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Research report

Cortical spreading depression recorded from the human brain using a multiparametric monitoring system

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Abstract

The number of parameters (i.e., EEG or ICP-intracranial pressure) routinely monitored under clinical situations is limited. The brain function analyzer described in this paper enables simultaneous, continuous on-line monitoring of cerebral blood flow (CBF) and volume (CBV), intramitochondrial NADH redox state, extracellular K^+ concentrations, DC potential, electrocorticography and ICP from the cerebral cortex. Brain function of 14 patients with severe head injury (GCS $\leq$ 8), who were hospitalized in the neurosurgical or general intensive care unit was monitored using this analyzer. Leao cortical spreading depression (SD) has been reported in many experimental animals but not in the human cerebral cortex. In one of the patients monitored, spreading depression was observed. This is the first time that spontaneous repetitive cortical SD cycles have been recorded from the cerebral cortex of a patient suffering from severe head injury. Typical SD cycles appeared 4–5 h after the beginning of monitoring this patient. During the first 3–4 cycles the responses of this patient were very similar to the responses to SD recorded in normoxic experimental animals. Electrocorticography was depressed whereas extracellular K^+ levels increased. The metabolic response to spreading depression was characterized by oxidation of intramitochondrial NADH concomitant to a large increase in CBF. During brain death, an ischemic depolarization, characterized by decrease in CBF and an irreversible increase in extracellular K^+, was recorded.

Keywords: Human brain monitoring; Cerebral blood flow; Extracellular K^+; NADH redox state; Cortical spreading depression; Intracranial pressure; Multiparametric monitoring; Head trauma

1. Introduction

Leao first discovered cortical spreading depression (SD) of the EEG in the rabbit brain 50 years ago [16]. Since then, this event has been identified and described in various animals including primates [2]. The depolarization caused by the electrical stimulation used by Leao to induce SD was characterized by EEG depression [2], pial vasodilation [15] and a slow negative potential shift [17]. Only one study in human stereotactic neurosurgery reported SD in the caudate nucleus or the hippocampus following KCl injection [36]. No direct evidence exists for spontaneous or elicited SD in the human cerebral cortex in vitro or in vivo [1,3,14,28,30,35].

During the past 20 years we have developed and applied a multiparametric monitoring system for studying the brain of various experimental animals. This technique has been modified and adapted for monitoring the human brain following severe head injury [7,19]. One aim of the present report is to demonstrate the feasibility of using this multiparametric monitoring system under clinical situations.

Cortical spreading depression has been implicated in various pathophysiological events including ischemia or stroke [6,34], seizures [18], migraine [29,30] and brain injury [29,31]. SD waves cause transient changes in hemodynamic, metabolic, ionic and electrical activities [11,13,14,23,27,33,38] and thus it is preferable to monitor all these parameters simultaneously. A second aim of this study is to present results indicating, for the first time, that cortical spreading depression occurs also in the human brain.

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2. Materials and methods

The multiparametric assembly (MPA) enables the simultaneous, continuous on-line measurement of relative cerebral blood flow (CBF) and volume (CBV) [9]; intramitochondrial NADH redox state [20,21]; extracellular K^+ concentrations [4]; spontaneous electrocorticography (ECoG); DC steady potential and intracranial pressure (ICP) [5]. The principles of the various sensors and parameters included in the MPA have been described in previous publications [4,7,19,22,23]. Therefore, only a short description of the principles of the various parameters measured by the MPA is presented (Fig. 1).

2.1. Laser Doppler flowmetry

During the past few years, laser Doppler flowmetry (LDF) has been calibrated against the H_2 clearance probe or against [^{14}C]iodoantipyrine autoradiography which are both well established methods for quantitative monitoring of CBF. LDF apparently measures relative changes demonstrating a significant correlation to the relative changes in CBF measured by the two other approaches (for review, see Ref. [39]). The principle of laser Doppler flowmetry is to utilize the Doppler shift (frequency change)

