Publication I

Voipio J, Tallgren P, Heinonen E, Vanhatalo S, Kaila K. Millivolt-scale DC shifts in the human scalp EEG: evidence for a non-neuronal generator. Journal of Neurophysiology, 2003, 89: 2208-2214.

"It is dangerous to be right in matters on which the established authorities are wrong."

Voltaire

J Neurophysiol 89: 2208–2214, 2003.
First published December 11, 2002; 10.1152/jn.00915.2002.

Millivolt-Scale DC Shifts in the Human Scalp EEG: Evidence for a Nonneuronal Generator

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Submitted 11 October 2002; accepted in final form 7 December 2002

Voipio, Juha, Pekka Tallgren, Erkki Heinonen, Sampsa Vanhatalo, and Kai Kaila. Millivolt-scale DC shifts in the human scalp EEG: evidence for a nonneuronal generator. *J Neurophysiol* 89: 2208–2214, 2003. First published December 11, 2002; 10.1152/jn.00915.2002. Slow shifts in the human scalp-recorded EEG, including those related to changes in brain CO_2 levels, have been generally assumed to result from changes in the level of tonic excitation of apical dendrites of cortical pyramidal neurons. We readdressed this issue using DC-EEG shifts elicited in healthy adult subjects by hypo- or hypercapnia. A 3-min period of hyperventilation resulted in a prompt negative shift with a rate of up to 10 μV/s at the vertex (Cz) and an extremely steep dependence (up to 100 μV/mmHg) on the end-tidal Pco_2. This shift had a maximum of up to -2 mV at Cz versus the temporal derivations (T3/T4). Hyperventilation-like breathing of 5% CO_2-95% O_2, which does not lead to a significant hypocapnia, resulted in a near-complete block of the negative DC shift at Cz. Hypoventilation, or breathing 5% CO_2 in air at normal respiratory rate, induced a positive shift. The high amplitude of the voltage gradients on the scalp induced by hyperventilation is not consistent with a neuronal origin. Instead, the present data suggest that they are generated by extracortical volume currents driven by a Pco_2-dependent potential difference across epithelia separating the cerebrospinal fluid and blood. Since changes in respiratory patterns and, hence, in the level of brain Pco_2, are likely to occur under a number of experimental conditions in which slow EEG responses have been reported (e.g., attention shifts, preparatory states, epileptic seizures, and hypoxic episodes), the present results call for a thorough reexamination of the mechanisms underlying scalp-recorded DC-EEG responses.

INTRODUCTION

Conventional EEG has been extensively used to explore both the physiological and pathophysiological aspects of brain function. This technique, however, does not permit detection of very slow EEG activity ($<$0.1 Hz) known as DC potential shifts (Birbaumer et al. 1990; Speckmann and Elger 1999). A genuine DC-EEG amplifier and DC-stable electrodes are required to record slow EEG signals such as those seen in association with changes in breathing patterns (Caspers et al. 1987), with transitions between wakefulness and sleep (Caspers 1963; Marshall et al. 1998; Wurtz 1965; Wurtz and O'Flaherty 1967), and during epileptic seizures (Chatrian et al. 1968; Goldring 1963; Vanhatalo et al. 2003) or sleep in preterm infants (Vanhatalo et al. 2002).

The currently prevailing hypothesis regarding the cellular mechanisms of DC shift generation (Birbaumer et al. 1990; Speckmann and Elger 1999; see also Roland 2002) is largely based on work on epileptic activity in experimental animals, and the slow negative DC-EEG shifts are thought to reflect tonic depolarization of the apical dendrites of cortical pyramidal neurons. In addition to somatodendritic neuronal dipoles, the current loops involved in the intracortical sustained potentials generated by epileptic activity most likely involve glial cells (Caspers et al. 1987; Laming et al. 2000; Somjen 1973) and localized shifts in the extracellular potassium concentration (Laming et al. 2000; Staschen et al. 1987; Voipio and Kaila 2000). For simplicity, we will call the above current generators that are located within the brain parenchyma (and more specifically, within the cortex) "neuronal," as opposed to the putative "nonneuronal" current sources (see following text). In this context, it is of much interest that large, CO_2-mediated DC shifts have been recorded between the cerebrospinal fluid (CSF) and blood in several animal species (Davies et al. 1984; Held et al. 1964; Hornbein and Pavlin 1975; Hornbein and Sorensen 1972; Kjällquist 1970; Revest et al. 1993; Sorensen and Severinghaus 1970; Tschirgi and Taylor 1958) and humans (Sorensen et al. 1978).

