Effects of Gamma-Hydroxybutyrate and Gamma-Butyrolactone on Cerebral Energy Metabolism During Exposure and Recovery From Hypoxemia-Oligemia

V. MacMillan, M.D.

SUMMARY Cerebral hypoxia-oligemia was produced by lowering of the arterial Po₂ to 30 mm Hg and by right common carotid artery occlusion in rats who were pretreated with intravenous Krebs' solution, gamma-hydroxybutyrate (GHB) (500 mg/kg) or gamma-butyrolactone (GBL) (300 mg/kg). At 0.5 h exposure the right cerebral hemisphere of animals receiving Krebs', GHB or GBL showed equivalent decreases of ATP and phosphocreatine and increases of ADP, AMP and lactate which indicated that these depressant drugs had no beneficial effect on the energy metabolism of the acutely hypoxic-oligemic brain. In a second series of rats in which Krebs' solution, GHB or GBL were administered to animals during the early recovery period from 0.5 h hypoxic-oligemic exposure, the brain metabolic patterns of the right hemisphere indicated that GHB retarded the restitution of energy phosphates and the oxidation of the accumulated lactate; whereas, GBL led to a delayed metabolic deterioration. It is concluded that GHB and GBL do not beneficially alter cerebral energy metabolism during acute hypoxia-oligemia and that their administration during restitution may result in metabolic alterations which suggest an unfavorable effect.

The administration of pharmacological doses of the naturally occurring central nervous system metabolite gamma-hydroxybutyrate (GHB) results in behavioral and cerebral metabolic changes which are similar in many respects to those seen with the barbiturates. Thus GHB causes depression of conscious behavior, reduction of cerebral glucose and high energy phosphate utilization rates, and increased glycogen and glucose and decreased pyruvate and lactate contents of brain tissue. Although earlier studies suggested that GHB produced its pharmacological actions via a direct effect on the pathways of cerebral carbohydrate metabolism, current experimental evidence favors the view that the metabolic effects are secondary phenomena resulting from a primary neuronal depression; a situation which also seems to apply to the cerebral metabolic effects of the barbiturates.

In addition to these effects on normoxic brain, GHB has been recently shown to ameliorate the cerebral metabolic abnormalities produced by acute arterial hypoxemia. Thus, animals receiving GHB (500 mg/kg) at the onset of a 0.5 hour exposure to arterial oxygen tensions of 30 mm Hg showed higher levels of brain phosphocreatine, glycogen and glucose and lower levels of lactic acid in comparison to hypoxic animals receiving saline. It has been well documented that depressant doses of barbiturates have a beneficial effect on the histopathology and eventual neurological status of animals exposed to global or focal cerebral hypoxia-ischemia. The studies reported indicated that GHB might also be beneficial in similar conditions. It is unclear whether the protective action of barbiturates for the hypoxic-ischemic brain can be entirely attributed to a depression of the tissue's metabolic activity. The factors contributing to the causation of cerebral damage in the various forms of hypoxia-ischemia may be different, and it is not possible to extrapolate directly the observed beneficial effects of the barbiturates to those which may prevail with the administration of GHB. The following study was done to determine the effects of GHB and its lactone analog, gamma-butyrolactone (GBL), on brain energy metabolism during exposure to a combination of acute hypoxemia and unilateral subtotal restriction of cerebral blood flow produced by carotid artery clamping (hypoxemia-oligemia).

Methods

Chemicals

Gamma-hydroxybutyrate, gamma-butyrolactone, substrates and co-enzymes for fluorometric assay were obtained from Sigma Chemical Corp. (St. Louis, Mo.). All enzymes were obtained from Boehringer-Mannheim.

