Rate of cerebral energy consumption in concussive head injury in the rat

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The metabolic rate was determined in the rat brain during the immediate concussive response to standardized impact accelerations of 7 and 9 m/sec velocity. In one series, the metabolic state was determined in freeze-clamped cortical and brain-stem tissue 20 seconds after the impact. The metabolic rate was calculated from the rate of energy depletion in the adjacent unclamped tissue during 10 seconds of total ischemia. The freeze-clamping procedure per se was shown to enhance the metabolic rate probably by inducing mechanical excitation. In another series, in situ freezing was used for tissue sampling in the same situation. A 10-second period of heart standstill induced a standardized period of ischemia. During the acute concussive response to impact acceleration at 7 m/sec velocity, there was an increase of the metabolic rate in the brain stem. A more intense concussive impact at 9 m/sec velocity further enhanced this reaction and also involved the cortex. It is concluded that the basis of the immediate concussive response is a mechanically elicited neuronal excitation. This may lead to energy depletion unless the increased metabolic demands are met.

Key Words: Experimental concussion · Cerebral energy consumption · Neuronal excitation · Freezing techniques

Cerebral concussion is characterized by a sudden change of cerebral function, the essence of which, according to the common use of the term, is loss of consciousness. Simultaneously there occur loss of reflex functions, respiratory and circulatory changes, and in most experimental models, motor phenomena. The physicochemical basis of this instantaneous change of neuronal function has not been clarified. Symptoms of sympathetic discharge and motor phenomena indicate a short-lasting excitatory state, primarily of the brain-stem region. Walker, et al., found evidence of seizure-like cortical activity in head trauma, and proposed that excitation was the general neuronal response to trauma. Others have not confirmed this finding. The effect of trauma on the metabolic rate was studied by Nelson, et al. Severe compressive head injury in mice induced an immediate increase of the utilization of the metabolites of the energy reserves in brain tissue.

We have described a model of graded acceleration concussion in rats, and analyzed the effects of trauma upon cerebral energy state and cerebral blood flow and oxygen consumption. Although it was not possible to make direct measurements of metabolic rate during the initial concussion response, there was evidence of an elevated cerebral metabolic rate. Thus, despite an increase of the cerebral blood flow (CBF) during the first minute, there were signs of energy failure at tissue level. Walker, et al., proposed that trauma not only elicited an immediate
Cerebral energy consumption in experimental head injury

depolarization, but also a self-sustained, repetitive firing. Our results are in favor of such a hypothesis.

The "closed system" method of Lowry, et al., has been extensively used for determination of cerebral metabolic rate, and is the only one available for the study of regional metabolic rate in non-steady state situations. The method is based on the assumption that, when total cerebral ischemia is abruptly induced, the metabolic rate is maintained for some time at preischemic levels. Since energy production due to oxidative processes can be neglected in this situation, the rate of energy use can be calculated from the rate of glycolysis (production of lactate (La) or decrease in stores of glycogen and glucose) and the rate of decrease in energy stores (phosphocreatine (PCr), adenosine triphosphate (ATP), and adenosine diphosphate (ADP)).

In the present study, the method of Lowry, et al., was used to evaluate the rate of energy utilization during the acute concussion reaction elicited by acceleration trauma. In one series, tissue was sampled with the freeze-clamping technique of Quistorff. This method permits the most accurate timing of the freezing of tissue. On the other hand, the technique of tissue sampling produces a new trauma, the significance of which has to be assessed. Therefore, a more conventional in situ freezing technique was used for tissue sampling in a second series.

Materials and Methods

Male Wistar rats weighing 300 to 420 gm were anesthetized with 2% to 3% halothane. The animals were then tracheotomized, and the femoral vessels on one side were dissected. Suxamethonium chloride (Celocurin) was injected intravenously, and anesthesia was continued under artificial ventilation with 75% nitrous oxide and 25% oxygen. Halothane was withdrawn after tracheotomy. One femoral artery and vein were cannulated. After the operation the animal was placed on its back in a plaster bed fitting the head and upper part of the body. The arterial blood pressure was monitored continuously. After about 10 minutes an arterial blood sample was taken for determination of arterial oxygen pressure (PaO₂), arterial carbon dioxide pressure (PaCO₂), and pH. Artificial ventila-

tion was adjusted to maintain PaO₂ at 100 mm Hg and PaCO₂ at 34 to 40 mm Hg. A second arterial sample was taken 5 to 10 minutes later to check that a respiratory steady state prevailed.