Manipulation of human brain CO_2 levels by changes in respiratory patterns or in ambient CO_2 levels offers an easily repeatable, noninvasive approach to study the origins of slow DC-EEG shifts. In the present work, we have used voluntary hyperventilation (HV), hypoventilation, and hypercapnia achieved by breathing a 5% CO_2-95% O_2 mixture to examine the amplitude and topography of the ensuing DC shifts as well as their dependence on end-tidal CO_2. Our observations cannot be explained on the basis of the prevailing view (Speckmann and Elger 1999) that slow fluctuations in the human EEG are attributable to changes in cortical activity only. The present work calls for a reexamination of a number of findings in which slow DC-EEG shifts have been measured under various conditions, ranging from attention shifts and preparatory states to epileptic seizures and hypoxic episodes (Birbaumer et al. 1990; Caspers et al. 1987; O'Leary and Goldring 1964).

METHODS

The experiments were carried out on 12 healthy human volunteers of either sex (age 22–44 yr, median 27 yr). Throughout the recordings the volunteers were asked to look at a fixed point and to avoid body

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movements. The EEG was recorded on the scalp using a custom-designed DC-EEG amplifier (long-term stability better than 1 μV/h, bandwidth DC –160 Hz) and sintered Ag/AgCl electrodes with 12 mm^2 of active area (type E220N-LP, In Vivo Metric, Ukiah, CA). A separate electrode holder lifted the Ag/AgCl electrode 6 mm above the skin, forming a closed space that was filled with electrode gel (Berner Ltd., Helsinki, Finland). EEG signals were sampled at 500 Hz by a 12-bit data acquisition pc-card with an amplitude resolution of 2.4 μV. The software for data recording and analysis was programmed under Labview (National Instruments, Austin, TX). End-tidal CO_2 was measured with a capnograph (Capnomac, Datex, Helsinki, Finland).

The skin beneath the electrodes was scratched until a minute amount of blood was seen. It has been repeatedly shown that perforating the skin to short circuit skin-generated potentials is crucial to obtain stable recordings of slow EEG responses (e.g., Bauer et al. 1989; Bauer 1998; Picton and Hillyard 1972; but see Tomita-Gotoh and Hayashida 1996). We confirmed this in a series of experiments comparing responses from intact versus perforated skin on five subjects, in which recordings from intact skin (in 3/5 subjects examined in 1 to 2 experiments) showed continuous, unpredictable DC drifts and often (in 4/5 subjects) a profound contamination by galvanic skin responses (see Grimnes 1984; Wallin 1981).

The large volume of the electrode gel in the electrode cup and holder and the airtight contact of the holder with the skin beneath prevented electrode gel from drying, which is imperative to avoid drifts generated by changes in electrode potentials (Geddes and Baker 1968). Looking for further sources of "contamination" of the DC responses, we made a series of experiments to find out whether signals possibly generated by sympathetic activity and/or blood flow within the subcutaneous tissue might contribute to the HV-induced DC responses. After a control response evoked by hyperventilation (cf. Fig. 1), a combination of adrenaline (10 mg/ml) and lidocaine (10 mg/ml) was injected into the tissue beneath the vertex (Cz) electrode. This kind of injection is a routine procedure in clinical practice to cause a complete local anesthesia and a near-complete vasospasm. After the injection the HV was repeated. None of the results from these experiments (amplitude, time course of the DC shift, interelectrode voltage gradients) provided any evidence that sympathetic nerve activity or subcutaneous blood flow would affect HV-induced DC responses (data not shown).

We carried out single-channel and two- to six-channel DC-EEG measurements. In the latter, voltages at Fz, Cz, Oz (frontal, central and occipital, respectively, along midline according to the ten-twenty electrode system), T3, T4 (left and right temporal, respectively), and right mastoid were recorded and displayed with reference to the left mastoid. Single-channel recordings were made at Cz against a left-mastoid reference. In quantitative analyses (e.g., Fig. 4*C*), the signals from Fz, Cz, Oz, T3, and T4 were measured against a calculated, linked-mastoid reference, and their amplitudes were read at the time of peak Cz response.