Animals and Experimental Exposures

The experiments were performed on male rats (250-300 g) of Wistar strain that had free access to water and food. The animals were briefly anesthetized with halothane in a closed jar, tracheotomized, paralyzed with intraperitoneal tubocurarine chloride and ventilated with 30% O₂-70% N₂O on a small animal respirator. A femoral artery and vein were cannulated for blood pressure recording, anaerobic sampling of arterial blood and intravenous drug administration. The right common carotid artery was exposed and separated from the vagus nerve for later occlusion with a Teflon-coated clamp. Body temperature was measured rectally and was kept close to 37°C by means of a heating lamp. When the
animals were in a respiratory steady state with arterial PCO₂'s of 35–40 mm Hg and PO₂'s exceeding 100 mm Hg. GHB (500 mg/kg) or GBL (300 mg/kg) diluted in 1 ml Krebs' solution was given intravenously over a period of 1 min and the clamp was then applied to the carotid artery. Controls were obtained by giving similarly prepared animals equivalent amounts of Krebs' solution containing no drugs. In the normoxic series the 30% O₂–70% N₂O gas mixture was continued, whereas in the hypoxic groups the O₂ flow was reduced at the time of carotid clamping to give arterial PO₂'s of about 30 mm Hg. In order to maintain the N₂O concentration at 70% when O₂ flow was reduced it was replaced with an equivalent volume of N₂. At the end of 0.5 h exposure to the various PO₂ levels the brain was frozen in situ by pouring liquid nitrogen into a funnel fitted to a scalp incision and the right and left cerebral hemispheres were dissected from the frozen brain and stored in a liquid nitrogen freezer until analysis.

A second series of experiments assessed the effects of GHB and GBL when given in the immediate recovery period following hypoxic-oligemic exposure. When this series of animals, prepared as detailed above, were exposed for 0.5 h to right carotid artery occlusion and hypoxemia, the clamp was removed and the original 30% O₂–70% N₂O gas mixture was readministered. This was then followed by an intravenous injection of Krebs' solution (control), GHB (500 mg/kg) or GBL (300 mg/kg) and in situ brain freezing 0.5 or 1 h later. In addition, this series included normoxic animals whose brains were sampled 0.5 or 1 h after a 0.5 h exposure to right carotid artery clamping.

Analytical Methods

Arterial PO₂, PCO₂ and pH were measured with direct reading electrodes (Eschweiler, Kiel and Radiometer, Copenhagen) operated at 37°C and the values were corrected for body temperature.

The brain samples were prepared for metabolite extraction in a refrigerated glove box maintained at −22°C. Cerebral tissue supplied by the middle cerebral artery was dissected from the frozen right and left hemisphere, weighed, homogenized in methanol–HCl and then extracted with 0.3N perchloric acid at 0°C. The perchloric acid extracts were centrifuged and the neutralized supernatants were assayed for ATP, ADP, AMP, phosphocreatine, glucose, pyruvate and lactate by the enzymatic fluorometric methods of Lowry and Passonneau. The tissue residues were prepared and assayed for glycogen as described by Bachelard and Strang.

The results were evaluated statistically using Wilcoxon's rank sum test.

Results

A. Exposure Series

Physiological Parameters

During exposure the arterial PO₂ (28–30 mm Hg) and PCO₂ (31–35 mm Hg) values of the hypoxic groups receiving Krebs', GHB or GBL were statistically equivalent (fig. 1). All hypoxic animals developed a progressive metabolic acidosis and significant reductions of mean arterial blood pressure (MABP). Values for both of these parameters were significantly lower in the GBL group when compared to the hypoxic Krebs' group (p < 0.05). Body temperature was maintained between the limits of 36–37.5°C in all animals.

The experimental conditions of the exposure study were associated with an incidence of acute cardiovascular collapse and death prior to the 0.5 h sampling in 14%, 12% and 54% of animals receiving Krebs', GHB and GBL, respectively.

