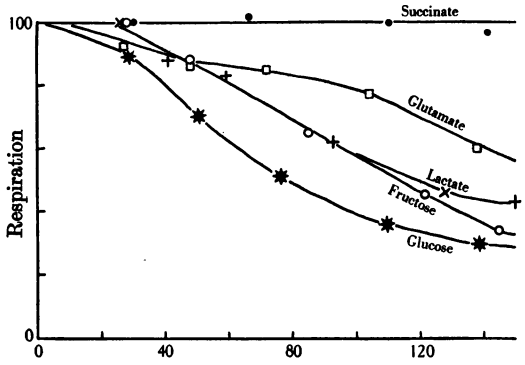

Fig. 9.

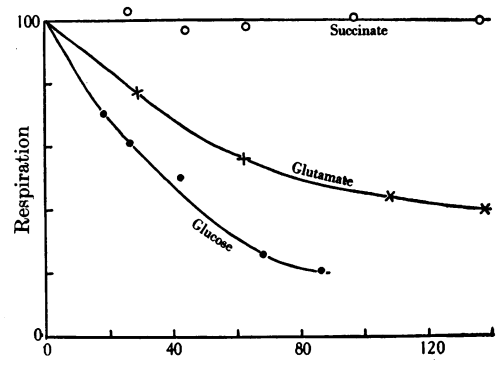

Fig. 10.

Fig. 9. The effect of ether (0·047 – 0·052*M*) on respiration of rat brain in presence of various substrates. 37°, K^+ 0·002*M*.

Fig. 10. The effect of ether (0·093 – 0·103*M*) on respiration of rat brain in presence of various substrates. 37°, K^+ 0·002*M*.

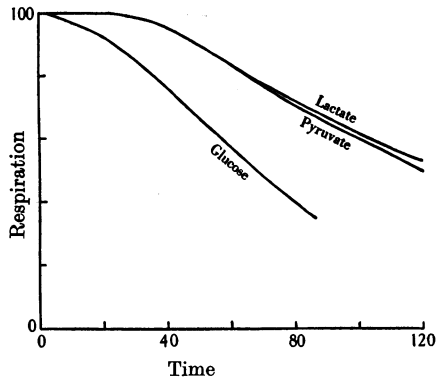

Fig. 11.

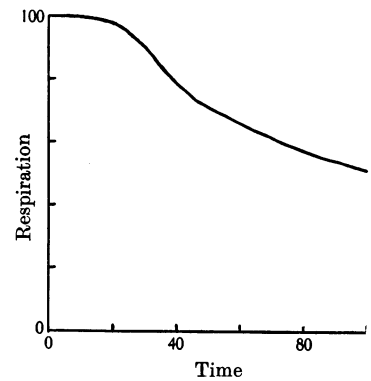

Fig. 12.

Fig. 11. Effect of 0·058*M* ether on respiration of guinea-pig brain in presence of various substrates. 39°, K^+ 0·002*M*.

Fig. 12. Effect of 0·10*M* ether on respiration of guinea-pig brain in presence of galactose or without added substrate. 39°, K^+ 0·002*M*.

The sensitivity of the respiration to ether in the absence of added substrate may also be placed in the fourth class, in which the effect of 0·05–0·06 *M* ether is very small or non-existent.

It is interesting that, roughly speaking, the same four classes represent the extents to which the various substrates are able to maintain the respiration of

brain over a period of time. Glucose maintains the respiration best. In the presence of the substrates in the fourth class (except succinate), the respiration falls off with time very rapidly, as it does in the absence of added substrate. When respiration decreases rapidly as the ether effect (if any) develops, it is difficult to measure the effect of ether accurately.

The relative sensitivity to ether of the oxidation of a number of the substrates investigated runs parallel with the sensitivity to other narcotics [Jowett & Quastel, 1937]. What part of the oxidizing mechanism renders glucose oxidation (for instance) sensitive to narcotics, while succinate oxidation is insensitive, still remains to be discovered.