In the hyperventilation experiments, subjects were asked to maximize their respiratory effort using an increase in the rate and depth of breathing without further instructions, which seemed to result in surprisingly similar DC-EEG responses for any given individual in recording sessions made at intervals of weeks or even months (see Fig. 1). The pattern of hypoventilation, in which the subjects minimized their breathing efficacy, was also subject specific. Finally, hypercapnia at a "free-running" breathing pattern was evoked by letting the subjects inhale a precision mixture of 5% CO_2-95% O_2 (Aga, Finland).

This study was approved by the Ethics Committee of the Helsinki University Hospital, and an informed consent was obtained from all subjects according to the Declaration of Helsinki. The data are presented as means ± SD.

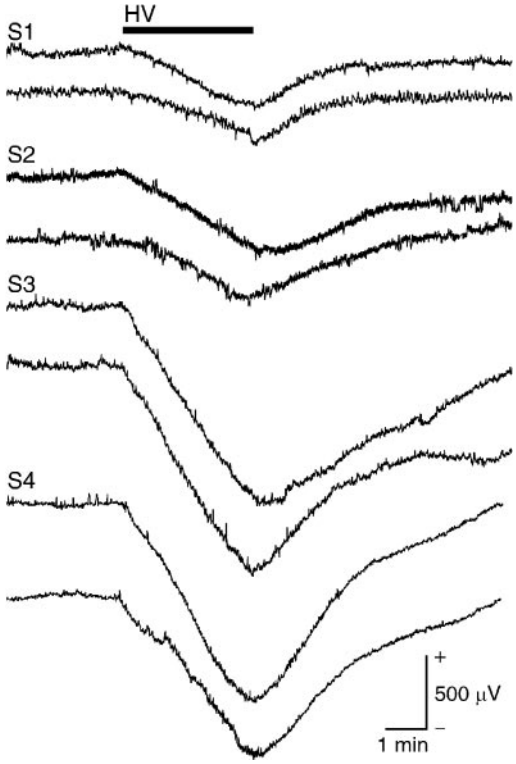

FIG. 1. Slow negative DC shifts associated with a 3-min hyperventilation (HV) in 4 different subjects recorded from the vertex (Cz) with a mastoid reference. Pairs of traces show the responses of the same subject recorded at 2 different sessions; note the striking similarity of the DC responses of a given subject.

RESULTS

Dependence of DC shifts on end-tidal CO_2

In the single-channel DC-EEG measurements, the recording electrode was placed on Cz, where the hyperventilation-induced negative shift has its maximum (see following text). In all subjects examined, a smooth monotonic negative shift in the DC-EEG started within 5–10 s with a rate of up to 10 μV/s following the onset of hyperventilation (Fig. 1). The 3-min HV period was not long enough to produce a saturation of the negative shift–in fact the rate of DC voltage change was about the same throughout the HV. Toward the end of HV, most subjects experienced subjective sensations of numbness and paresthesia (cf. Huttunen et al. 1999). With regard to the maximum amplitude of the DC shift after 3 min of hyperventilation, there was considerable interindividual variation (range −350 to −1,900 μV; mean −1,100 μV; $n = 10$). However, as is evident in Fig. 1, for a given subject the maximum shift was strikingly similar in amplitude when obtained in recording sessions made at intervals of several weeks or even months (see METHODS).