Energy Phosphates and Glycolytic Metabolites

Table 1 gives the concentrations of the energy phosphates and measured glycolytic metabolites in the left and right cerebral hemispheres of the normoxic and hypoxic groups. The left hemisphere (non-clamped) of hypoxic animals receiving Krebs' solution showed a pattern of unchanged adenylates, decreased phosphocreatine and increased glucose, pyruvate and lactate which agreed quantitatively with previous results obtained in animals exposed to equivalent degrees of unifactorial arterial hypoxemia. Hypoxic animals receiving GHB or GBL showed a similar pattern, with the exceptions that glucose was higher in the GHB group and pyruvate and lactate were lower in the GBL group.

The combination of right carotid artery clamping and hypoxemia produced alterations of the metabolic pattern which signified the presence of a more advanced degree of tissue hypoxia in the right cerebral hemisphere. Thus, the "Krebs"-treated group showed large decreases of ATP and glycogen, increases of ADP and AMP, and additional decreases and increases of phosphocreatine and lactate, respectively. The corresponding hypoxic groups treated with GHB and GBL showed only minor differences from this pattern (i.e. higher ADP and lower pyruvate in GHB group) which indicated that the drugs had no significant beneficial modifying effects on energy metabolism during the hypoxic-oligemic exposure.

B. Recovery Series

Physiological Parameters

Figure 2 gives the physiological parameters of the experimental groups in which Krebs' solution, GHB or GBL were given at the onset of restitution. In this series the values for arterial PO₂, PCO₂, pH and MABP during hypoxic exposure were statistically equivalent to those obtained for the Krebs' hypoxic group of series A. Upon returning to the original 30% O₂–70% N₂O gas mixture, all groups showed a prompt return to normal arterial PO₂ and MABP. The arterial PCO₂ of all hypoxic groups showed significant increases (45–55 mm Hg) in the early reoxygenation period with a subsequent decline to near control values by 1 h. The infusion of GBL resulted in a large additional reduction of the arterial pH in the early...
FIGURE 1. Arterial \( \text{P}_\text{O}_2 \), \( \text{P}_\text{CO}_2 \), \( \text{pH} \) and mean blood pressure (MABP) in rats receiving i.v. Krebs' solution, GHB (500 mg/kg) or GBL (300 mg/kg) at onset of exposure to arterial hypoxemia and right common carotid clamping. Values are means ± SEM with filled symbols representing values significantly different from the normoxic control group (\( p < 0.05 \)). (*) normoxia; (•) hypoxemia-Krebs; (○) hypoxemia-GHB; (▲) hypoxemia-GBL.

recovery period and, consequently, this group showed a persistent advanced metabolic acidosis throughout the entire restitution period.

During the 0.5 h exposure to hypoxemia-oligemia 9% of animals died from cardiovascular collapse, but once reoxygenation was established all animals survived to the 0.5 and 1 h sampling times.

Energy Phosphates and Glycolytic Metabolites

Tables 2 and 3 give the metabolite values of the reoxygenated groups. The normoxic control group consisted of animals sacrificed at each of the recovery times and since the values were statistically equivalent they have been pooled and presented in both tables.

TABLE 1 Left and Right Cerebral Hemisphere Contents of ATP, ADP, AMP, Phosphocreatine (PCR), Glycogen, Glucose, Pyruvate and Lactate in Rats Receiving Krebs' Solution, GHB (600 mg/kg) or GBL (300 mg/kg) with Subsequent 30 min Exposure to Normoxia or Hypoxemia and Right Carotid Artery Clamping