Table II. *The effect of ether on the respiration of brain in presence of various substrates*

K^+ 0·002 *M*. Substrate concentrations usually 0·02 *M*

Species	Substrate	Temp. ° C.	Inhibition after 80 min. in presence of (*a*) 0·05–0·055 *M* ether	(*b*) 0·10–0·11 *M* ether
Rat	Glucose	37	52	79
	Lactate	37	32	—
	Fructose	37	32	—
	Glutamate	37	18	50
	Succinate	37	0	0
Guinea-pig	Glucose	39	60	80
	Lactate	39	29	—
	Pyruvate	39	29	—
	Galactose	39	—	42
	α-Glycerophosphate	37	0	—
	Hexosediphosphate	39	0	—
	Nil	39	—	42

The effect of ether on oxidations in liver

The respiration of liver has been found to be much less sensitive to ether than is the respiration of brain.

In presence of lactate the respiration is slightly depressed by ether. At concentrations of ether of 0·05–0·10 *M*, an inhibition of respiration of 10–20 % is rapidly produced. A concentration of 0·025 *M* seems to produce a similar inhibition rather more slowly. The inhibitions do not change in a regular manner with time. In the absence of added substrate, or with glucose added, the respiration of rat liver is not definitely affected by ether. It may be concluded that lactate oxidation in liver is inhibited by ether, but that some other oxidations are less sensitive.

The study of the effect of narcotics on tissue respiration gives less definite results with tissues of mixed metabolism than with brain. Further work might most profitably be done on individual substrates or processes.

The inhibition of lactate oxidation observed with liver may be related to the accumulation of lactate in blood found in ether anaesthesia [Ronzoni *et al.* 1924].

The nature of the effects of ether

The inhibitory action of ether on respiratory processes in brain shows a number of similarities with those of other narcotics already referred to.

The oxidation processes affected are similar. Ether, like other narcotics, inhibits the oxidations of glucose, lactate, pyruvate and to less extent glutamate.

Like other narcotics, it does not inhibit oxidation of succinate. The inhibitory effects of ether, like those of other narcotics, are affected at certain concentrations by the potassium ion concentration. From the similar order of sensitivity to ether and to other narcotics of a variety of substrates, it is probably correct to conclude that ether affects the same components of respiratory systems as other narcotics do.

The differences between ether and a number of other narcotics are also very striking. Ether causes progressive inhibitions, other narcotics may produce steady inhibitions. The action of some other narcotics is reversible, the action of ether has only a very limited reversibility, if any, *in vitro*. The progressive inhibitions due to ether have a high temperature coefficient, the steady inhibition caused by chloretone has a low one. The steadying influence of potassium ion on respiration in presence of ether disappears at high ether concentrations.

We consider that the differences between ether and other narcotics investigated are due to the observed inhibitory effects of ether, at concentrations which produce easily measurable effects on respiration, being of an irreversible nature. Ether, we suggest, causes at sufficient concentrations progressive irreversible changes in the cortical cells. The high temperature coefficient of ether inhibitions may then be a measure of the varying sensitivity of the cell to irreversible changes produced by ether. We have already suggested [Jowett & Quastel, 1937] that at low potassium concentrations brain cells more rapidly undergo irreversible change and have shown that the effect of potassium ion has a similar temperature coefficient. The necessity for high potassium ion as a stabilizing agent disappears at low temperatures because the cell is less sensitive. The effect of potassium ion disappears at high ether concentrations, we suggest, because the cell is undergoing irreversible change to an extent that potassium ion cannot influence.

All these effects of ether described are at concentrations higher than those used in surgical anaesthesia,[1] and which would cause death very rapidly.

We cannot at present entirely dismiss the possibility that formation of one of the so-called peroxides of ether may play a part in the effects attributed to ether. Evidence against this possibility would be provided if on investigation other narcotics were found to behave like ether.