To assess the relationship between the DC shift and the HV-associated fall in end-tidal CO_2, we made simultaneous measurements of these two parameters (Fig. 2*A*). The negative voltage shift was closely paralleled by a progressive fall in Pco_2, and both parameters recovered to their original values upon cessation of the HV. Data pooled from six experiments of the kind shown in Fig. 2*A* provided a control value of 37.7 ± 3.6 mmHg ($n = 6$) for the end-tidal CO_2, which fell by 51 ± 18% upon 3 min of HV. The DC shifts recorded at 20-s

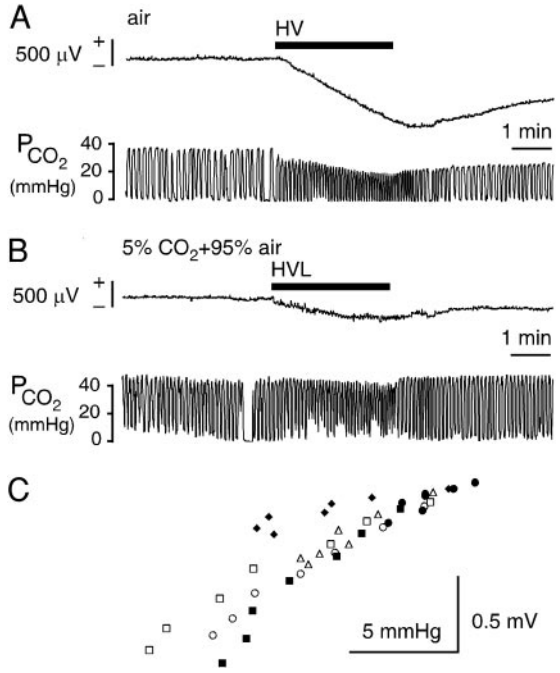

FIG. 2. Dependence of the DC shifts on end-tidal Pco_2. *A*: simultaneous recording of a HV-induced DC shift at Cz and of end-tidal Pco_2. *B*: an experiment similar to that above, but with 5% CO_2-95% O_2 throughout the experiment including a 3-min period of hyperventilation-like (HVL) breathing. *C*: HV-induced DC shifts plotted against Pco_2 for 6 subjects, indicated by distinct symbols. Values were taken at 20-s intervals with the first data point at 40 s after the start of HV.

intervals, with the first datapoint at 40 s after the start of HV, are plotted against the changes in Pco_2 for six subjects in Fig. 2*C*, and they reveal an extremely steep dependence of the EEG responses on end-tidal Pco_2, with a mean slope of 71 ± 32 μV/mmHg ($n = 6$).

The above data demonstrate a tight correlation, but not a cause–effect relationship, between end-tidal Pco_2 and the DC shift. Evidence for a causal relationship was sought in experiments in which subjects were asked to use their standard HV-like breathing pattern while inhaling a mixture of 5% CO_2 plus 95% air. As shown in Fig. 2*B*, hyperventilation-like breathing of 5% CO_2 produced a considerably smaller change in the DC-EEG compared with genuine HV recordings from the same experimental session. On average, the DC shift with 5% CO_2-95% O_2 was 22 ± 6% ($n = 6$) of that seen in 100% air, and this shift was fully accounted for by the small decrease in Pco_2 that took place in experiments of this kind.

The above results indicate that the fall in brain Pco_2, not the motor activity related to excessive breathing during HV (Huttunen et al. 1999), is responsible for the negative shift in the DC-EEG. If this is so, one might predict that hypercapnia, caused by voluntary hypoventilation, should produce an opposite effect, i.e., a positive shift in DC-EEG. This prediction was verified in three experiments, in which hypoventilation caused a positive shift of ≤80 μV (Fig. 3*A*). Further evidence for a causal dependence of the DC shifts on Pco_2 was obtained by examining the effects of breathing the 5% CO_2-95% O_2 mixture at a normal, "free-running" rate (Fig. 3*B*). Here, the ensuing 30 ± 17% increase in end-tidal CO_2 was accompanied by a positive DC shift of 203 ± 61 μV ($n = 4$).

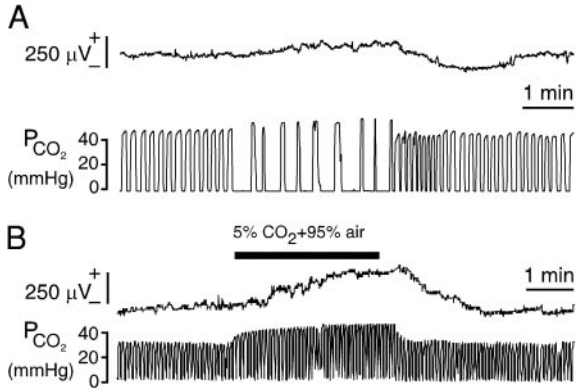

FIG. 3. Hypercapnia leads to a positive DC-EEG shift at Cz. *A*: hypoventilation for 3 min results in a small positive DC shift associated with a slight elevation in end-tidal Pco_2. *B*: breathing of 5% CO_2-95% O_2 at a normal rate also causes a positive DC shift and an increase in Pco_2.