<table>
<thead>
<tr>
<th>Experimental group</th>
<th>ATP (m mole/kg)</th>
<th>ADP (m mole/kg)</th>
<th>AMP (m mole/kg)</th>
<th>PCR (m mole/kg)</th>
<th>Glycogen (m mole/kg)</th>
<th>Glucose (m mole/kg)</th>
<th>Pyruvate (m mole/kg)</th>
<th>Lactate (m mole/kg)</th>
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<td><strong>Left Hemisphere</strong></td>
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<tr>
<td>Normoxia + Krebs (6)</td>
<td>2.88 ± 0.06</td>
<td>0.29 ± 0.02</td>
<td>0.02 ± 0.01</td>
<td>4.48 ± 0.14</td>
<td>3.85 ± 0.33</td>
<td>0.38 ± 0.01</td>
<td>1.78 ± 0.01</td>
<td>0.12 ± 0.01</td>
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<tr>
<td>Hypoxemia + Krebs (6)</td>
<td>2.92 ± 0.04</td>
<td>0.33 ± 0.04</td>
<td>0.02 ± 0.01</td>
<td>3.20 ± 0.09</td>
<td>4.77 ± 0.21</td>
<td>0.35 ± 0.02</td>
<td>1.45 ± 0.01</td>
<td>0.30 ± 0.02</td>
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<tr>
<td>Hypoxemia + GHB (7)</td>
<td>2.97 ± 0.04</td>
<td>0.30 ± 0.02</td>
<td>0.02 ± 0.01</td>
<td>3.72 ± 0.31</td>
<td>2.10 ± 0.03</td>
<td>0.63 ± 0.01</td>
<td>2.10 ± 0.01</td>
<td>0.26 ± 0.02</td>
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<tr>
<td>Hypoxemia + GBL (6)</td>
<td>3.02 ± 0.04</td>
<td>0.33 ± 0.03</td>
<td>0.03 ± 0.01</td>
<td>3.82 ± 0.34</td>
<td>2.03 ± 0.43</td>
<td>0.48 ± 0.02</td>
<td>2.03 ± 0.01</td>
<td>0.21† ± 0.02</td>
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<td><strong>Right Hemisphere</strong></td>
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<tr>
<td>Normoxia + Krebs</td>
<td>2.88 ± 0.08</td>
<td>0.30 ± 0.01</td>
<td>0.02 ± 0.01</td>
<td>4.53 ± 0.10</td>
<td>3.81 ± 0.25</td>
<td>0.48 ± 0.01</td>
<td>1.71 ± 0.01</td>
<td>0.12 ± 0.01</td>
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<tr>
<td>Hypoxemia + Krebs</td>
<td>2.15† ± 0.38</td>
<td>0.62† ± 0.12</td>
<td>0.24† ± 0.13</td>
<td>1.59† ± 0.47</td>
<td>3.14 ± 0.36</td>
<td>0.85† ± 0.28</td>
<td>1.59† ± 0.13</td>
<td>0.22† ± 0.05</td>
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<tr>
<td>Hypoxemia + GHB</td>
<td>1.67† ± 0.63†</td>
<td>0.62‡ ± 0.07</td>
<td>0.24‡ ± 0.16</td>
<td>1.00† ± 0.28</td>
<td>2.83 ± 0.15</td>
<td>0.68‡ ± 0.15</td>
<td>1.00† ± 0.16</td>
<td>0.13* ± 0.05</td>
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<tr>
<td>Hypoxemia + GBL</td>
<td>2.23‡ ± 0.30‡</td>
<td>0.65‡ ± 0.07</td>
<td>0.41‡ ± 0.16</td>
<td>1.50‡ ± 0.37</td>
<td>3.06 ± 0.37</td>
<td>1.11‡ ± 0.37</td>
<td>1.50‡ ± 0.37</td>
<td>0.15 ± 0.04</td>
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Values are means ± SEM in m mole/kg. Hypoxic vs normoxic group, *p <0.05; Hypoxic GHB-GBL vs Hypoxic Krebs, †p <0.05.
FIGURE 2. Arterial $P_{O_2}$, $P_{CO_2}$, pH and mean blood pressure in rats exposed for 0.5 h to hypoxemia and right common carotid clamping with subsequent i.v. administration of Krebs’ solution, GHB (500 mg/kg) or GBL (300 mg/kg) and re-oxygenation for 0.5 or 1 h. Values are mean ± SEM with filled symbols representing values significantly different from the normoxic control group (p < 0.05). (•) normoxia; (※) hypoxemia-Krebs; (●) hypoxemia-GHB; (k) hypoxemia-GBL.