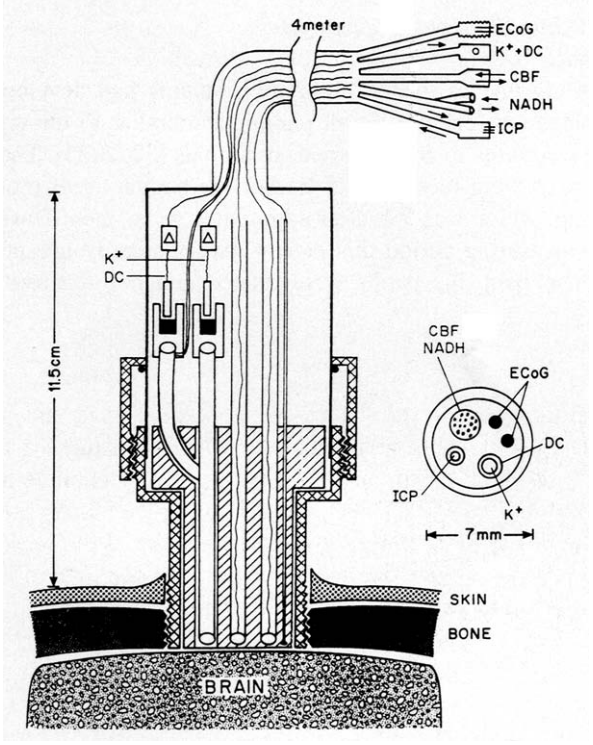

Fig. 1. The multiprobe assembly (MPA) used for monitoring the brain of head-injured patients. The MPA is connected to the brain via a special holder screwed into the skull. ICP, intracranial pressure probe; CBF, NADH, fiber optic light guide probe to measure local cerebral blood flow (CBF) and mitochondrial redox state (NADH); K^+, DC, extracellular K^+ mini surface-electrode surrounded by a DC steady potential monitoring space; ECoG, bipolar electrocortical electrodes.

that light undergoes when reflected by moving red blood cells. A beam of low power laser light is transmitted to the brain by an optical fiber. After multiple scattering of the light, two other optical fibers pick up the reflected light which enters the photodetector. The run signal is analyzed by a complicated algorithm developed by the manufacturer and the results are presented as percent of a full scale (0–100%), providing relative blood flow values. The change in the total back-scattered light is an indirect indicator for the blood volume in the tested tissue volume. The calibration of the CBV is more complicated as compared to the CBF due to the construction of the laser Doppler flowmeter by the manufacturer.

2.2. NADH surface fluorometry

The principle of NADH monitoring from the surface of the brain is that excitation light (366 nm) is passed from the fluorometer to the brain via a bundle of quartz optical fibers. The emitted light (450 nm), together with the reflected light at the excitation wavelength, is transferred to the fluorometer via another bundle of fibers. The changes in the reflected light are correlated to changes in tissue blood volume and also serve to correct for hemodynamic artifacts appearing in the NADH measurement [20,21]. The changes in the fluorescence and reflectance signals are calculated relative to the calibrated signals under normoxic conditions. This type of calibration is not absolute, but provides reliable and reproducible results from different animals and between different laboratories. Details on this technique have been published by our group [20,21].

2.3. Extracellular K^+ levels

In order to monitor extracellular K^+ concentrations, specially designed mini-electrodes manufactured by WPI (Sarasota, Florida, USA) were used. A flexible PVC tube (1.2 mm diameter) was sealed at one end with a K^+ sensitive membrane. The tube was filled with the appropriate solution and connected to an electrode holder (WPI) with a salt bridge connecting between the membrane and the Ag/AgCl pellet located inside the electrode holder. The interface between the PVC tubing and the holder was glued using 5 min Epoxy. The selectivity coefficients ($-\log$) of the K^+ electrode is 4.0 for Na^+, 3.9 for Ca^{2+} and 3.0 for Mg^{2+}. The impedance of new K^+ electrode is in the range of 10^9–10^{10} Ω. The DC potential was measured concentrically around the potassium electrode. An Ag/AgCl electrode connected via a saline bridge under the skin of the patient's head was used as a reference electrode.

2.4. Construction of the multiprobe assembly

The solution used for the sensor holder (Fig. 1) was basically a modification of the Lucite cannula described by

Crowe et al. [4] for the light guide and the potassium-sensitive electrode. The hole accommodating the K^+ electrode was divergent at the top to facilitate handling and sealing of the probes [7]. An additional hole was drilled obliquely from the upper surface to merge with the K^+ electrode channel at approximately middistance to the lower surface. This hole was used to accommodate a polyethylene tubing for recording the local DC potential concentrically to the K^+ electrode.