Topography of the DC-EEG response

To examine the topography of the HV-induced DC-EEG response, we made simultaneous recordings from Fz, Cz, Oz, T3, and T4 in five subjects (Fig. 4). In all measurements of this kind, the maximum of the negative shift was located at Cz.

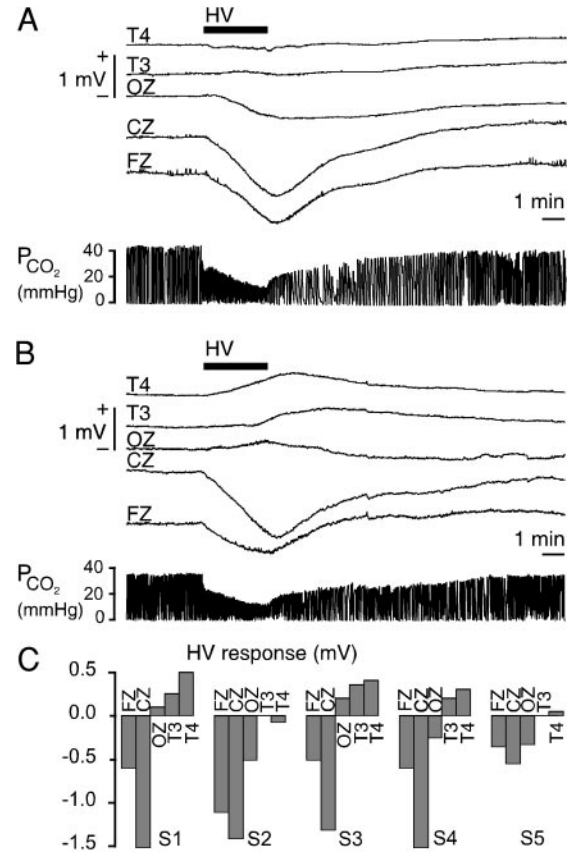

FIG. 4. Topography of the HV-induced DC-EEG response obtained using 6-channel recordings. In the responses of the subject illustrated in *A*, large negative shifts are seen at Cz and Fz while the response is smaller at Oz and negligible at the temporal sites. In another subject (*B*), negative shifts are again seen at Cz and Fz, but the other sites produce responses with an opposite polarity. *C*: summary of data (5 subjects) obtained from recordings of the above kind. Note the large voltage gradient that develops between Cz and the temporal electrodes during HV. Traces in *A* and *B* as recorded against a left mastoid reference, data in *C* with a linked-mastoid reference (see METHODS).

Along the midline, the negativity decreased in both the frontal and parietooccipital directions.

With regard to the signals at T3 and T4, the subjects had either no clear DC shifts (2 subjects) or a positive shift (3 subjects) indicating a very steep voltage gradient between Cz and temporal derivations. In two of the subjects, a clear positive shift was seen at Oz (Fig. 4*B*). While the negative shifts peaked 5–30 s after the end of the HV period, the positive ones were less pronounced and at temporal derivations often more delayed, peaking up to 160 s after HV. Hence, they may partly reflect secondary mechanisms that contribute to the generation of DC shifts (see Somjen and Tombaugh 1998).

A key finding in the experiments above was that the voltage gradients induced by HV on the scalp attain extremely large values compared with "conventional" scalp-recorded EEG signals, with amplitudes at most of 200–500 μV and durations of a few seconds even under pathophysiological conditions (see Niedermayer and Lopes da Silva 1999). A compilation of the data related to the HV-induced DC shifts at various sites is given in Fig. 4*C*. In four of five subjects, the difference in peak responses between the Cz and the temporal electrodes achieved levels of up to −1.9 mV, which indicates a gradient exceeding 100 μV/cm on the scalp within this region.

