J Neurol (1983) 230:259–266

Journal of
Neurology

Intracranial pressure during prolonged experimental convulsions in cats

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Summary. Experiments were carried out in cats to examine the relationship between prolonged convulsions and intracranial pressure. The convulsions were induced by pentylenetetrazole or bicuculline. Blood pressure, intracranial pressure and electroencephalogram were continuously monitored. Generalized tonic-clonic convulsions appeared with typical changes in the electroencephalogram 7–35 s after administration of the epileptogenic drugs. These convulsions persisted for 1–2 h. Concomitant with the clinical convulsions, intracranial pressure increased three- to fivefold, reaching maximal pressures of 20–94 mm Hg after 20–420 s. The intracranial pressure remained high for between 47 s and 10 min, then began to fall gradually, reaching preictal levels after 2–30 min despite the continuation of convulsions. The variations in intracranial pressure were found to be independent of changes in blood pressure. The intracranial pressure, after dropping to preictal values, remained unchanged for up to 6 h after the induction of convulsions.

Key words: Convulsions, experimental - Intracranial pressure - Pentylenetetrazole - Bicuculline

Zusammenfassung. An der Katze wurden Versuche durchgeführt, die den Zusammenhang zwischen langdauernden Krämpfen und intrakraniellem Druck klären sollten. Die Anfälle wurden durch Pentylentetrazol oder Bicucullin erzeugt. Blutdruck, intrakranieller Druck und Elektroencephalogramm wurden fortlaufend registriert. Tonisch-klonische Krampfanfälle zugleich mit typischer Veränderung des Elektroencephalogrammes traten 7 bis 35 s nach der Applikation der epileptogenen Substanz auf. Diese Krämpfe dauerten ein bis zwei h. Zugleich mit den klinischen Anfällen nahm der

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intrakranielle Druck um das drei- bis fünffache zu, um einen Maximaldruck von 20 bis 94 mm Hg nach 20 bis 420 s zu erreichen. Der intrakranielle Druck blieb während 47 s bis 10 min hoch und begann dann allmählich zu fallen, wobei er nach 2 bis 30 min den Wert vor Beginn der Anfälle erreichte, selbst wenn die Anfälle weiterhin andauerten. Die Modifikationen des intrakraniellen Druckes waren unabhängig von den Blutdruckveränderungen. Nachdem der intrakranielle Druck zu den präiktalen Werten wieder zurückgekehrt war, blieb er bis zu sechs h nach Einleiten der Anfälle unverändert.

Introduction

Intracranial pressure (ICP) is dependent on the volume of the three major components of the cranial cavity: vascular bed, CSF compartment and volume of brain tissue. An increase in the volume of one of these components will entail an increase in ICP unless a compensatory reduction occurs in the volume of the other components.

Generalized convulsions are accompanied by a marked increase in the energy metabolism of neuronal cells [2]. Cerebral blood flow (CBF) and therefore substrate supply are maintained adequate for energy demand by changes in cerebral vascular resistance (CVR) [6, 9]. Extensive research, both experimental and clinical, has been directed at attempts to elucidate the autoregulatory mechanisms that ensure adaptation of CBF to local metabolic demand [4, 5, 12]. In sharp contrast, there has been little experimental work to examine the relationship between convulsions and ICP [3, 6].

In the present study changes in ICP during experimental convulsions were examined in an attempt to define more clearly the relationship between convulsions and ICP.