After the second blood sample, acceleration concussion was induced by a piston, driven by compressed nitrogen, moving through a hole in the plaster bed, and hitting the occipital crest of the head. The movement of the unrestrained animal thus induced was an upward acceleration of the head with combined translation and rotation in the sagittal plane, and a marked retroflexion of the neck. A soft cushion 5 cm above the table braked the motion. The immediate concussive response was evaluated from the blood pressure reaction. As previously described, the blood pressure response is a reliable sign of concussion in the anesthetized and paralyzed animal. Two impact velocities were used: 7 and 9 m/sec. Both give a concussion reaction, but, as estimated from the symptoms resulting, there are quantitative differences, and the reaction after 9 m/sec impact is more intense and prolonged.

Freeze-Clamping

Twelve animals were used: four were controls, four were concussed with a 7 m/sec impact, and four with a 9 m/sec impact. Control animals were handled in the same way as the injured animals except for the trauma. Immediately after trauma the animal was transferred to the tube of the freeze-clamping machine, in which tissue freezing was performed 20 seconds after the concussion impact. According to this technique, two rotating circular knives cut out a cylinder of tissue which is clamped between two aluminum blocks precooled in liquid nitrogen. The freezing of the cut tissue surfaces starts 0.1 second after the start of the cutting.

In the present study this technique was used for determination of metabolic rate, since it permitted sampling of paired regional samples of brain tissue, according to the following procedure. The knives were set 6 mm apart, and the rat so placed that the frontal cross section was in the middle of the forebrain, and the caudal one in the region of the brain stem. The freeze-clamped tissue, that is, the section between the knives, was
used for measuring control levels of metabolites at the onset of ischemia. The adjacent pieces of brain tissue (that contained in the frontal, detached part of the head, and that attached to the body) were kept in room air for 10 seconds (that is, 10 seconds of ischemia). After exactly 10 seconds, freezing was started by pressing these cut surfaces against aluminum blocks in liquid nitrogen. To secure ischemia of the brain-stem tissue, heart standstill was induced by an intravenous injection of saturated KCl at the moment of freeze-clamping.

For metabolite analyses, sections of the four frozen brain surfaces 1 mm thick were cut with a buzz saw in a refrigerated box at \(-22^\circ\) C. Cortical tissue (frontal section) and total brain-stem tissue (caudal section) were used for extraction.

**In Situ Freezing**

Eighteen animals were included in this series: six were control animals, six were concussed with a 7 m/sec impact, and six with a 9 m/sec impact. After the trauma (or, in the control group, without trauma) the animal was turned to a supine position during uninterrupted ventilation. Preparation for *in situ* freezing started immediately. A longitudinal skin incision was made over the head and back of the neck, the skull bone was exposed, and the neck muscles were dissected away from the occipital bone, the atlantooccipital membrane, and the upper part of the cervical spine. At 20 seconds after the impact an intravenous bolus of saturated potassium chloride was injected to induce heart standstill. The blood pressure fell within 2 to 4 seconds to near zero level. During the next few seconds, the dissection could be finished. The moment when the declining blood pressure passed the 50 mm Hg level (the steepest part of the falling curve) was arbitrarily taken as zero time. Ten seconds later, the tissue freezing was induced by pouring liquid nitrogen into a funnel over the skull and cervical spine formed by the lifted skin. After about 1 minute, freezing was continued with the whole head dipped into liquid nitrogen. The metabolic state of the tissue thus represented the situation after a standardized period of total ischemia. The technique did not permit sampling of tissue representative of the starting point of ischemia, that is, the metabolic state 20 seconds after trauma. The reason for this was that an accurate uncovering of the occipital bone, atlantooccipital membrane, and the dorsal part of the cervical spine, was necessary to standardize the distance of freezing. This preparation could not be performed if there was bleeding from the cut muscles. Therefore, the values obtained after the standardized period of ischemia had to be compared with the control data from a previous series for the calculation of metabolic rate (see below).