DISCUSSION

The present data based on DC-EEG indicate that a 3-min period of voluntary HV leads to large sustained negative voltage shifts of up to −2 mV on the human scalp. The responses at Cz versus T3/T4 revealed the largest EEG-voltage gradients reported so far under appropriate recording conditions in which skin potentials have been excluded by perforation (see METHODS) (cf. Tomita-Gotoh and Hayashida 1996). The amplitudes of the HV-induced DC shifts measured presently are an order of magnitude higher than signals recorded even during pathological conditions (e.g., seizure), and their duration of several minutes outlasts by far the slowest "conventional" EEG events (Niedermeyer and Lopes da Silva 1999). One should also note that, in the present experiments, no ceiling level of the DC shift was evident within the 3-min HV (see e.g., Fig. 1), which means that even larger DC responses would have been caused simply by prolonging the duration of the HV period. Hypercapnia, in turn, induced a shift with an opposite, positive polarity, which corroborates the idea that DC shifts are directly caused by changes in Pco_2.

There are no data indicating that, within cortex, the Pco_2-dependent DC deflections have a laminar profile similar to those observed during epileptic activity. Rather, several studies have shown that homogeneously distributed Pco_2-dependent DC shifts are observed not only throughout the cortex, but also in the underlying white matter (Amzica et al. 2002; Caspers et al. 1987; O'Leary and Goldring 1964; Wurtz 1967). Thus, in sharp contrast to prevailing views (e.g., Birbaumer et al. 1990; Caspers et al. 1987; Speckmann and Elger 1999; Tomita-Gotoh and Hayashida 1996), it appears that only a small fraction of the DC shifts seen during changes in brain Pco_2 can be explained on the basis of currents generated by the apical dendrites of cortical pyramidal neurons. Indeed, as discussed in the following text, the magnitude, amplitude, and other salient features of the long-standing DC gradients at the scalp evoked by changes in Pco_2 are consistent with the assumption that they are largely attributable to an intracranial nonneuronal generator.

Nonneuronal mechanisms underlying DC shifts

There are several lines of previously published evidence that support the idea of nonneuronal generation of DC shifts. In the early literature numerous laboratories have reported a millivolt scale, Pco_2/pH-sensitive potential gradient between cerebrospinal fluid (CSF) and venous blood (Held et al. 1964; Kjällquist 1970; Sorensen et al. 1978; Tschirgi and Taylor 1958). Among the putative intracranial current generators, this CSF–blood voltage gradient appears to be the only one capable of producing DC shifts of the magnitude presented in our study. Indeed, Sorensen et al. (1978) studied changes in electric potential between human CSF and venous blood during HV, and they demonstrated a tightly pH-related reduction in the potential difference between these compartments. The amplitude of the change in the CSF–blood potential related to the change in blood pH was roughly similar (−4.16 mV/pH unit) to what we found between the Cz electrode and mastoid reference (−3.5 mV/pH unit; blood pH estimated from end-tidal CO_2 by the Henderson–Hasselbalch equation).

A question that has not been addressed in earlier work is how a brain–blood (or CSF–blood) potential difference might generate potential gradients along the scalp. An answer can be derived from the simple model shown in Fig. 5. The essential features of this model are as follows. *1*) The blood–brain barrier (BBB) forms a voltage source (V_{BB}, the potential of brain tissue or CSF vs. blood; shown in a conventional manner in Fig. 5 as an electromotive force E_{BB} connected in series with an associated internal resistance R_{BB}). *2*) Blood has a rather low specific resistance (Geddes and Baker 1967; see also Oostendorp et al. 2000) and forms a well-conducting continuous space between brain and the other parts of the body. *3*) A potential difference comparable to that across the BBB (or blood–CSF barrier) is not found in most tissues of the body, where diffusion of plasma solutes from blood is free compared with that within the brain (Davson et al. 1987). *4*) Points *1–3* above directly imply that there is a DC-potential difference between brain tissue and the body. *5*) This potential difference generates a current that flows from the brain into the tissue layers between brain surface and scalp and proceeds (see arrows in Fig. 5*A*) along these layers toward the return path that runs within blood back to the BBB. Note that the resistances of the conducting layers between brain surface and skin surface as well as the access resistances to these layers have been pooled together in this simplified model and are represented by the two distributed resistances, R_S and R_B, respectively, in Fig. 5*A*.