Materials and methods

The experiments were conducted in 27 adult cats weighing 2.2–3.7 kg. The cats were first anaesthetized with an intraperitoneal injection of ketamine (20 mg/kg). A catheter was inserted into the femoral vein for infusion of normal saline and drug administration. A femoral artery catheter was introduced to monitor blood pressure (BP) and for blood sampling for blood gas and acid-base balance analysis. Through a burr hole drilled in the mid-parietal region 3–5 mm lateral to the superior sagittal suture, a catheter was introduced into the subdural space for monitoring of ICP. The burr hole was then sealed with dental cement. The bipolar electroencephalogram (EEG) was recorded from two screws drilled in the frontal region, 5–10 mm on either side of the midline. The cats were then anaesthetized with intravenous α-chloralose 50 mg/kg and oro-tracheally intubated. The cats remained intubated and were artificially ventilated with a Harvard Respirator (Harvard Apparatus Co. Inc. Millis, Mass.), at 10–15 breaths/min and a tidal volume of 100–150 ml as necessary to maintain normocarbia throughout the experiment. BP, ICP and EEG were continuously recorded on a Grass Polygraph (Grass Instrument Company, Quincy, Mass.). All lines were tightly secured and since the cats were not paralyzed, they were lightly restrained to prevent dislodgement of catheters during convulsions. BP and ICP were allowed to stabilize. After these parameters had remained unchanged for at least 10 min, convulsions were induced by rapid intravenous injection of 75–100 mg/kg pentylenetetrazole (PTZ) in 19 experiments and 1.2 mg/kg bicuculline

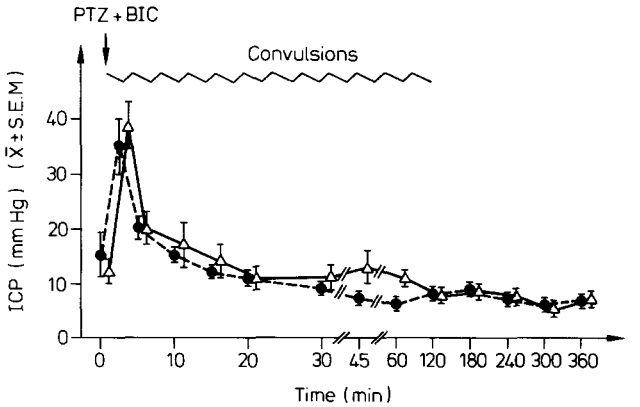

Fig. 1. Intracranial pressure (ICP) during 6 h following induction of convulsions by pentylenetetrazole (PTZ) and bicuculline (BIC), PTZ △——△; BIC ●- - -●

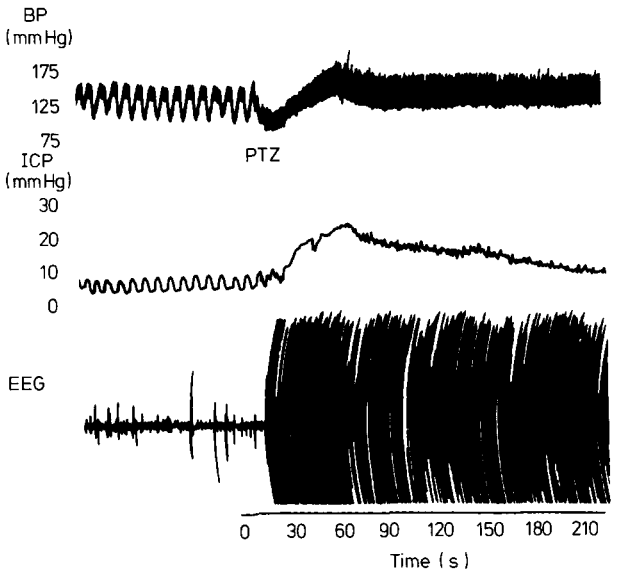

Fig. 2. Changes in blood pressure (BP), ICP and EEG in convulsions induced by PTZ

(BIC) in 8 experiments. The cats were followed for up to 6 h. Throughout this period, normothermia was maintained by a heating lamp and acidosis corrected by intravenous injection of sodium bicarbonate, as necessary.

Results

The results of the experiments may be divided into two groups according to the epileptogenic drug administered (Fig.1).

