BIOCHEMICAL EVENTS IN CEREBRAL ISCHAEMIA

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Cerebral ischaemia can be defined as a decrease in cerebral blood-flow (CBF) to values which are insufficient to maintain normal cerebral function and metabolism. The statement implies that it is difficult to define ischaemia on the basis of measurements of CBF alone. Thus, whereas a reduction of CBF to below about 50% of normal is accompanied by functional and metabolic signs of ischaemia in normal man and in experimental animals, a larger reduction can be tolerated if the cerebral energy demands are decreased by hypothermia or anaesthesia. To take an extreme example, when rats are hyperventilated at a body temperature of 22°C, a reduction of cortical CBF to 15% of normal is compatible with a normal tissue energy state (Hägerdal, Harp and Siesjö, 1975).

The present article attempts to summarize metabolic events in the brain in different types of cerebral ischaemia. For a more detailed account of the literature, the reader is referred to the selected number of original articles quoted, and to some recent review articles (Maker and Lehrer, 1971; Cohen, 1972; Cohen, 1973; Siesjö and Plum, 1973; Siesjö et al., 1974). Before the biochemical changes in ischaemia are described, it seems warranted to discuss briefly the definition of the various types of ischaemia, and to summarize the metabolic characteristics of brain tissues.

(A) Definition of cerebral ischaemia

Ischaemia can be general, affecting the entire brain, and is then usually caused by a decrease in cerebral perfusion pressure as a result of arterial hypotension or of increased intracranial pressure; or focal, such as occurs with interruption of flow in cerebral vessels in cerebrovascular disease or trauma. Ischaemia in either of these types can be incomplete. The conditions of incomplete ischaemia are ambiguous. Thus, general, incomplete ischaemia does not involve a uniform degree of underperfusion, since a decrease in perfusion pressure, as in arterial hypotension, preferentially affects certain border-zone areas between the distribution territories of the major cerebral arteries (Brierley et al., 1969; Brierley, 1973). Accordingly, general, incomplete ischaemia usually has focal components. It is also clear that in focal ischaemia there is a non-homogeneous flow pattern. Special attention should be drawn to the relative ischaemia encountered in situations of arterial hypoxia. The availability of oxygen to the brain is determined thus:

$$O_2 \text{ availability} = \text{CBF} \times C_a O_2$$

where $C_a O_2$ is the arterial oxygen content. If this is decreased because of a decrease in $P_a O_2$ (hypoxic hypoxia), or in anaemic hypoxia, cerebral oxygen availability is upheld by an increase in CBF. In such situations, signs of cerebral ischaemia may occur if the compensatory increase in CBF is curtailed by a decrease in the perfusion pressure (Siesjö and Nilsson, 1971; Salford, Plum and Siesjö, 1973).

(B) Metabolic characteristics of brain tissues

Figure 1 summarizes the main features of cerebral energy metabolism (Kety, 1950, 1957; Lassen, 1959; Sokoloff, 1960, 1972; Balázs, 1970; McIlwain and Bachelard, 1971; Maker and Lehrer, 1972). The following points should be emphasized: (i) The brain has special energy requirements, reflected in the fact that it receives 15% of cardiac output and consumes about 20% of the basal oxygen consumption of the body. In all probability, neurones, although outnumbered by glial cells, are responsible for the largest part of the oxygen consumption of the brain (Elliott and Heller, 1957; Korey and Orchen, 1959; Hess, 1961). (ii) Under normal circumstances glucose is the main, or sole, substrate and it is only in special circumstances (e.g. starvation) that other exogenous substrates such as ketone bodies are used (Owen et al., 1967; Ruderman et al., 1974). (iii) About 90% of the...
glucose consumed is oxidized to carbon dioxide and water, the rest appearing as lactate and pyruvate in cerebral venous blood (Kety, 1957; Gottstein, Bernsmeier and Sedlmeyer, 1963; Cohen et al., 1967). However, the “production” of lactate by the normal brain does not signify that brain cells live on the brink of hypoxia (Rowe et al., 1959; Hawkins et al., 1973; Nemoto, Hoff and Severinghaus, 1974; Norberg and Siesjö, 1974). (iv) Metabolic energy is conserved in the form of ATP, which is then used for the work tasks of the cells, mainly active transport and biosynthesis. In all probability, a substantial fraction of the ATP energy produced is used for ion transport. However, it is difficult to predict the relative energy requirements of transport processes and biosynthetic activities since these vary with the degree of functional activity.