The distributed model in Fig. 5*A* can be presented as an equivalent circuit (Fig. 5*B*), where R_T is the overall tissue resistance that connects R_S to the BBB. The potential difference across R_S (V_{DC}) is obtained as

$$V_{DC} = R_S I_{BB} = \frac{R_S}{R_B + R_S + R_T} \times V_{BB}$$

The large DC shifts observed in this work correspond to changes in V_{DC} (ΔV_{DC}). It is important to note that such changes can be brought about by changes in V_{BB} and/or by changes in the resistances. On purely geometrical grounds, R_S

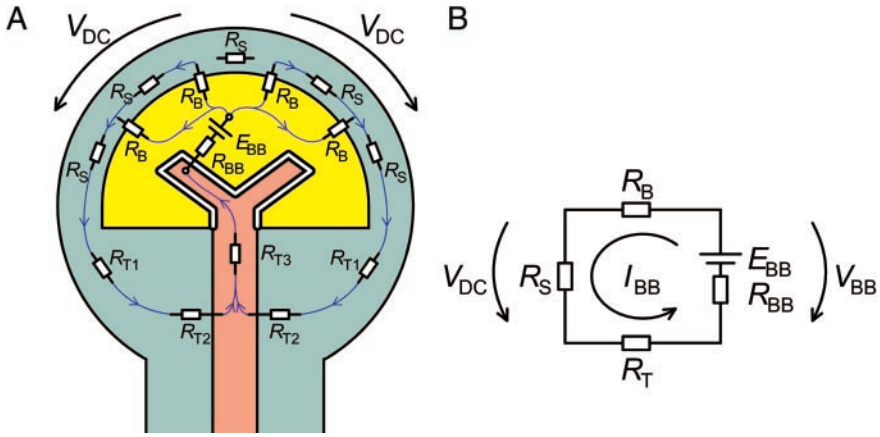

FIG. 5. Generation of DC-EEG signals on scalp by a volume current driven by the brain–blood potential difference. *A*: schematic drawing of the human head divided into four compartments: brain (yellow), blood (pink), the blood–brain or blood–CSF barrier (black double line), and all other tissues (light green). E_{BB}, the electromotive force of the voltage source across the brain–blood interface; R_{BB}, its internal resistance. This voltage source generates a volume current (blue lines with arrowheads) that flows first through R_B (the distributed resistance that couples brain potential to the surrounding extracortical tissue layers) and R_S (the distributed resistance of the layers between brain surface and skin surface pooled together) and gives rise to the voltage drop V_{DC} that can be measured on scalp. Current returns back to the brain–blood interface through R_{T1} (resistance of wider tissue pathways below the level of cranial fossae), R_{T2} (access resistance to blood), and R_{T3} (resistance of blood). *B*: simplified equivalent circuit of the scheme depicted in *A*. I_{BB}, denotes the current that is driven in the circuit by the brain–blood potential difference (V_{BB}); other symbols are as in *A*. For further details, see text.

must have a relatively high value compared with R_B and R_T and, therefore, a significant part of V_{BB} or ΔV_{BB} is seen across R_S as V_{DC} or ΔV_{DC}.

The present findings fit strikingly well with the idea that the brain/CSF–blood interface is the generator of the scalp-recorded high-amplitude DC potential changes. This is in line with early findings (Held et al. 1964; Sorensen et al. 1978; Wurtz 1967) that large DC shifts related to modulation of Pco_2 are generated at epithelial interfaces. As a consequence, the volume currents underlying DC-EEG shifts most likely have a wide and rather homogenous spatial distribution, which suggests that DC-EEG shifts do not necessarily have a well-defined DC-MEG correlate (cf. Carbon et al. 2000).