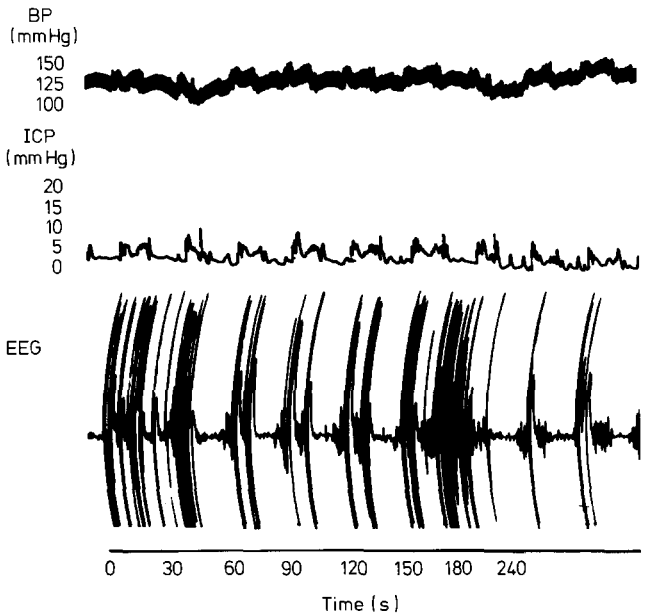

Fig. 3. BP, ICP and EEG following the acute stage of convulsions. BP and ICP are at preictal pressures. The EEG demonstrating recurrent spikes with 5- to 10-s periods of burst suppression

A. Convulsions were induced by PTZ in 19 cats. An example of BP, ICP and EEG recording in these experiments, during the first 3 min, is shown in Fig. 2; 7–35 s (15 ± 2 s; mean $\pm$ SEM) after injection, generalized tonic-clonic convulsions appeared with mass spikes in the bipolar EEG tracing. These lasted 5–10 min and were then replaced by recurrent, 1- to 2-s clonic jerks and short periods of tonic convulsions followed by 5- to 10-s periods of burst suppression on the EEG (Fig. 3). Convulsions continued for up to 2 h. The cats did not regain consciousness throughout the experiment. Immediately after injection of PTZ, BP dropped significantly from the control level, 148 ± 8 mm Hg, reaching minimal pressure of 110 ± 6 mm Hg after 15 ± 3 s. BP stabilized after 37 ± 8 s at 153 ± 9 mm Hg without significant change for the remainder of the experiment. Concomitant with convulsions, ICP rose rapidly to reach maximal pressures of 20–94 mm Hg (mean 39 ± 4 mm Hg) after 111 ± 22 s. ICP remained at 34 ± 4 mm Hg for 160 ± 30 s and then began to gradually fall reaching the preictal pressure after 12 ± 2 min. The ICP did not change significantly during up to 6 h of continued measurement.

B. In 8 cats convulsions were induced by BIC (example shown in Fig. 4). Patterns of convulsions, similar to those seen after administration of PTZ, appeared after 14 ± 4 s. In these cats BP increased significantly from control levels of 152 ± 12 mm Hg, to reach maximal pressures of 199 ± 14 mm Hg after 21 ± 3 s. BP stabilized at 139 ± 10 mm Hg after 73 ± 17 s. It then remained essentially unchanged for the duration of the experiment. Simultaneous with the appearance of clinical convulsions, ICP rose to reach pressures of 21–56 mm Hg (mean 35 ± 5 mm Hg) after 70 ± 1 s. ICP remained at 25 ± 2 mm Hg for 182 ± 33 s and