Cerebral glycolysis. In the brain, the glycolytic chain essentially represents a one-way pathway for conversion of glucose (or glycogen) to pyruvate (or lactate) (Hostetler et al., 1970; Baláz, 1970; McIlwain and Bachelard, 1971). The glycolytic conversion of 1 mole of glucose has a yield of 2 moles of ATP, while the complete oxidation to carbon dioxide and water yields 38 moles of ATP (fig. 2). Thus, glycolysis is far from efficient in supporting energy production in the tissue. The glycolytic rate is exquisitely sensitive to oxygen lack, the main factors affecting glycolysis being changes in the tissue concentrations of phosphates such as phosphocreatine (PCr), ATP, ADP, AMP, and Pi (Lowry and Passonneau, 1964, 1966). Lactate accumulates in the tissue even when changes in phosphates are difficult to detect (Bachelard et al., 1974; Norberg and Siesjö, 1975a) and, therefore, increased production of lactate is one of the most sensitive indices of cellular hypoxia.

Relationship between carbohydrate and amino acid metabolism. There is an intimate relationship between the metabolism of citric acid cycle intermediates and of amino acids belonging to the “glutamate group” (glutamate, glutamine, aspartate, gamma aminobutyric acid (GABA) and alanine) (fig. 3). Thus, when 14C-glucose is administered to experimental animals a large fraction of the 14C-carbon is retained for long periods in the amino acid pools (Baláz, 1970; Berl and Clarke, 1969). It has been estimated that close to 10% of the glucose carbon is metabolized via the GABA shunt (Baláz, Machiyama and Patel, 1973). However, in...
hypoglycaemia a reversed net flux of carbon occurs between the carbohydrate and amino acid pools. Then, amino acid carbon is fed into the citric acid cycle via transamination and deamination mechanisms (Lewis et al., 1974). A further relationship between the citric acid cycle and the amino acid pools is provided by the mechanisms leading to ammonia detoxification. In the brain, these include reductive amination of α-ketoglutarate (αKG) to glutamate, and amidation of glutamate to glutamine (Berl, 1971).

Transmitter metabolism. Since ion transport across cell membranes requires ATP, there is an obvious relationship between energy failure and loss of cellular function. However, there is indication that neuronal function may suffer in hypoxia or ischaemia even if energy failure is minimal, or undetectable. The synthesis of some neurotransmitters (e.g. acetylcholine) requires ATP. The indole- and catecholamines, dopamine, noradrenaline and serotonin (5-HT) are synthesized in reactions utilizing molecular oxygen (Snyder, 1972). Since the rate-limiting reactions of these sequences have K_m values for oxygen far in excess of those of the respiratory chain, neurotransmitter synthesis may fail in hypoxia at P_o_2 values that do not cause overt energy failure (Davis and Carlsson, 1973; Davis et al., 1973). The synthesis of other transmitters or compounds with inhibitory or excitatory actions, like GABA, glutamate and aspartate, depends on reactions linking citric acid cycle metabolism to amino acids which can be altered without signs of energy failure (Baxter, 1970; van den Berg, 1970; Roberts and Hammerschlag, 1972).

(c) Biochemical changes in brain in complete ischaemia

We shall start the discussion of biochemical events by considering complete ischaemia, as this is the most well-defined condition. When CBF ceases, either generally or focally, the slender oxygen stores in the tissue are used up in a few seconds. The following metabolic events then occur: (i) the energy stores in the tissue are depleted at a rate which is determined by the metabolic activity of the tissue and by its capacity for anaerobic energy production, (ii) substrates which can be metabolized anaerobically are exhausted, and (iii) waste products accumulate. We shall discuss these points in turn.

