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 consciousness,1 reduction of cerebral glucose and high energy phosphate utilization rates,3,4 and increased glycogen and glucose and decreased pyruvate and lactate contents of brain tissue.4,5 Although earlier studies suggested that GHB produced its pharmacological actions via a direct effect on the pathways of cerebral carbohydrate metabolism,1 current experimental evidence favors the view that the metabolic effects are secondary phenomena resulting from a primary neuronal depression;3,6,7 a situation which also seems to apply to the cerebral metabolic effects of the barbiturates.8

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 hypoxemic animals receiving saline.6 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.6 The studies reported indicated that GHB might also be beneficial in similar conditions.6,8 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,9 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 
Pco_2's of 35-40 mm Hg and Po_2'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% O_2-70% N_2O gas mixture was con-
tinued, whereas in the hypoxemic groups the O_2 flow 
was reduced at the time of carotid clamping to give 
arterial Po_2's of about 30 mm Hg. In order to main-
tain the N_2O concentration at 70% when O_2 flow was 
reduced it was replaced with an equivalent volume of 
N_2. At the end of 0.5 h exposure to the various Po_2 
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 hypoxemic-oligemic ex-
posure. 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% O_2-70% N_2O gas mix-
ture 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 Po_2, Pco_2 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 ex-
traction 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, pyru-
vate 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 Po_2 (28-30 mm Hg) 
and Pco_2 (31-35 mm Hg) values of the hypoxemic 
groups receiving Krebs', GHB or GBL were 
statistically equivalent (fig. 1). All hypoxemic animals 
developed a progressive metabolic acidosis and signifi-
cant reductions of mean arterial blood pressure 
(MABP). Values for both of these parameters were 
significantly lower in the GBL group when compared 
to the hypoxemic 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 cardio-
vascular 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 hypoxemic animals receiving Krebs' solu-
tion 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.

Hypoxemic 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 ad-
vanced 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 in-
creases of phosphocreatine and lactate, respectively. 
The corresponding hypoxemic 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 hypoxemic-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 Po_2, Pco_2, pH and 
MABP during hypoxemic exposure were statistically 
equivalent to those obtained for the Krebs' hypoxemic 
group of series A. Upon returning to the original 30% 
O_2-70% N_2O gas mixture, all groups showed a prompt 
return to normal arterial Po_2 and MABP. The arterial 
Pco_2 of all hypoxemic groups showed significant in-
creases (45-55 mm Hg) in the early reoxygenation 
period with a subsequent decline to or near control 
values by 1 h. The infusion of GBL resulted in a large 
additional reduction of the arterial pH in the early
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 (500 mg/kg) with Subsequent 30 min Exposure to Normoxia or Hypoxemia and Right Cerebral Artery Clamping**

<table>
<thead>
<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><strong>Left Hemisphere</strong></td>
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</tr>
<tr>
<td>Normoxia + Krebs  (6)</td>
<td>2.88</td>
<td>0.29</td>
<td>0.02</td>
<td>4.48</td>
<td>3.85</td>
<td>0.12</td>
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<td>0.33</td>
<td>0.02</td>
<td>3.20†</td>
<td>1.45</td>
<td>4.77†</td>
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<td>±0.04</td>
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<td>0.02</td>
<td>3.72†</td>
<td>2.10</td>
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</tr>
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<td>±0.01</td>
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<td>3.02</td>
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<td>0.03</td>
<td>3.82†</td>
<td>2.03</td>
<td>5.24†</td>
<td>0.21†</td>
<td>8.91†</td>
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<td>±0.04</td>
<td>±0.03</td>
<td>±0.01</td>
<td>±0.34</td>
<td>±0.43</td>
<td>±0.48</td>
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<td>±1.88</td>
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<td>Normoxia + Krebs</td>
<td>2.88</td>
<td>0.30</td>
<td>0.02</td>
<td>4.53</td>
<td>3.81</td>
<td>0.12</td>
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<td>±0.01</td>
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<td>±0.48</td>
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<td>0.24†</td>
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<td>0.85†</td>
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<td>18.76†</td>
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<td>Hypoxemia + GHB</td>
<td>1.67†</td>
<td>0.65†</td>
<td>0.22†</td>
<td>1.00†</td>
<td>0.68†</td>
<td>2.83</td>
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<td>±0.36</td>
<td>±0.07</td>
<td>±0.16</td>
<td>±0.28</td>
<td>±0.15</td>
<td>±0.66</td>
<td>±0.03</td>
<td>±1.28</td>
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<td>Hypoxemia + GBL</td>
<td>2.25†</td>
<td>0.65†</td>
<td>0.41†</td>
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<td>1.11†</td>
<td>3.06</td>
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<td>18.71†</td>
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<td>±0.35</td>
<td>±0.08</td>
<td>±0.26</td>
<td>±0.43</td>
<td>±0.37</td>
<td>±0.73</td>
<td>±0.04</td>
<td>±1.65</td>
</tr>
</tbody>
</table>