The long and rigid steel stem of the light guide used in this study occupies a straight vertical hole in the cannula and serves as an axis to hold the cannula and the cable holder at a convenient distance from each other. Spontaneous electrical activity (ECoG) was measured by two polished platinum rods inserted into the multiprobe assembly holder. Parenchymal ICP monitoring was performed using a fiber optic ICP probe (Camino Lab., USA) which was inserted into the MPA so as to have the same contact area with the brain surface as the other probes. The values measured by the optical probe correlated well to the standard ICP monitoring device [5]. The complete assembly was protected and shielded by an aluminum sleeve sliding over the cable holder. For stronger construction, the sleeve was permanently screwed into the cannula and cable holder. The MPA was prepared for clinical use by gas sterilization which was found to be harmless to all the sensors.

2.5. Patient preparation

Informed consent was obtained from 14 patients in accordance with institutional review board procedures (Tel Aviv Medical Center).

The patients monitored by this multiparametric assembly were hospitalized due to a comatose state induced by severe head injury (GCS $\leq$ 8). Preparation of the patient for brain monitoring was performed in the neurosurgical operating theater under general anesthesia. The patients were prepared for monitoring as follows.

1. A 15 mm diameter hole was carefully drilled in the frontal bone area selected according to the CT scan. The hole was drilled in a 'normal' looking section of the brain.
2. After cleaning the exposed area of bone residues, the dura mater was cut to enable direct contact between the MPA probes and the brain.
3. The MPA holder was screwed into the skull to a predetermined depth to avoid any undue pressure on the brain.
4. The operated area was closed by suturing the skin around the MPA holder (covered until the beginning of the monitoring).
5. The patient was transferred to the intensive care unit (either general or neurosurgical) and after stabilization and connection to the routine patient monitoring system the sterilized MPA was introduced into the holder (for contact with the brain) and fastened to it in order to ensure measurements for up to 48 h (sometimes even longer). The average monitoring time in the 14 patients was 40 h. Three out of the 14 have died during the monitoring period due to the severity of the trauma upon admission. The other 11 recovered and were discharged from the hospital.

3. Results

In this study, the brain function of 14 patients suffering from severe head injury was monitored using a multiparametric analyzer. Due to the circumstances of the traumas, it was not possible to measure all the parameters in all patients. In general, it was possible to monitor ECoG, ICP and CBF in most patients. NADH fluorescence was less easily measured, and the most problematic parameter was the extracellular K^+ concentration. This was probably due to the fact that the K^+ electrode is a high impedance electrode, which is very sensitive to ground noise.

The typical response of most patients to treatments aimed at reducing the intracranial pressure (ICP), such as mannitol infusion and hyperventilation, was a measurable decrease in ICP and a resultant increase in CBF and oxidation of NADH (Fig. 2).

3.1. Spreading depression cycles

Only one of the 14 monitored patients had developed spontaneous changes in all parameters similar to the typical responses to SD recorded in animals [22,23,25]. These changes were recorded 4.5 h after the beginning of monitoring, which was 7 h after admittance to hospital. During the measuring period this patient was bilaterally irresponsive to pain, his pupils were dilated and non-reactive to

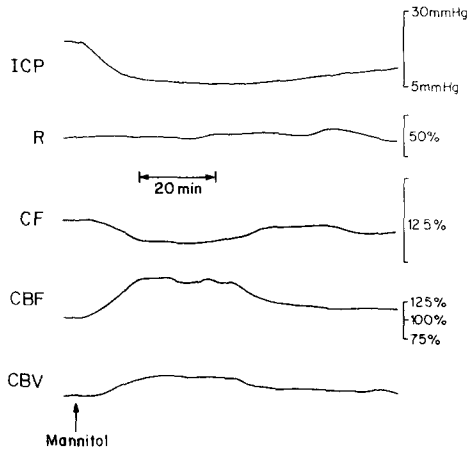

Fig. 2. Metabolic and hemodynamic responses of a severe head injured patient to an i.v. infusion of mannitol. ICP, intracranial pressure; R, CF, 366 nm reflectance and 450 nm corrected NADH fluorescence; CBF, CBV, cerebral blood flow (CBF) and volume (CBV).