(i) Depletion of energy stores. When oxidative production of ATP ceases, its stores will decrease because of continued hydrolysis, catalysed by cellular ATPases:

\[
\text{ATP} + \text{HOH} \rightarrow \text{ADP} + \text{Pi}
\]

In the cerebral cortex of man it can be estimated that ATP utilization is 0.2 μmole.g⁻¹.sec⁻¹. If this utilization continued during the period of ischaemia, an ATP store of 2 μmole.g⁻¹ would suffice for 10 sec. However, three reactions provide additional ATP and therefore delay energy depletion. One reaction, catalysed by creatine phosphokinase (c.p.k.), provides ATP at the expense of the PCr stores:

\[
\text{c.p.k.}
\]

\[
\text{PCr} + \text{ADP} + \text{H}^+ \rightarrow \text{Cr} + \text{ATP}
\]

Another reaction, catalysed by adenylate kinase (AK), converts ADP to ATP and AMP:

\[
\text{AK}
\]

\[
\text{ADP} + \text{ADP} \rightarrow \text{ATP} + \text{AMP}
\]

A third reaction is the glycolytic conversion of glucose or glycogen to lactic acid, which proceeds with formation of ATP:

\[
\text{Glucose} + 2\text{ADP} + 2\text{Pi} \rightarrow 2\text{lactate} + 2\text{ATP}
\]

\[
\text{Glycogen} + 3\text{ADP} + 3\text{Pi} \rightarrow 2\text{lactate} + 3\text{ATP}
\]

As a result of these reactions, ATP is not depleted until the stores of PCr and glucose are nil. The data shown in figure 4, which pertain to the cerebral cortex of rats, indicate that no useful energy remains after 5 min of ischaemia. In the cerebral cortex of man, the normal rate of ATP utilization is probably less than half of that in the rat (Nilsson and Siesjo, 1975). However, since also the stores of PCr and ATP are smaller (Schmiedek et al., 1974), energy depletion may occur in less than 10 min. It has been clearly documented that hypothermia and anaesthesia delay the utilization of high energy phosphates (Lowry et al., 1964; Gatfield et al., 1966). This reduction in the metabolic rate probably explains why hypothermia and anaesthesia with barbiturates prolong the maximal period of ischaemia which can be tolerated without causing permanent neurological damage (see below).

(ii) Utilization of substrates and accumulation of waste products. Changes in phosphate compounds during ischaemia (see above) induce a massive stimulation of glycolysis, mainly at the phosphofructokinase step (Lowry et al., 1964). The increase in pyruvate is a transient event and, later,
pyruvate disappears (Ljunggren, Schutz and Siesjö, 1974). This is caused by depletion of NAD+ and accumulation of NADH and H+?, favouring a shift in the lactate dehydrogenase (LDH) reaction:

\[
\text{LDH} \quad \text{Pyruvate} + \text{NADH} + \text{H}^+ \rightarrow \text{lactate} + \text{NAD}^+
\]

Lactate accumulates until the stores of glucose and glycogen are lost, and there is a rough relationship between the amount of glucose and glycogen lost and the lactate accumulated (fig. 5). An increase in the carbohydrate stores (e.g. as a result of hyperglycaemia) undoubtedly affects the amount of energy made available to the ischaemic tissue, but the contribution is relatively small and occurs at the expense of an exaggerated tissue acidosis (Ljunggren, Norberg and Siesjö, 1974). It appears that a small fraction of the pyruvate (or phosphoenolpyruvate) that accumulates early in ischaemia is carboxylated to oxaloacetate (OAA) (or malate) and eventually ends up as succinate (Goldberg, Passonneau and Lowry, 1966; Folbergrová et al., 1974).

This sequence of events—carboxylation of glycolytic intermediates and reversal of the terminal steps in the citric acid cycle—has been observed to occur in certain invertebrate tissues, and is believed to add to the energetic yield under anaerobic conditions (Saz, 1971; Hochachka and Mustafa, 1972). In the brain, the reactions may not be energetically important (Folbergrová et al., 1974), but the results show that, apart from lactate, succinate enters as a product of anaerobic reactions.

Apart from the massive increase in succinate, the changes in citric acid cycle intermediates are dominated by pronounced decreases in αKG and OAA (fig. 6). These changes (Goldberg, Passonneau and Lowry, 1966; Folbergrová et al., 1974),
in addition to those affecting amino acids and ammonia (fig. 7), are best understood if it is assumed that ischaemia shifts all redox systems, for example the NADH/NAD⁺ and FADH₂/FAD couples, towards a completely reduced state. Loss of NAD⁺, and a large increase in the NADH/NAD⁺ ratio, explains why OAA disappears from the tissue. Thus, all substrate couples which are linked to NAD systems (e.g. lactate/pyruvate and malate/OAA) are drastically affected in anoxic conditions.