Metabolic restitution in the left hemisphere of Krebs’ solution-treated hypoxemic animals was rapid with return of phosphocreatine, pyruvate and lactate to control values by 0.5 h. The restitution in the GHB-GBL groups was equally rapid with the additional features of higher phosphocreatine, glycogen and glucose at 0.5 and 1 h when compared to the Krebs’ hypoxemic group. Although pyruvate and lactate were generally lower in the GHB-GBL groups at 0.5 h, this trend was only maintained for the GHB group at 1 h. The hypoxemic-oligemic right hemisphere of Krebs’ animals showed a less rapid restitution which was characterized by small decreases of ATP and phosphocreatine and increased lactate at 0.5 h and by a continuing minor lactacidosis at 1 h. The groups receiving GHB or GBL showed major deviations from the restitution pattern of the Krebs’ group. Thus at 0.5 h, GHB animals continued to show marked decreases

<table>
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<tr>
<th>Experimental group</th>
<th>ATP</th>
<th>ADP</th>
<th>AMP</th>
<th>PCR</th>
<th>Glycogen</th>
<th>Glucose</th>
<th>Pyruvate</th>
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<td>Normoxia + Krebs (8)</td>
<td>2.89</td>
<td>0.29</td>
<td>0.03</td>
<td>4.56</td>
<td>2.34</td>
<td>3.48</td>
<td>0.15</td>
<td>1.79</td>
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<tr>
<td>Hypoxemia + Krebs (8)</td>
<td>2.81</td>
<td>0.33</td>
<td>0.04</td>
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<td>2.46</td>
<td>5.24†</td>
<td>0.14</td>
<td>2.18</td>
</tr>
<tr>
<td>Hypoxemia + GHB (9)</td>
<td>2.92</td>
<td>0.26</td>
<td>0.03</td>
<td>4.82†</td>
<td>3.26†</td>
<td>9.06‡</td>
<td>0.09‡</td>
<td>1.72</td>
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<tr>
<td>Hypoxemia + GBL (7)</td>
<td>2.82</td>
<td>0.26</td>
<td>0.03</td>
<td>4.92†</td>
<td>3.04‡</td>
<td>8.40‡</td>
<td>0.09‡</td>
<td>1.54‡</td>
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<tr>
<td>Right Hemisphere</td>
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<tr>
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<td>2.88</td>
<td>0.31</td>
<td>0.04</td>
<td>4.55</td>
<td>2.47</td>
<td>3.32</td>
<td>0.14</td>
<td>1.65</td>
</tr>
<tr>
<td>Hypoxemia + Krebs</td>
<td>2.69†</td>
<td>0.30</td>
<td>0.04</td>
<td>4.17†</td>
<td>2.07</td>
<td>6.44†</td>
<td>0.19†</td>
<td>3.95†</td>
</tr>
<tr>
<td>Hypoxemia + GHB</td>
<td>1.60*</td>
<td>0.48*</td>
<td>0.28*</td>
<td>2.67†</td>
<td>1.35*</td>
<td>8.26†</td>
<td>0.19†</td>
<td>15.62*</td>
</tr>
<tr>
<td>Hypoxemia + GBL</td>
<td>2.54†</td>
<td>0.30</td>
<td>0.06</td>
<td>4.18†</td>
<td>1.89</td>
<td>8.65‡</td>
<td>0.20‡</td>
<td>7.97‡</td>
</tr>
</tbody>
</table>

Values are means ± SEM in m mole/kg. Hypoxemic vs normoxic group, †p <0.05; Hypoxemic GHB-GBL vs Hypoxemic Krebs, *p <0.05.
in ATP, phosphocreatine and glycogen and increases in lactate which, however, were subsequently normal by 1 h. In GBL animals a converse pattern was observed: although the initial 0.5 h metabolite values showed a trend toward restitution, the 1 h sampling indicated a secondary metabolic deterioration with decreasing ATP, phosphocreatine and glycogen and increasing ADP, AMP and lactate.