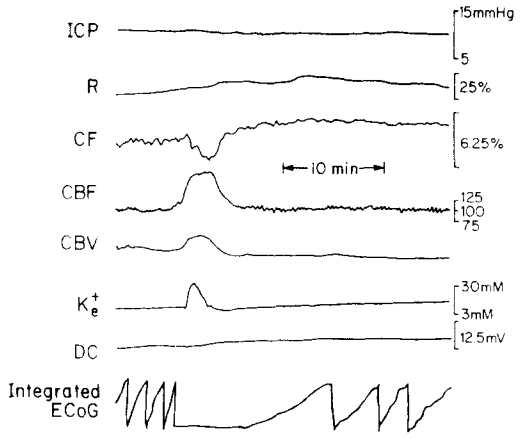

Fig. 3. Spontaneously developed cortical spreading depression cycle in a head injured patient. ICP, intracranial pressure measured by the parenchymal probe; R, CF, 366 nm reflectance and 450 nm corrected NADH fluorescence; CBF, CBV, cerebral blood flow (CBF) and volume (CBV); K_e^+, DC, extracellular potassium and DC steady potential; Integrated ECoG, amplitude-integrated electrocortical activity.

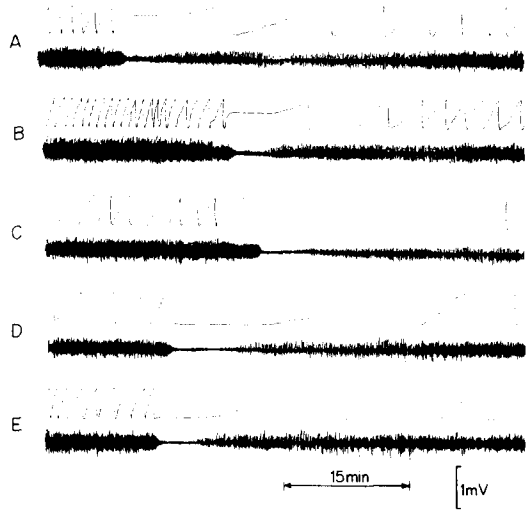

Fig. 4. Raw analog and integrated ECoG signals monitored during five spreading depression cycles. Records A–E were taken 4.4, 6.6, 7.6, 9.4 and 13.5 h after the beginning of the monitoring. During the initial phase of part A, a suction procedure was used in the patient while the other four SD cycles occurred spontaneously.

light (6 mm), he was mechanically ventilated and his brain CT scan showed evidence of severe brain edema in the left hemisphere and right parietal hemorrhagic contusion. The measurements were taken from the right frontal lobe. As seen in Fig. 3, the ECoG became depressed for 10–15 min and, at the same time, a cycle of elevated extracellular K^+ and a small negative shift (in this cycle) in the DC potential were recorded. These three changes are typical of transient depolarization, which is a dominant part of spreading depression. Hemodynamic and metabolic compensation for the depolarization was observed in the other parameters. An oxidation cycle was observed in the NADH redox state (decreased CF), while blood flow and volume increased. The calibration of the CBV trace shown in Fig. 2 and Fig. 3 is missing due to an error recorded during this interval of time.

This patient exhibited repetitive SD cycles every 20–30 min, although at various times during the monitoring period, SD cycles were recorded at shorter or longer intervals. Five fragments of 1 h analog and integrated ECoG recordings are presented in Fig. 4. It can be seen that the deep depression lasted between 5 and 10 min while complete recovery was not achieved even after 30–45 min. In part E of the figure, which corresponds to the SD cycle shown in Fig. 3, the ECoG demonstrated very slow recovery as compared to the other parameters. The DC potential negative shifts of those 5 depolarization cycles were 4 ± 0.35 mV (S.E.M.). The first five cycles recorded in this patient were very similar, i.e., NADH was oxidized while blood flow increased significantly (as in Fig. 3). However, in all the other cycles recorded later in the same patient (starting 4.5 h after the SD cycle shown in Fig. 3), the metabolic and hemodynamic responses were different (Fig. 5) from the initial cycles. The leakage of potassium and negativation of the DC potential were very similar in all SD cycles, whereas the NADH oxidation cycle was replaced by a biphasic cycle comprised mainly of a phase of increased NADH followed by a small oxidation phase. The compensation of blood flow and volume was also reversed at this time. The monophasic increase in CBF and CBV (Fig. 3) was replaced by an initial decrease followed by a smaller increase in flow and volume.