The increased NADH/NAD⁺ ratio also contributes to loss of α-KG. As stated, detoxification of ammonia occurs by means of reductive amination of α-KG:

\[
\text{NH}_3 + \text{NADH} + \text{H}^+ \rightleftharpoons \alpha\text{-KG} \rightleftharpoons \text{NAD}^+ + \text{glutamate}
\]

Thus, since citric acid cycle flux is reduced and ammonia production is increased, α-KG virtually disappears. Furthermore, since α-KG cannot be replenished at an adequate rate, ammonia accumulates (fig. 5).

The initial increase in the pyruvate concentration, and the decrease in α-KG, contribute to shift the alanine aminotransferase reaction towards formation of alanine:

\[
\text{glutamate} + \text{pyruvate} \rightleftharpoons \text{alanine} + \alpha\text{-KG}
\]

The breakdown of GABA occurs by a reaction catalysed by GABA transaminase and by the further oxidation of succinic semialdehyde to succinate. Since GABA removal, but not its production via the glutamate decarboxylase reaction, is blocked because of shortage of NAD⁺ and α-KG, GABA accumulates during ischaemia (Balázs, Machiyama and Patel, 1973; Folbergrová et al., 1974).

FIG. 6. Changes affecting citric acid cycle intermediates in rat cerebral cortex in complete ischaemia of 5-min duration. Data (Means ± SEM) from Folbergrová and colleagues (1974). Pyruvate (Pyr) is close to zero, the tissue is depleted of α-ketoglutarate (α-KG) and oxaloacetate (OAA), and there is massive accumulation of succinate (Succ). This accumulation, which is probably secondary to carbon dioxide fixation and reversal of the terminal steps in the Krebs cycle, suffices to increase the size of the pool of Krebs cycle intermediates.

FIG. 7. Changes affecting amino acids and ammonia in rat cerebral cortex following 5 min of complete ischaemia. Data (Means ± SEM) from Folbergrová and colleagues (1974). During ischaemia, there are no significant changes in glutamate (Glut) or aspartate (Asp), a small decrease in glutamine (Gln), and marked increases in GABA and alanine (Ala). The sum of ammonia equivalents remains essentially constant but there may be a small increase, representing ammonia liberated from AMP (see above). For changes occurring in the postischaemic restitution period, see Ljunggren, Ratcheson and Siegjo (1974) and Folbergrová and colleagues (1974).
Biochemical events in incomplete ischaemia

The biochemical events occurring in incomplete ischaemia, which may vary in severity from a degree of underperfusion which barely affects function and metabolism, to almost complete cessation of flow, are qualitatively similar to those occurring in complete ischaemia. The special features with incomplete ischaemia will be discussed under the headings (i) critical decrease in tissue perfusion, (ii) general characteristics of incomplete ischaemia, and (iii) non-homogeneity of flow distribution.

(i) Critical decrease in tissue perfusion. It is common knowledge that the cerebral circulation shows the capacity for autoregulation, that is, flow remains constant even if the perfusion pressure varies over a relatively wide range. If the perfusion pressure decreases below this range, the cerebral blood-flow is reduced. A certain reduction of CBF may be compatible with a sufficient oxygen availability and an essentially unaltered cerebral metabolism. However, a further decrease in CBF leads to ischaemic changes. Hyperventilation represents a condition in which CBF is homogeneously decreased. With moderate reductions in PaO₂ (PaO₂ > 20 mm Hg), CMRO₂ (cerebral metabolic rate for oxygen) is maintained (Kety and Schmidt, 1948; Alexander et al., 1968) and ischaemia is not present. However, when PaCO₂ is reduced to about 10 mm Hg, CBF decreases to about 50% of normal and there is an increased production of lactate (Alexander et al., 1968). Also, animal experiments show that the tissue lactate content gradually increases when PaCO₂ is lowered (MacMillan and Siesjö, 1973). Since alkalosis by itself may accelerate glycolysis, it has been a matter of speculation whether or not ischaemia is present. Three observations strongly indicate that when PaCO₂ is reduced below about 20 mm Hg mild tissue hypoxia occurs: (a) hyperventilation carried out under conditions of hyperbaric oxygenation reduces the accumulation of lactate (Plum, Posner and Smith, 1968), (b) when decreasing PaO₂ below 15 mm Hg, additional lactate accumulates in spite of the fact that the intracellular pH swings back to normal or subnormal values (MacMillan and Siesjö, 1973) and (c) at PaO₂ values of about 10 mm Hg, there is a small decrease in PCr and a small increase in ADP concentration (MacMillan and Siesjö, 1973). Thus, when a reduction in PaO₂ decreases CBF to about 50% of normal, a moderate degree of ischaemia is present. However, this degree of ischaemia has not been shown to cause neuronal damage.