With regard to data from animal experiments, it should be emphasized that the above model predicts a critical dependence of the polarity of scalp-recorded DC shifts on the gross anatomy of the skull and brain as well as on the locations of the recording and reference electrodes. An interesting issue here is the apparent discrepancy related to the opposite polarities between DC shifts measured on scalp and on brain surface on hypercapnia in artificially ventilated rats (Lehmenkühler et al. 1999). In fact, this discrepancy can be attributable to the location of the reference electrode, which was placed on the nose, with the recording electrodes lateral to midline near the bregma. With regard to the scheme in Fig. 5*A*, the site generating the maximum scalp signal in the human Cz corresponds to a much more rostral site in the rat. Therefore the rostral reference electrode may have seen a larger fraction of the brain–blood potential shift than a scalp electrode near the bregma, resulting in a reversed polarity between the DC shifts recorded on the bregma surface and the brain parenchyma beneath this site.

DC-EEG shifts and changes in cerebral blood flow

It is a well-established fact that the HV-induced fall in brain Pco_2 leads to a decrease in cerebral blood flow (CBF). Early animal studies have shown that modulation of CBF is associated with marked changes in transcephalic or CSF–blood DC potentials (Besson et al. 1970; Cowen 1976; Held et al. 1964; Sorensen et al. 1978; Tschirgi and Taylor 1958). In humans, DC shifts during transition from wakefulness to sleep follow essentially the same time course: the decrease in CBF that takes place during sleep onset is paralleled by a negative DC shift at midline electrodes (Marshall et al. 1994, 1998). In fact, we are not aware of any observations in humans that would contradict a correlation of the above kind between changes in CBF and DC-EEG shifts, which, obviously, points to a causal relationship.

In animal experiments, the CO_2-dependent DC shifts in the BBB potential have been found to exhibit an opposite polarity in cats and monkeys compared with rats, rabbits, goats, and dogs, although the polarity of the responses in cats and monkeys could be reversed by preceeding hypoventilation or by manipulation of intracranial pressure (Woody et al. 1970). These results together with the data on the time courses of the DC shifts in relation to "arachnoid" (brain surface) pH shifts and carotid flow provided evidence for distinct pH- and blood flow–dependent mechanisms controlling BBB potential (Woody et al. 1970). Such mechanisms may contribute to the variability and often positive polarity of HV-induced shifts seen in temporal locations in the present work (Fig. 4*C*). In particular, gross anatomical differences between individuals will inevitably lead to a change the distribution of the BBB-driven volume current and hence produce subject-specific voltage-gradient distributions.

Implications and conclusions

The steep CO_2 dependence of the DC-EEG signal shown in Fig. 2 implies that a tiny fall of 0.15 mmHg in Pco_2 (i.e., from 5.00 to 4.98%) will produce a shift of around 10 μV at Cz. Given this extremely high sensitivity of the DC-EEG shifts to CO_2, it is of much interest to reconsider the mechanism(s)

underlying the scalp-recorded slow potentials that have been reported, e.g., during attempts to develop means for self-regulation of epileptic activity (Elbert et al. 1992; Kotchoubey et al. 1997). In one such study (Birbaumer et al. 1992), the subjects were asked to report their behavioral activities during the test and, interestingly, breathing activity was markedly altered during the time when changes in the DC-EEG were observed. Other laboratories have shown that respiratory training per se may similarly control epilepsy (Fried et al. 1990). While emotional state may unconsciously influence a subject's breathing pattern (Harper et al. 1998), it is obvious that breathing, in turn, has a powerful effect on scalp-recorded DC potential changes. Therefore it is tempting to speculate that the reported "self-regulation" of slow EEG signals may at least partly reflect unconscious (or conscious) alterations in breathing patterns.

While there is no doubt that changes in pH/Pco_2 within brain tissue have a powerful influence on neuronal excitability (Chesler and Kaila 1992; Jensen et al. 2002; Kaila and Ransom 1998; Somjen and Tombaugh 1998), the present data are inconsistent with the widely accepted idea that slow DC shifts in the human EEG have a purely neuronal origin. Our present study demonstrates that slow potential changes in human DC-EEG are easily elicited, and they show a remarkably high sensitivity to variations in Pco_2 levels. During intense hyperventilation, these DC shifts are much too large in amplitude and duration to originate from neuronal activity. All the available data are consistent with the idea that a volume current that is driven by the BBB produces DC shifts that can be recorded on the scalp.

This work was supported by grants from the Academy of Finland, from the Sigrid Jusélius Foundation, and from Arvo and Lea Ylppö Foundation.

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