Significant correlations were found between the amplitude of the changes in the monitored parameters shown in Fig. 5 – NADH and CBF: $P < 0.05$ ($r = 0.903$, df = 4). NADH and K^+: $P < 0.001$ ($r = 0.994$, df = 4). CBF and K^+: $P < 0.01$ ($r = 0.940$, df = 4).

Fig. 6 shows eight consecutive SD cycles recorded from the same patient. Downward deflections in the DC potential represents a negative shift and the average value calculated is 5.3 ± 0.3 mV (S.E.M). The comparable values in gerbils were 10 mV [24] and in rats 14–16 mV (Sonn and Mayevsky, in preparation) using the same monitoring approach.

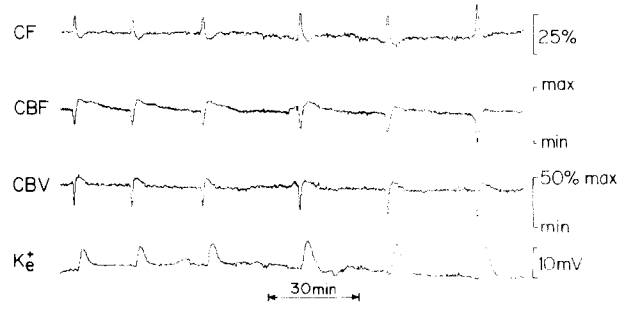

Fig. 5. Repetitive spreading depression cycles monitored in a head injured patient 29.5 h after the beginning of monitoring. CF, 450 nm corrected NADH fluorescence; CBF, CBV, cerebral blood flow and volume; K_e^+, extracellular potassium.

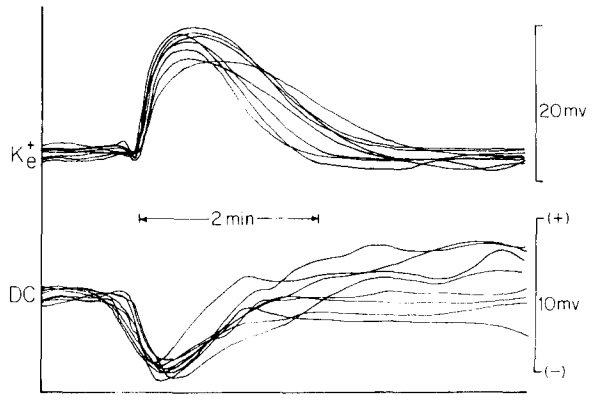

Fig. 6. Responses of extracellular K^+ (K_e^+) and DC steady potential to eight repetitive SD cycles. The absolute values of K_e^+ were estimated to be 3–4 mM, but due to measurements artifacts occurring periodically, absolute values are missing.

The patient who developed SD cycles (presented in Fig. 3 and Fig. 5) showed signs of brain deterioration leading to brain death. The tracing presented in Fig. 7 demonstrates that metabolic and ionic changes preceded brain death by several hours. The ECoG became isoelectric 3 h prior to the beginning of the recording in Fig. 7 (68 h from beginning of monitoring). A gradual increase in ICP up to the level of 100 mmHg was measured, followed by a sharp decrease in cerebral blood flow (CBF) and volume (CBV) (Fig. 7A). During the terminal ischemic phase a large increase in the extracellular K^+ level was recorded. Part B is a continuation of Part A after a 54 min interval due to a technical problem in the computer recording.

4. Discussion

Monitoring of the human brain exposed to clinical pathophysiological conditions has long presented a challenge. However, the lack of appropriate measuring techniques has so far prevented progress in this field. Attempts have been made to monitor the human brain in the operating room as well as in the intensive care unit. For example, the standard technique of intraoperative EEG monitoring has been applied to patients exposed to surgical excision of their epileptogenic focus [8]. Spreading depression of the cerebral cortex was never recorded. Sramka et al. [36], using DC steady potential together with EEG recording, were able to elicit and record SD in the caudate nucleus and hippocampus. Somjen et al. [35] stated that "The electrical signs of SD have never been actually demonstrated in any condition of intact human brain", but they were able to do so in hippocampal tissue slices.