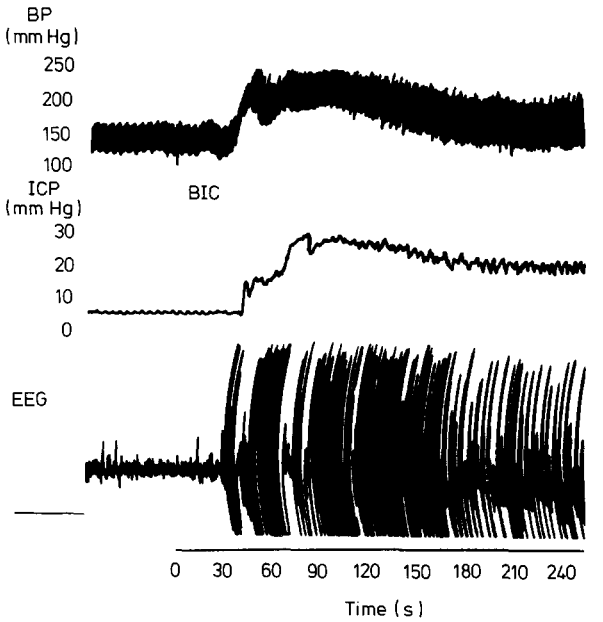

Fig. 4. Changes in BP, ICP and EEG in convulsions induced by BIC

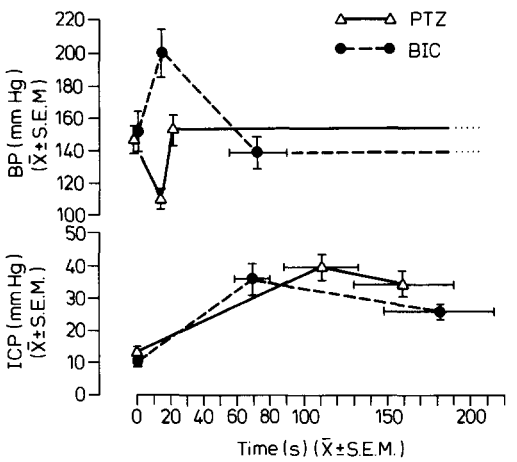

Fig. 5. Changes in BP and ICP during the initial 220 s after induction of convulsions by PTZ or BIC

then fell gradually to control levels after 15 ± 4 min. Thereafter, ICP remained essentially unchanged for the remainder of the experiment.

The PTZ experiments differed significantly from the BIC experiments only in the acute change of BP after administration of the epileptogenic drug with a sharp fall of BP after administration of PTZ and a marked rise after injection of BIC. Student *t*-test analysis demonstrated a significant ($P<0.001$) difference between the mean maximal BP occurring after injection of PTZ and mean maximal BP after BIC.

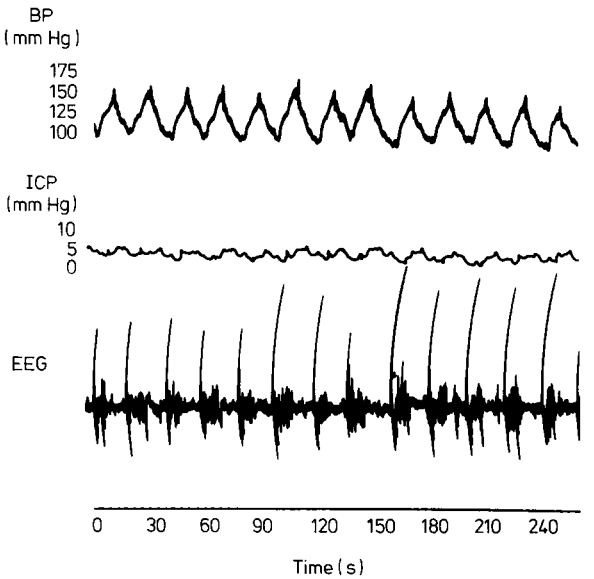

Fig. 6. BP, ICP and EEG following the initial stage of convulsions. BP has returned to control pressure but shows marked changes during respiration. The ICP shows only minor variations with respiration.

Paired *t*-test analysis revealed significant differences between control ICP and both maximal ICP and ICP after 5 min ($P<0.001$) for both the PTZ and BIC experiments. ICP at 10 min was not significantly different from preictal ICP. Maximal ICP was independent in both time and magnitude from the acute changes in BP after injection of the epileptogenic drug, showing no correlation (Wilcoxon) with either the time of maximal rise after injection of BIC or fall after injection of PTZ in BP (Fig. 5). The time until ICP returned to the control level was not correlated with the time from administration of the epileptogenic drug to the time of appearance of clinical convulsions, the time of maximal ICP, time to maximal change in BP, nor the time of stabilization of BP.