The brain, including the upper part of the brain stem, was chiseled out *en bloc* during irrigation with liquid nitrogen. The tissue was dissected in a refrigerated glove box at \(-22^\circ\) C. A 1-mm thick piece of dorsocaudal cortex and a 2-mm thick piece of brain-stem tissue immediately underlying the cisterna magna were selected for analysis.

**Metabolite Analysis**

The tissue was extracted at \(-22^\circ\) C and tissue metabolites were analyzed with fluorometric, enzymatic techniques as described previously. All values are given in \(\mu\text{mol/gm wet tissue}\).

**Calculations**

The method of calculation of the metabolic rate in a certain condition requires determination of 1) the metabolic state of the tissue at a certain moment during the condition studied (0 sec of ischemia), and 2) the metabolic state of tissue, which during conditions identical to those at the onset of ischemia has in addition been exposed to a defined period of total ischemia.

The energy utilization during the period of ischemia can be calculated from the formula:

\[
\Delta P = 2 \Delta ATP + \Delta ADP + \Delta P\text{Cr} + \Delta \text{lactate.}
\]

In the freeze-clamped series, paired values of adjacent tissue (0 sec of ischemia/10 sec of ischemia), were used to calculate \(\Delta P\) during the 10-second ischemic period. In the group frozen *in situ*, the ischemic values were compared to the mean values of the control series of Nilsson and Pontén, to derive the \(\Delta\) values. Student's t-test was used to test the significance of differences between groups.
Cerebral energy consumption in experimental head injury

TABLE 1
Regional metabolic state in freeze-clamped animals with and without trauma*

<table>
<thead>
<tr>
<th>Group†</th>
<th>Tissue</th>
<th>Trauma</th>
<th>No. of Rats</th>
<th>PCr</th>
<th>ATP</th>
<th>ADP</th>
<th>La</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 sec of ischemia</td>
<td>cortex</td>
<td>none</td>
<td>4</td>
<td>3.52 ± 0.18</td>
<td>2.70 ± 0.04</td>
<td>0.35 ± 0.03</td>
<td>1.01 ± 0.08</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7 m/sec</td>
<td>4</td>
<td>3.73 ± 0.12</td>
<td>2.58 ± 0.12</td>
<td>0.35 ± 0.03</td>
<td>1.09 ± 0.17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9 m/sec</td>
<td>4</td>
<td>3.69 ± 0.09</td>
<td>2.67 ± 0.04</td>
<td>0.36 ± 0.03</td>
<td>1.11 ± 0.26</td>
</tr>
<tr>
<td></td>
<td>brain stem</td>
<td>none</td>
<td>4</td>
<td>3.83 ± 0.10</td>
<td>2.54 ± 0.15</td>
<td>0.32 ± 0.02</td>
<td>1.12 ± 0.08</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7 m/sec</td>
<td>2</td>
<td>3.41</td>
<td>2.27</td>
<td>0.32</td>
<td>0.76</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.48</td>
<td>2.62</td>
<td>0.37</td>
<td>1.15</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>9 m/sec</td>
<td>4</td>
<td>3.91 ± 0.25</td>
<td>2.49 ± 0.06</td>
<td>0.27 ± 0.02</td>
<td>0.99 ± 0.09</td>
</tr>
<tr>
<td>10 sec of ischemia</td>
<td>cortex</td>
<td>none</td>
<td>4</td>
<td>0.62 ± 0.18</td>
<td>1.37 ± 0.30</td>
<td>1.11 ± 0.15</td>
<td>3.00 ± 0.31</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7 m/sec</td>
<td>3</td>
<td>0.83 ± 0.11</td>
<td>1.62 ± 0.09</td>
<td>0.95 ± 0.08</td>
<td>2.46 ± 0.10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9 m/sec</td>
<td>3</td>
<td>0.57 ± 0.12</td>
<td>1.24 ± 0.10</td>
<td>1.12 ± 0.10</td>
<td>2.91 ± 0.12</td>
</tr>
<tr>
<td></td>
<td>brain stem</td>
<td>none</td>
<td>2</td>
<td>0.66</td>
<td>1.29</td>
<td>0.83</td>
<td>1.63</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7 m/sec</td>
<td>1</td>
<td>0.92</td>
<td>1.31</td>
<td>0.83</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>1.18</td>
<td>1.62</td>
<td>0.69</td>
<td>1.42</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>9 m/sec</td>
<td>2</td>
<td>0.97</td>
<td>1.42</td>
<td>0.81</td>
<td>2.23</td>
</tr>
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</table>

*Values are mean (μmol/gm) ± SEM (except for groups with one or two samples).
†0 second of ischemia refers to the immediately freeze-clamped tissue; 10 seconds of ischemia to adjacent tissue frozen with a 10-second lag after the guillotining procedure.