Observations in patients, and experiments in animals, show that a certain reduction in CBF may be tolerated, when caused by arterial hypotension. In normotensive subjects, mean arterial pressure must be reduced to 30–35 mm Hg before symptoms of ischaemia develop, and at this point the overall CBF is reduced to 60–70% of normal (Finnerty, Witkin and Fazekas, 1954). Patients with hypertension show less tolerance to reductions in arterial pressure (Kety et al., 1950). In normoxic and normocapnic rats, cortical CBF must be reduced below 50% of normal before biochemical signs of ischaemia develop (Eklof and Siesjö, 1972a). With further reduction in flow, there is marked derangement of cortical energy state and massive accumulation of lactate (Eklof and Siesjö, 1972b). However, because of non-homogeneous reduction in CBF, it is difficult to evaluate the correlation between the degree of ischaemia and the severity of the overall derangement of energy metabolism (see below).

(ii) General characteristics of incomplete ischaemia. At moderate degrees of cerebral ischaemia, induced by haemorrhagic hypotension, the continued perfusion of the tissue allows delivery of substrates. In such situations, the biochemical changes in the tissue are similar to those observed in pure hypoxia (Norberg and Siesjö, 1975a,b). With further reduction in flow, the combination of severe tissue hypoxia and continued supply of substrates leads to a massive accumulation of lactate, with individual values exceeding 40 μmole.g⁻¹ (Eklof and Siesjö, 1972b; Salford and Siesjö, 1974). Thus, incomplete and relative ischaemia may induce a degree of tissue acidosis which is considerably more severe than is observed in complete ischaemia. Although proof is lacking (Ljunggren, Norberg and Siesjö, 1974), such excessive acidosis may affect adversely the capacity for revival. At very low CBF values, when the glucose availability becomes limiting (Eklof and Siesjö, 1972b), the metabolic pattern takes on the characteristics of complete ischaemia, with the important exception that a more severe lactic acidosis is present.

(iii) Non-homogeneity of flow distribution. When CBF is reduced, there is an increased extraction of oxygen from the blood and a decrease in sagittal sinus venous Po₂ (Pvo₂). It has been proposed that Pvo₂ is a useful indicator of cerebral oxygenation, and that a Pvo₂ of about 20 mm Hg
can be reduced
for example hypoxic hypoxia, the Pvo₂ is reduced to 20 mm Hg and detectable changes in energy state appear (MacMillan and Siesjö, 1973). However, in other conditions, for example hypoxic hypoxia, Pvo₂ can be reduced much further without larger effects on cerebral energy state (Bachelard et al., 1974); and at reduced perfusion pressure, signs of tissue ischaemia are apparent at higher values of Pvo₂ than 20 mm Hg. Thus, when CBF is reduced by combining hypotension with bilateral ligation of the carotid arteries, gross energy failure occurs at Pvo₂ values well above 20 mm Hg (Eklöf and Siesjö, 1972a); while if hypotension is induced at moderate degrees of hypercapnia, there may be marked derangement of cerebral energy metabolism at Pvo₂ values that are higher than normal (Eklöf, MacMillan and Siesjö, 1973).

The results quoted are best interpreted if it is assumed that the dissociation between the overall cerebral energy metabolism and Pvo₂, occurring at reduced perfusion pressure, is the result of uneven flow distribution, and that conditions of extreme vasodilatation, such as hypercapnia, exaggerate the tendency towards non-homogeneity. It follows that measurements of Pvo₂ in ischaemia have limited usefulness in predicting the severity of the cellular hypoxia.