Throughout the experiment there were minor fluctuations in ICP, which varied with systolic and diastolic BP and respirations. After stabilization of BP and ICP following the acute changes described, significant changes in BP during respiration were noted in some cats. The ICP, however, showed only minor changes in amplitude, at the same time demonstrating intact autoregulatory function (Fig. 6). Control PO_2 was 71 ± 4 mm Hg and PCO_2 37 ± 2 mm Hg for the combined groups of experiments. During the first 2-10 min of the experiments (time of tonic-clonic convulsions and maximal changes in ICP) PO_2 varied between 51 and 94 mm Hg. Thereafter, PO_2 remained at control levels throughout the experiment. By constant monitoring and changes in ventilator setting PCO_2 was maintained between 34 and 46 mm Hg. Paired *t*-test and Wilcoxon correlation analysis did not reveal a significant correlation between changes in PO_2 or PCO_2 and the changes observed in ICP.

Surviving cats were followed for up to 6 h with continuous monitoring of BP, ICP and EEG (Fig. 1). The ICP remained essentially unchanged throughout this period.

Discussion

The metabolic demand of neuronal tissue is greatly increased during convulsions. Adaptation of CBF to metabolic demand may cause an increase in blood volume in the cranial cavity, with a resultant rise in ICP. In our experiments a three- to fivefold increase in ICP was noted simultaneously with the onset of convulsions. This marked rise in ICP was not significantly different in experiments in which PTZ-induced convulsions were accompanied by a significant acute drop in BP and in experiments in which the epileptogenic drug was BIC, which was followed by a significant rise in BP. Furthermore, the time sequence of changes in ICP was independent of changes in BP. A close similarity between changes in ICP in our experiments and changes in CBF reported in similar models of experimentally induced convulsions [9], might suggest that the increase in ICP noted was dependent on changes in CBF. The cats in our experiments demonstrated intact autoregulatory mechanisms throughout the experiment and the changes in ICP were independent of marked changes in BP. We would, therefore, assume that autoregulatory mechanisms functioned to change CVR during the early stage of the experiments allowing CBF to increase in accordance with metabolic demand independent of changes in cerebral perfusion pressure (CPP) incurred by variations in BP. These mechanisms function, in the intact brain, as long as adequate CPP is maintained and the limits of changes in CVR have not been reached.

Impaired venous return as a mechanical consequence of convulsions, as a cause of the acute rise in ICP at the onset of convulsions, can not be completely ruled out, since the cats in the experiments were nor paralyzed. Continuous mechanical ventilation would, however, prevent increased intrathoracic pressure and obstruction to venous outflow. Furthermore, a marked rise and fall in ICP, concomitant with respiration, should have been evident. This did not occur in our experiments.

The return of ICP to preictal levels within 2–30 min, despite continued convulsions, might result from a reduction in CBF, an increase in venous outflow from the cranial cavity or a shift of CSF to the spinal compartment. It has often been reported [1, 7, 8, 10, 11] that prolonged convulsions cause ischaemic brain damage. Controversy still exists as to whether these ischaemic changes are caused by the excessive neuronal discharge itself or by gross energy failure. Our experimental data would support the postulate that after the acute stage of convulsions, autoregulatory mechanisms functioned to reduce CBF. This uncoupling between metabolic demand and substrate supply would deplete neuronal cells and cause ischaemia. In the experimental animals, failure to regain consciousness and widely dilated pupils would indicate that severe brain damage had occurred. Our results, therefore, support the theory that neurological damage in convulsions is caused by depletion of substrate and energy failure.

In summary, although CBF was not directly measured in our experiments, it is suggested that the changes in ICP observed may best be explained by changes in intracranial blood volume due to variations in CBF. After the acute stage of convulsions, autoregulatory mechanisms function to restore CBF to preictal levels with resultant uncoupling between metabolic demand and substrate supply. This might cause ischaemic brain damage if increased neuronal activity persists in prolonged convulsions.

Further research is required to elucidate the pathophysiological processes involved in prolonged convulsions. It is hoped that our experimental results will encourage research to define further the relationship between ICP and prolonged convulsions in the intact and diseased brain.

Acknowledgements. The authors would like to thank R. Goitein and H. Sohmer for their constant advice and constructive criticism and V. Morgenstern for his help in the complex statistical analysis of the data. This research was supported by the Joint Research Fund of the Hebrew University and Hadassah and the Boris Corsy and Athanese Ebling Medical Research Fund.

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Received June 7, 1983