Discussion

The objective of this study was to assess the effects of the cerebral depressant GHB and its lactone analog GBL on the energy metabolism of the brain during exposure and recovery from a hypoxic-oligemic insult. The study was motivated by the observation that these agents have a beneficial action on cerebral energy metabolism in unifactorial hypoxemia and, therefore, could be potentially useful in more complex hypoxic situations involving elements of cerebral circulatory insufficiency. The overall results of the present study, which indicated that GHB and GBL were without apparent beneficial effects on the energy metabolism of the hypoxic-oligemic brain, will be discussed under headings 1) acute exposure and 2) restitution.

Acute Exposure

The experimental model used in any study of cerebral hypoxia-ischemia may introduce specific variables which influence the interpretation and general application of the results. In the present study the combination of hypoxemia and unilateral carotid artery occlusion was used since it provided a well documented model in which the critical threshold for hypoxic neuronal damage could be reached while retaining the potential for recovery studies. Thus, previous studies have shown that 0.5 h exposure of rats to arterial Po2's of 25-30 mm Hg and to carotid artery clamping results in marked deficiencies of energy homeostasis with massive lactacidosis and the histological abnormality of neuronal mitochondrial swelling in the cerebral hemisphere ipsilateral to the carotid occlusion. In addition, since circulatory studies have indicated that these events occur in the presence of a patent microvascular bed and a two-fold increase of the cerebral blood flow the basic variable in this model seems to be a critical, but not absolute, deficiency of the tissues' oxygen supply. The model therefore seemed applicable for the assessment of the therapeutic usefulness of neuronal depressant agents which would be expected to exert their major action by decreasing the O2 needs of the acutely hypoxic-oligemic brain.

The doses of GHB and GBL used in the present study produce behavioral nonresponsiveness and suppression of glycolysis which are well established in the normoxic animal within 2.5-5 minutes of injection. In the more chronic state (0.5-1 h post-injection) these behavioral and metabolic changes are associated with a 37% decrease of the cerebral high energy phosphate utilization rate and a 55% and 40% reduction of gray and white matter glucose consumption, respectively. Despite this ability of GHB and GBL to reduce cerebral metabolic activity and, as a consequence, the tissues' O2 needs, the results indicate that infusion of these agents just prior to the onset of exposure results in no obvious beneficial modifications of the oligemic hemisphere's energy metabolism. Thus, although the non-clamped or hypoxic hemisphere of GHB-GBL animals showed a minor drug effect with a trend for higher phosphocreatine and glucose and lower lactate...
levels, the hypoxic-oligemic or clamped hemisphere showed deteriorations of energy phosphates and accumulations of lactate which were equivalent to those of animals receiving only Krebs' solution. The rationale for the use of depressant drugs during hypoxia-ischemia rests on their ability to suppress that part of the cerebral oxygen consumption which is used to support functional expression and, as a consequence, no beneficial metabolic effect would be expected during pathological states which produce marked depression or loss of conscious behavior. This is well demonstrated by the absence of any beneficial effect of barbiturates during complete or near complete cerebral ischemia; a state in which functional parameters such as the EEG are rapidly lost. Whether the present results can be explained on this basis is open to question and will require further direct study and comparison of functional parameters in the hypoxic and hypoxic-oligemic hemispheres. In addition to the absence of a favorable metabolic effect, GBL increased the exposure mortality by 40% and thus indicated that this agent was clearly detrimental to survival during acute hypoxemia. The most probable reason for this effect is that the acidic nature of GBL led to an aggravation of the hypoxic systemic metabolic acidosis with an attendant lethal action on cardiovascular function.