The effect of anaesthesia on subsequent respiration of brain

It has been claimed by Mayer [1935] that when rats are anaesthetized, and killed under anaesthesia, the respiration of brain slices found subsequently *in vitro* may be lower than that found when the rats have not been anaesthetized. The effect is stated to depend on the narcotic in question and on the part of the brain examined. Among Mayer's results is that ether anaesthesia lowers the subsequent respiration of the cortex substance by about 65%, the Q_{O_2} falling from 6·7 to 2·4. No exact details are given of the medium employed, which is stated to be a Locke solution used at 37°.

We have made some experiments on similar lines, in which rats were anaesthetized with ether and killed while anaesthetized by cutting the throat. The anaesthesia was usually sufficient to abolish the corneal and tail reflexes and lasted up to 50 min. The time elapsing between death and the placing of the brain slices in their vessels in the thermostat was 18–24 min. Control experiments, without previous anaesthesia, were made in exactly the same way.

The results of the experiments show no measurable effect of the ether anaesthesia on the subsequent respiration of the grey matter of the cerebral

[1] Or alternatively, if at concentrations of this order (e.g. curves in Figs. 1 and 2), the effects are at low concentrations of potassium ion predisposing to irreversible change.

cortex, whether in presence or absence of glucose (Table III). Possibly in presence of glucose there is a depression of 5–10 % in respiration, but this is not outside the possible experimental error.

By the time the respiration measurements are made, there has been ample opportunity for ether to leave the tissue slices. As will be shown in the next section, ether at the anaesthetic concentration has only a very small effect on brain respiration *in vitro*. If its effect *in vivo* is similar, we should expect only a very small effect *in vitro*, after exposure of the animal to ether and opportunity for loss of ether after death. Our experimental result therefore agrees with expectations from our other experiments.

Table III. *The effect of ether anaesthesia on subsequent respiration of rat brain*

Medium: K^+ 0·002 *M*, Ca^{++} 0·001 *M*, Mg^{++} 0·0008 *M*, phosphate 0·02 *M*, *p*H 7·2. Isotonic with 0·16 *M* NaCl, glucose (when present) 0·02 *M*. O_2. 39°.

The figures each represent the mean of four experiments, and the percentage deviations given are the mean deviations of individual experiments from the mean values.

A. In presence of glucose:				
Time in thermostat (min.)	24	40	60	80
Anaesthetized rats. Mean Q_{O_2}	17·8	15·7	13·6	11·05
Mean deviation (%)	±7	±6	±8	±12
Control rats. Mean Q_{O_2}	19·1	17·25	14·3	12·3
Mean deviation (%)	±6	±5	±7	±7
% effect of anaesthesia on Q_{O_2}	−7	−9	−5	−10
B. In absence of added substrates:				
Time in thermostat (min.)	24	40	60	80
Anaesthetized rats. Mean Q_{O_2}	9·3	6·3	4·0	2·5
Control rats. Mean Q_{O_2}	8·3	5·8	3·5	2·4
% effect of anaesthesia on Q_{O_2}	+11	+9	+14	+4

The effects of ether at anaesthetic concentrations in vitro

Very valuable quantitative studies on ether anaesthesia in dogs have been made by Ronzoni [1923] and Haggard [1924], from whose work the following data have been extracted:

State	Mean concentration of ether in blood (*M*)
Loss of consciousness	0·006
Corneal reflex disappears	0·016
Full surgical anaesthesia	0·018–0·020
Homolateral flexion reflex disappears	0·021
Respiratory failure after some hours	0·024
Early respiratory failure	0·029

It appears that the concentrations effective in other animals and in man are similar, and the ether concentration in blood at full surgical anaesthesia can be taken as 0·02 *M*. An equal concentration in water has nearly the same thermodynamic activity. The anaesthetic concentration of ether is about ten times higher than the concentrations of chloretone, evipan and luminal which we have roughly estimated to be effective; ether is evidently less active as a narcotic.