Reversible and irreversible changes in cerebral ischaemia

It is common clinical experience that the longest periods of complete ischaemia which can be tolerated by the brain without permanent neurological damage are 5–8 min. A number of experimental results lead to a similar conclusion (Dennis and Kabat, 1939; Hirsch, Euler and Schneider, 1957). However, recent results show that neuronal cells studied in vitro (Ames and Gurian, 1963; Webster and Ames, 1965) or in vivo (Hossmann and Sato, 1970a,b) can tolerate much longer periods of anoxia or complete ischaemia without permanent structural or functional damage. These results indicate that neuronal damage observed after 5–8 min of ischaemia may be caused, not by the initial ischaemia, but rather by failure of adequate reperfusion of tissue upon restitution of cerebral perfusion pressure (Ames et al., 1968; Fischer and Ames, 1972; Hossmann, Lechatpe-Grüter and Hossman, 1973). Biochemical results tend to support this new concept. Thus, at least under optimal conditions, the derangement of the energy metabolism is largely reversible even after relatively longlasting ischaemia. Gross restitution of cerebral energy state was observed after 30–60 min of ischaemia in cats (Hossmann and Sato, 1970b) and after 30 min of ischaemia in perfused dogs' brains (Hinzen et al., 1972). These experiments were carried out during barbiturate anaesthesia, which may have afforded some protection. However, in rats anaesthetized with nitrous oxide, there was also almost complete restitution of PCr concentration and ATP/ADP ratio, and disappearance of accumulated lactate, when cerebral perfusion pressure was restored after 15 min of ischaemia (Ljunggren, Ratcheson and Siesjö, 1974). In such animals very few cells show signs of structural damage (Brierley, Ljunggren and Siesjö, 1975), and the majority of neurones thus appear to withstand ischaemic periods of at least 15 min.

Following ischaemia, there is a discrepancy between restitution of cerebral energy metabolism and of cerebral function. It is conceivable that at least part of the functional deficit is more closely related to "transmission failure" than to "energy failure" (Salford, Plum and Siesjö, 1973; Ljunggren, Ratcheson and Siesjö, 1974). Thus, in the restitution period there is a pronounced increase in GABA, which is considered to be an inhibitory transmitter, and decreases in glutamate and aspartate, amino acids which have excitatory properties. Furthermore, the overall tissue concentrations of serotonin and noradrenaline decrease during the recirculation of the tissues (Brown et al., 1974). The metabolism of amino acids and of indole- and catecholamines are highly compartmented in the tissue, and overall tissue concentrations may bear a very remote relationship to changes occurring at synapses. However, the changes recorded in tissue concentrations of amino acids and amines following ischaemia may well represent a true derangement in the metabolism of these transmitter compounds, and thus give an explanation of the delay in functional restitution.

There is surprisingly little information on the specific biochemical events which lead to irreversible neuronal damage. Cellular acidosis has been proposed to contribute to such damage, possibly by enhancing release of lysosomal, hydrolytic enzymes. On the other hand, oxidative phosphorylation is restored after 15 min of complete ischaemia

("critical threshold") indicates the beginning of cellular anoxia (Opitz and Schneider, 1950; Thews, 1963). Results obtained with hyperventilation tend to support this hypothesis since, at PaO₂ 10 mm Hg, the Pvo₂ is reduced to 20 mm Hg and detectable changes in energy state appear (MacMillan and Siesjö, 1973). However, in other conditions, for example hypoxic hypoxia, Pvo₂ can be reduced much further without larger effects on cerebral energy state (Bachelard et al., 1974); and at reduced perfusion pressure, signs of tissue ischaemia are apparent at higher values of Pvo₂ than 20 mm Hg. Thus, when CBF is reduced by combining hypotension with bilateral ligation of the carotid arteries, gross energy failure occurs at Pvo₂ values well above 20 mm Hg (Eklöf and Siesjö, 1972a); while if hypotension is induced at moderate degrees of hypercapnia, there may be marked derangement of cerebral energy metabolism at Pvo₂ values that are higher than normal (Eklöf, MacMillan and Siesjö, 1973).
Factors affecting resistance to ischaemia

In situations when cerebral blood-flow is decreased, attention must be paid to the possibility of increasing the resistance of the brain to ischaemia. The main measures used in clinical practice are hypothermia and anaesthesia. Experimentally, it has been clearly established that, in complete ischaemia, hypothermia prolongs the maximal period that can be tolerated without permanent neuronal damage (Hirsch, Euler and Schneider, 1957; Anabtawi and Brockman, 1962; Boyd and Conolly, 1962). A similar effect has been reported for barbiturates (Goldstein, Wells and Demopoulos, 1973). Such damage, and also irreversible inactivation of enzymes needed for synthesis of lipids (Yatsu and Moss, 1971) and proteins, (Yanagihara, 1974) may well be responsible for the final biochemical lesions resulting from ischaemia.

References