Results

All the animals used for metabolite analysis were in respiratory steady state, as described above. A concussion response was elicited in all trauma animals as evidenced by the immediate blood pressure reaction.

Freeze-Clamping

The metabolic state of the freeze-clamped series is shown in Table 1. Because of technical difficulties, all four samples were not obtained from each animal. Neither the "0 sec of ischemia" metabolites nor those measured after 10 seconds of ischemia differed between untreated and trauma groups. This indicates a similar metabolic state in the control group and in the trauma groups 20 seconds after concussion impact. It also indicates a similar energy consumption during 10 seconds of ischemia.

Δ~P was calculated from animals in which paired data (0 sec of ischemia/10 sec of ischemia) were obtained. Since no difference was found between control and trauma groups (Table 1) the values are given as mean data in Table 2.

The results were compared to those of Nilsson, et al.18 (Table 3). In the latter series, measured after 10 seconds of ischemia differed between untreated and trauma groups. This indicates a similar metabolic state in the control group and in the trauma groups 20 seconds after concussion impact. It also indicates a similar energy consumption during 10 seconds of ischemia.

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in situ freezing of the frontoparietal cortex was performed with isopentane at -160°C after craniectomy. The period of ischemia, which was induced by decapitation, was identical to that of the present series (10 seconds). It can be seen that the control values for PCr and ATP were less optimal in the freeze-clamped tissue, while the lactate levels were lower. After 10 seconds of ischemia, there were marked decreases of PCr and ATP in the tissue of the freeze-clamped series as compared to that frozen in situ, while the increase of lactate was of the same order in both materials. The resulting ~P change during 10 seconds of ischemia was significantly higher in the freeze-clamped groups. This indicates an increased metabolic rate as a result of the trauma of sampling. However, as mentioned, there were no differences between animals without and animals with concussive impact acceleration.

**In Situ Freezing**

The metabolic state of brain tissue frozen in situ after ischemia elicited by heart standstill is shown in Table 4 together with the normal values reported previously. Although standardized, the period of ischemia cannot be exactly defined, but should be in the range of 10 to 15 seconds for the cortex and 20 to 25 seconds for the brain stem. In the cortex, the rate of energy depletion (PCr and ATP decrease) was similar in the "no trauma" and 7 m/sec injury groups, while it was increased in the 9 m/sec injury group. The rate of lactate formation was not significantly different in the "no trauma" and trauma groups. The calculated ~P values show an
Cerebral energy consumption in experimental head injury

increased metabolic rate during the acute concussion reaction, involving the brain stem in 7 m/sec concussion, and the brain stem and cortex in 9 m/sec concussion.

Discussion

The method of determining cerebral metabolic rate from the energy flux during the initial period of total ischemia is the only one that can be used in the present experimental situation, which involves a short-lasting, non-steady state change in functional activity. However, the method has its limitations. It was remarked by Lowry, et al., that the initial metabolic rate is maintained for 15 seconds at most in the mouse brain. Our results in rats have shown that ~P utilization is maximum in the first 5 seconds following decapitation, and that it gradually decreases with prolongation of the ischemia. The results indicate that 10 seconds may be too long a period to measure preischemic metabolic flux, even in control animals. If metabolic flux is increased, additional underestimation of ~P use rate is to be expected. Thus, the Δ~P values calculated in the present series cannot be used for quantitative determination of preischemic metabolic rate. However, since high metabolic rates should be systematically underestimated with the method, the results indicate that trauma is accompanied by an appreciable increase in metabolic rate. The possibility of shortening the period of ischemia to a few seconds is, for practical reasons, limited by difficulties in estimating the influence of a remaining tissue oxygen content, and to exactly time the onset of ischemia and freezing. The freeze-clamping method, which would seem ideal for exact timing of events, turned out to have its limitations.