Values are means ± SEM in m mole/kg. Hypoxic vs normoxic group, †p < 0.05; Hypoxic GHB-GBL vs Hypoxic Krebs, *p < 0.05.
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 2** Left and Right Cerebral Hemisphere Contents of Energy Phosphates and Glycolytic Metabolites in Rats Exposed to Hypoxemia and Right Carotid Artery Clamping with Subsequent Administration of Krebs' Solution, GHB (500 mg/kg) or GBL (500 mg/kg) and Reoxygenation for 50 min

<table>
<thead>
<tr>
<th>Experimental group</th>
<th>ATP (mM)</th>
<th>ADP (mM)</th>
<th>AMP (mM)</th>
<th>PCR (mM)</th>
<th>Glycogen (mM)</th>
<th>Glucose (mM)</th>
<th>Pyruvate (mM)</th>
<th>Lactate (mM)</th>
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<tr>
<td>Normoxia + Krebs (8)</td>
<td>2.89 ± 0.03</td>
<td>0.29 ± 0.01</td>
<td>0.03 ± 0.01</td>
<td>4.56 ± 0.09</td>
<td>2.34 ± 0.21</td>
<td>3.48 ± 0.23</td>
<td>0.15 ± 0.01</td>
<td>1.79 ± 0.12</td>
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<td>Hypoxemia + Krebs (8)</td>
<td>2.81 ± 0.08</td>
<td>0.33 ± 0.04</td>
<td>0.04 ± 0.01</td>
<td>4.43 ± 0.11</td>
<td>2.46 ± 0.14</td>
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<td>Hypoxemia + GHB (9)</td>
<td>2.82 ± 0.03</td>
<td>0.28 ± 0.02</td>
<td>0.03 ± 0.01</td>
<td>4.82* ± 0.10</td>
<td>3.26* ± 0.22</td>
<td>9.06* ± 0.39</td>
<td>0.09* ± 0.01</td>
<td>1.72 ± 0.26</td>
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<tr>
<td>Hypoxemia + GBL (7)</td>
<td>2.82 ± 0.05</td>
<td>0.26 ± 0.01</td>
<td>0.03 ± 0.01</td>
<td>4.92* ± 0.04</td>
<td>3.04* ± 0.11</td>
<td>8.40* ± 1.50</td>
<td>0.09* ± 0.01</td>
<td>1.54* ± 0.20</td>
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<tr>
<td><strong>Right Hemisphere</strong></td>
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</tr>
<tr>
<td>Normoxia + Krebs</td>
<td>2.88 ± 0.06</td>
<td>0.31 ± 0.03</td>
<td>0.04 ± 0.01</td>
<td>4.55 ± 0.08</td>
<td>2.47 ± 0.19</td>
<td>3.32 ± 0.26</td>
<td>0.14 ± 0.01</td>
<td>1.65 ± 0.12</td>
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<tr>
<td>Hypoxemia + Krebs</td>
<td>2.69* ± 0.06</td>
<td>0.30 ± 0.03</td>
<td>0.04 ± 0.01</td>
<td>4.17* ± 0.14</td>
<td>2.07 ± 0.14</td>
<td>6.44* ± 0.54</td>
<td>0.19* ± 0.02</td>
<td>3.95* ± 0.73</td>
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<tr>
<td>Hypoxemia + GHB</td>
<td>1.60* ± 0.28*</td>
<td>0.48* ± 1.10</td>
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<td>2.67* ± 0.58</td>
<td>1.35* ± 0.48</td>
<td>8.26* ± 0.67</td>
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<tr>
<td>Hypoxemia + GBL</td>
<td>2.94* ± 0.14</td>
<td>0.30 ± 0.03</td>
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<td>8.65* ± 1.20</td>
<td>0.20* ± 0.03</td>
<td>7.97* ± 2.66</td>
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</table>