As already pointed out, the medium in which brain slices are immersed influences the inhibitions of brain oxidation caused by ether. The medium containing more potassium (0·0128 *M*) is to be regarded as more physiological than the medium containing less (0·002 *M*).

Experiments in the high potassium medium have shown that the effect of ether at a concentration of about 0·02 *M* on the respiration of rat and guinea-pig brain in presence of glucose at 39° does not exceed the experimental error, which is of the order of 10 %. At higher concentrations of ether (about 0·03 *M* with rat brain, 0·04 *M* with guinea-pig brain) a progressive inhibitory effect can be observed.

At the lower potassium concentration, inhibitory effects with rat brain are observable at about 0·02 *M* ether, and with guinea-pig brain at about 0·03 *M*. These effects are regarded as unphysiological.

Our conclusion is that anaesthetic concentrations of ether do not inhibit by more than 10 % the respiration of the grey matter of the cerebral cortex of rat or guinea-pig, as measured *in vitro* under our best approximation to physiological conditions. At rather higher concentrations of ether progressive inhibitory effects on respiration appear, which may well be connected with the lethal effects of these concentrations.

It may be noted that Emerson [1936] states, without giving many details, that anaesthetic concentrations of ether do not affect the lactic dehydrogenase activity of brain, although higher concentrations are inhibitory.

Our conclusion does not negative the hypothesis that ether acts as a narcotic because of an inhibitory effect on oxidations in the central nervous system. The inhibition of respiration to be expected during narcosis as a mean effect spread over the whole of the grey matter of the cerebral cortex is not necessarily large. The effects of narcotics on function are often localized, and effects on oxidations may also be localized.

Localized effects on oxidations may appear at an ether concentration which is a threshold value for more general effects. The larger inhibitions appear to be irreversible, but this does not necessarily conflict with the possibility that small inhibitions are reversible. Moreover, it is to be noticed that during ether narcosis damage is sustained by the brain, which is evidence that narcosis can produce irreversible effects.

The large temperature coefficient of the effect of ether on brain oxidations has its parallel in the finding of Meyer (quoted by Haggard [1924]) that with increase in temperature there is a decrease in the concentration of ether required to anaesthetize some lower forms of life.

Likewise the increase with time of the effect of ether on brain oxidations corresponds with the fact [Ronzoni, 1923; Haggard, 1924] that the concentration of ether applied during anaesthesia must be lowered progressively as time passes in order to prevent the anaesthesia from becoming deeper.

These two parallelisms support the view that during ether anaesthesia brain oxidations may be inhibited to a small extent.

Summary

1. The effect of ethyl ether on the respiration of slices of cerebral cortex has been investigated.

2. Ether may cause inhibitory effects on respiration, dependent on the substrate which the brain is oxidizing. With glucose, fructose, lactate, pyruvate and glutamate inhibition occurs. With succinate and some other substances there is little inhibition.

3. When an inhibition occurs it is progressive. No immediate inhibition is found, but it develops as a function of time and ether concentration.

4. Inhibitions tend to be larger when the potassium ion concentration of the medium is low than when it is high.

5. The inhibitory action of ether on the oxidation of glucose and lactate by brain has a large temperature coefficient.

6. When the inhibitory effects of ether on oxidations are large, they do not disappear on removing the ether, but the progressive fall is arrested. These large inhibitions appear to be irreversible.

7. Anaesthetizing rats with ether does not affect measurably the subsequent respiration of their brains *in vitro*.

8. Ether has a smaller effect on liver respiration than on brain respiration.

9. The inhibitory effects of ether at the anaesthetic concentration on the oxidation of glucose by cerebral cortex are within the experimental error of 10%. Only small effects would be expected. At higher concentrations of ether large inhibitory effects are found.

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