The Δ~P results of the freeze-clamped series indicate an increased metabolic rate elicited by the compressing or cutting trauma of the sampling procedure. It also seems probable that the "0 sec of ischemia" values, showing lower concentrations of PCr and, to a lesser extent, of ATP, as compared to the normal values of in situ frozen tissue, in fact reflect the initial energy consumption during the 1 to 2 seconds required to freeze the tissue down to a depth of 1 mm.

In the second series, data were obtained only at the end of the ischemic period. Provided the corresponding control values can be assumed to be identical in all groups, the results show that the concussive response was accompanied by an increase of the cerebral metabolic rate, and that the increase was larger in animals with acceleration impact at 9 m/sec. The Δ~P calculations were based upon the control values reported previously. In that series, there were changes in energy state after the 9 m/sec impact, and, to some degree, also after the 7 m/sec impact, when the tissue was frozen 1 minute after the trauma. It may be argued that similar changes might already have occurred 20 seconds after the trauma. However, the following facts indicate that this potential source of error does not invalidate the conclusions drawn. First, there were no differences in lactate concentrations between the groups at the end of the period of ischemia. Since ischemia is associated with maximum stimulation of glycolytic rate, this finding indicates that there were similar lactate concentrations at zero time, namely, at the onset of ischemia. Second, in the freeze-clamped material, the "0 sec of ischemia" values for all metabolites were similar in the "no trauma" and trauma groups. Third, if it is assumed that the degree of energy derangement (PCr and ATP depletion) observed 60 to 90 sec after trauma has already occurred at 20 seconds, the increases in calculated ~P utilization following trauma are still found.

The finding of an increase in energy consumption during the concussive response is in agreement with the theory of Walker, et al., implying that traumatic neuronal excitation analogous to epileptic discharge is the primary mechanism in concussion. Electroencephalographic (EEG) changes similar to those described by Walker, et al., have been reported by others, but most authors report EEG extinction and slowing. The present findings show not only an increase of the metabolic rate at the moment of a trauma (freeze-clamping technique), in agreement with Nelson, et al., but also a sustained increase, lasting at least to 20 seconds after the concussive impact acceleration, possibly indicating an activation of "reverberating circuits."

The symptoms of such sustained abnormal activity probably depend upon the region primarily involved, the intensity and exten-
sion of the stimulus, and the functional and structural state of the neuronal chains. The present concussion model, like most experimental models, predominantly involves the brain stem. Also the general biomechanics of blunt head injury indicate that the final common path of cerebral concussive trauma (causing unconsciousness) is in shear stress along the brain-stem axis. Clinical and metabolic data of the present model showed a graded concussive response with a more intense and prolonged reaction in 9 m/sec than in 7 m/sec concussion. We also found evidence of abolition of the reaction with more severe trauma. Thus, with an impact velocity of 11 m/sec, which caused gross brain-stem lesions, there were no signs of the sympathetic discharge consistently observed with 7 to 9 m/sec trauma. The basic neuronal reaction to trauma described may well occur in other regions and produce other types of symptoms. Whether such symptoms should be termed cerebral concussion in a clinical sense may be questioned, although the Committee of the Congress of Neurological Surgeons defined concussion in such general terms.

The mechanically induced neuronal depolarization can be mediated by a transmitter release, but can also be a direct membrane phenomenon. Blair and Julian and Goldman found a depolarizing effect of mechanical stimulation of the frog sciatic nerve and the lobster giant axon. Krems, et al. elicited repetitive firing in the frog sciatic nerve with blast injury. It is reasonable to assume similar effects in the brain, and thus to consider that the initiation of concussion represents a basic mode of reaction of excitable membranes to mechanical stimuli.

Conclusions

The immediate concussive response is explained by an abnormal neurophysiological activity, implying a high energy consumption. Direct involvement of membrane and transmitter function, independent of the overall energy state of the tissue, is probably the prime event. Whether energy failure develops depends mainly upon the energy production, namely, substrate and oxygen availability. Thus, adequate CBF and arterial oxygen content can prevent energy depletion. In the absence of circulatory adjustments and in hypoxia, energy failure develops and a more prolonged state of cerebral dysfunction (prolonged post-traumatic coma) ensues. In concussion both the immediate excitation and the energy depletion may attain various degrees of severity and extend over various regions. The wide range of clinical symptoms that appears may be explained on this functional basis.

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Cerebral energy consumption in experimental head injury


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