Restitution

It has been conventional to invoke metabolic depression as the prime mechanism by which barbiturate anesthesia prevents or minimizes hypoxic-ischemic brain damage. The present study and the results of others, indicate that pretreatment with depressant doses of GHB, GBL or barbiturates do not alter the metabolic abnormalities during hypoxemia-oligemia or ischemia. These observations, applied to barbiturates, have resulted in the speculation that under certain hypoxic conditions depressants can retard the ability of brain to quickly restitute the energy phosphates and a massive lactacidosis. Direct testing of this hypothesis has led to results which vary with the experimental model. Thus in complete ischemia energy metabolism shows major restitution irrespective of the use or non-use of barbiturates, whereas in severe incomplete ischemia (CBF 10% of control) only those animals pretreated with phenobarbital showed significant metabolic recovery. These findings have led to the suggestion that ischemic states with a small residuum of blood flow are more harmful to cellular survival than is complete absence of the cerebral blood flow and that the mechanisms of cellular damage in the 2 conditions are potentially different. Although a number of these mechanisms have been proposed (i.e., free radical membrane damage, acidosis induced cellular autolysis, microvascular damage with deficient post-ischemic recirculation), it at least seems established that restitution and maintenance of the energy generating systems is necessary in the full functional-histological recovery of the preparation.

The restitution pattern of the hypoxic-oligemic Levine model shows certain features which seem to make it well suited for the assessment and therapeutic manipulation of the possible post-exposure causative factors involved in hypoxic cerebral damage. Thus, although the initial 0.5-1 hour of re-oxygenation in this model is characterized by a near complete normalization of energy metabolism, a patent microvascular bed and an adequate cerebral blood flow, a large percentage of the previously oligemic hemispheres show a progressive pathological picture characterized by neuronal mitochondrial swelling, "ischemic" neurons, hemisphere swelling and tissue necrosis. These observations are highly suggestive that the tissue damage resulting from transient hypoxemia-oligemia may, at least in part, be mediated by processes active in the recovery period and thus be subject to therapeutic modification. Despite these favorable features of the Levine model, the present results failed to indicate a clear beneficial metabolic effect of post-exposure administration of GHB or GBL. Thus, the hypoxic-oligemic hemisphere of animals receiving GHB showed a continuing gross derangement of the energy phosphates and a massive lactacidosis at 0.5 h re-oxygenation which indicated that under certain hypoxic conditions depressants can retard the ability of brain to quickly reestablish the energy stores and to oxidize the accumulated lactate. Although the metabolic state of the GHB animals eventually reached that of nontreated controls, it may be assumed that this type of retarded restitution is undesirable since it represents an undue prolongation of the two main metabolic abnormalities which are frequently correlated to cellular damage — insufficient ATP and lactacidosis.

The observation that the pattern of metabolic restitution of GBL animals at 1 hour was significantly different from that of the GHB group is seemingly paradoxical since this drug is rapidly converted to GHB by plasma and liver lactonase and is thus believed to exert its central actions sowell through formation of GHB. The drug, however, has the additional property of being highly acidic and its infusion in artificially ventilated animals leads to a significant metabolic acidosis and hypercapnia due to release of $\text{CO}_2$ from the bicarbonate-carbonic acid buffer system. It is thus possible to speculate that the augmentation of the post-exposure metabolic acidosis by GBL (see fig. 2) resulted in a cumulative unfavorable action on the cellular metabolic processes or on the patterns of cerebral circulation with a resultant secondary metabolic deterioration.

In summary, the results indicate that prior administration of the non-barbiturate depressants GHB and GBL does not favorably influence the metabolism of the brain during acute hypoxemia-oligemia. In addition, when given in the immediate recovery period these drugs give rise to restitution patterns which suggest a real or potential detrimental effect. Due to
its association with a very significant increase of the exposure mortality and a prominent delayed deterioration of energy metabolism during restitution, the acidic analog GBL seems contraindicated in hypoxic-ischemic states.

Acknowledgment

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References

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