CBF has been monitored in the operating room (O.R.) using laser Doppler flowmetry [32]. Other groups have applied spectrophotometric techniques to the monitoring of mitochondrial redox state in the neurosurgical O.R. [12]. Nevertheless, until now a standard practical approach for monitoring the brain in the O.R. or in the intensive care unit has not been adopted. Even in less severe neurological disorders such as stroke, the need exists for a reliable monitoring technique. Wiebers et al. [40] made the following very lucid statement on the issue of human brain monitoring:

"Ultimately, however, the answers to many of our questions regarding the underlying pathophysiology and treatment of stroke do not lie with continued attempts to model the human situation perfectly in animals, but rather with development of techniques to enable the study of more basic metabolism, pathophysiology and anatomical imaging detail in living humans."

The results presented in this study suggest that the human brain can be monitored under various pathophysiological conditions. The development and implementation of the surface probes organized in the multiprobe assembly (MPA) for animal studies [4,7,21], has made it relatively simple to adapt this assembly to clinical situations. Indeed, in a preliminary study [22] we demonstrated a correlation between CBF and NADH redox state measured under partial ischemia induced in the human brain during neurosurgical procedures.

The recording of spreading depression in the human cerebral cortex in one of the patients, which was found to be qualitatively similar to that observed in rats, gerbils or cats [22,25,33], suggests that the basic mechanisms of pathophysiological processes may be similar in the animal

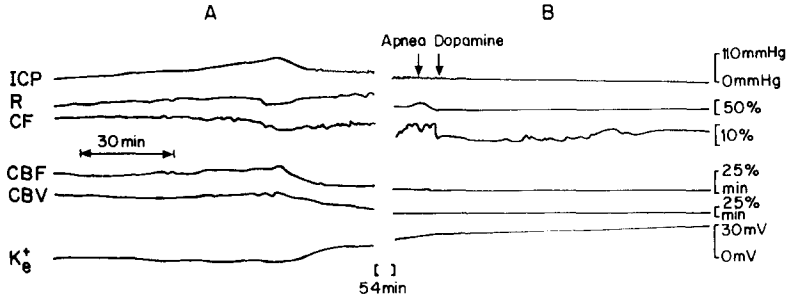

Fig. 7. Multiparametric recording of a patient 5 h before brain death. All abbreviations are as in Fig. 3 and Fig. 5. The absolute values of extracellular K^+ were calculated by the final calibration of the electrode done after its removal from the brain.

and human brain. It is well documented that during the SD wave, which is basically the propagation of depolarization through the entire hemisphere, there is a concomitant large increase in O_2 consumption due to stimulation of the ion pumps (for review, see Ref. [25]). A large increase in CBF (measured by various techniques) compensates for this increased O_2 demand [10,14,37]. When SD is induced in animals under normal conditions, complete coupling occurs between the increased O_2 consumption and the increase in CBF. If the O_2 supply is limited (ischemia, hypoxia), the responses of the brain to SD are different. We have found that under various pathophysiological conditions NADH demonstrates a cycle of reduction (increased NADH) instead of the typical normal oxidation cycle (decreased NADH) [26]. The combined measurement of NADH and CBF used in the present study indicated that the reversed NADH response (an increase instead of a decrease) was due to the limited compensation of CBF as indicated by its initial decrease (Fig. 5).

The results presented in this report demonstrate that cortical spreading depression can develop in the human brain. We suspect that with this patient, one of the suction procedures (used to clear the airway system) was the stimulus for initiating the first SD wave. We do not know what caused the repetitive SD waves. The fact that the nature of the hemodynamic and metabolic responses changed in this patient as a function of time may be due to the deterioration of CBF autoregulation in the head-injured patient. Indeed, Oka et al. [29] claim that in head-injured patients, a unique traumatic spreading depression syndrome could be identified, although they were unable to correlate behavior and physiological parameters.

In conclusion, this study demonstrates that the multiparametric analyzer can be used for monitoring the human brain in the neurosurgical as well as the general intensive care unit. This assembly could be used for monitoring other pathophysiological conditions, such as ischemia, epilepsy and migraine, which are considered inducive of spreading depression, especially since it has been shown in this study that spreading depression may occur in vivo in the human cerebral cortex.

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