Values are means ± SEM in mM or % of control. Hypoxemia vs normoxic group, *p < 0.05; Hypoxemic GHB-GBL vs Hypoxemic Krebs, **p < 0.05.
TABLE 3 Left and Right Cerebral Hemisphere Contents of Energy Phosphates and Glycolytic Metabolites in Rats Exposed to Hypoxemia and Right Carotid Artery Clamping with Subsequent Administration of Krebs' Solution, GHB (600 mg/kg) or GBL (800 mg/kg) and Reoxygenation for 60 min

<table>
<thead>
<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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<tr>
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<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 (6)</td>
<td>3.04</td>
<td>0.29</td>
<td>0.02</td>
<td>4.23</td>
<td>1.74</td>
<td>4.43</td>
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<td>Hypoxemia + GHB (6)</td>
<td>2.89</td>
<td>0.29</td>
<td>0.03</td>
<td>4.73</td>
<td>2.72</td>
<td>6.01</td>
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<td>0.96†</td>
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<td>Hypoxemia + GBL (7)</td>
<td>2.82</td>
<td>0.32</td>
<td>0.05</td>
<td>4.80</td>
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<td>7.47</td>
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<td>2.68</td>
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<tr>
<td>Normoxia + Krebs</td>
<td>2.88</td>
<td>0.31</td>
<td>0.04</td>
<td>4.55</td>
<td>2.47</td>
<td>3.32</td>
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<tr>
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<td>0.05</td>
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<tr>
<td>Hypoxemia + GBL</td>
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<td>1.44†</td>
<td>7.77†</td>
<td>0.24†</td>
<td>10.72†</td>
</tr>
</tbody>
</table>

Values are means ± SEM in mmol/kg. Hypoxemic vs normoxic group, *p <0.05; Hypoxemic GHB-GBL vs Hypoxemic Krebs, †p <0.05.

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 metabolic activity and, as a consequence, the tissues' O₂ needs, the results indicate that infusion of 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.14-18 In addition, since circulatory studies have indicated that these events occur in the presence of a patent microvascular bed18 and a two-fold increase of the cerebral blood flow19 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.20 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 rate25 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, retaining the potential for recovery studies.16 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.14-18 In addition, since circulatory studies have indicated that these events occur in the presence of a patent microvascular bed18 and a two-fold increase of the cerebral blood flow19 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.

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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 hypoxemic and hypoxemic-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 anesthetics prevent or minimizes hypoxic-ischemic brain damage. The present study and the results of other, 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 depressants possibly exert their protective action on metabolic processes during the restitution period. The recent demonstration that the metabolic activity of the post hypoxic-ischemic brain can show increases of up to 50%, despite continuing evidence of defective energy homeostasis, provides some theoretical basis for this proposal.

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 hypoxemic-oligemic Levine model shows certain features which seem to make it well suited for the assessment and therapeutic manipulation of the possible postexposure 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 restitute 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 a plasma and liver lactonase and is thus believed to exert its central actions solely 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 CO₂ 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.

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Effects of gamma-hydroxybutrate and gamma-butyrolactone on cerebral energy metabolism during exposure and recovery from hypoxemia-oligemia.

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