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Effect of non-steroid anti-inflammatory drugs on neurovascular coupling in humans ☆

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ABSTRACT

Background/Aims: Neuronal activation induced cerebral blood flow increase was shown in animal experiments to require the presence of functioning cyclooxygenase. Our aim was to study whether widely used, non-steroid anti-inflammatory drugs (NSAIDs), given orally in usual therapeutic doses, inhibit neurovascular coupling in humans.

Methods: By using a visual cortex stimulation paradigm, the flow velocity response was measured by transcranial Doppler sonography in both posterior cerebral arteries of fifteen young healthy adults. The investigation was repeated in the same subjects after 2-day administration of 3 × 25 mg indomethacin (indomethacin phase) and 2 × 550 mg naproxen (naproxen phase). Visual-evoked-potentials were also recorded during the control phase and after administration of NSAIDs.

Results: Basal flow velocity significantly decreased while the pulsatility index increased after administration of either indomethacin or naproxen ($p < 0.01$). Despite unchanged visual-evoked-potentials, the visually evoked flow velocity increase (26 ± 7% in the control phase) significantly declined after administration of indomethacin (19 ± 5%; $p < 0.01$) or naproxen (20 ± 5%; $p < 0.02$).

Conclusion: Oral administration of indomethacin or naproxen in their usual therapeutic doses significantly impaired the resting and the visually evoked blood flow regulations in healthy human subjects. Together with stable evoked potentials, our findings indicate disturbance of neurovascular coupling.

1. Introduction

Neurovascular coupling assures adequate regional cerebral blood flow (CBF) according to the actual energy need of the activated brain tissue [1]. The close spatial and temporal relationship between neuronal activity and CBF has been extensively investigated, however, the exact mechanism still remains unclear [2–7]. In animal experiments, the neuronal activation evoked regional CBF increase was shown to require the presence of functioning cyclooxygenase as well as nitric oxide synthase [4–6,8].

Cyclooxygenase (COX), a prostanoid-synthesizing enzyme, is one of the most common therapeutic drug target in the world. This enzyme is responsible for the conversion of arachidonic acid to prostaglandin G2 and prostaglandin H2 that are metabolized further by different enzyme pathways to other prostaglandins (PG) with potent biological effects. Since some of these mediators (prostacyclin, thromboxan, PGE2, PGD2, PGF2 alpha) have vasoactive properties, it is not surprising that the inhibition of COX, besides pain relief and an anti-inflammatory effect, influences the vascular system, including cerebral circulation [9]. The main COX inhibitors are the non-steroid anti-inflammatory drugs (NSAIDs). Classical NSAIDs are not selective, thus they inhibit all types of COX. Undoubtedly, the most extensively examined NSAID is indomethacin, a non-selective COX inhibitor with a potent vasoconstrictor effect. Indomethacin was shown to decrease basal CBF by 20% to 40% in both animal models [10–15] and human studies [16–19]. Furthermore, it attenuated both hypercapnia [10–12,19–22] and acetazolamide induced vasodilation [20,22], as well as neurovascular coupling [4,6,23].

Most studies investigating the influence of NSAIDs on cerebral circulation included animals (mice, rats, pigs and piglets), human infants with patent ductus arteriosus [24–27], or human adults with traumatic brain injury [28–31], but relatively few reports are available in healthy human adults [18,19,23,32]. Moreover, in human studies, cerebral hemodynamics were mostly investigated after a bolus injection or intravenous administration of NSAIDs [18,19,23,25–27], and when NSAIDs were given orally [32], or as a suppository [16], they were usually used in a single high dose [30]. Comparative studies revealed that NSAIDs given as a slow continuous infusion had no or less significant effect on cerebral circulation, than bolus injections [25–28], supporting the importance of the way of administration.

☆ The study was performed at the Department of Neurology, Medical and Health Science Center, University of Debrecen.

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Since in every-day clinical practice NSAIDs are usually given orally, we aimed to test whether oral administration of NSAIDs in the usual clinical dose influences cerebral circulation. Neuronal activation evoked flow response requires vasodilation but indomethacin has a potent vasoconstrictor effect, therefore we sought to determine whether indomethacin, administered orally in the usual therapeutic dose, inhibits neurovascular coupling in healthy human subjects. In order to investigate the neuronal activation induced flow response, visually evoked flow velocity changes were detected by transcranial Doppler (TCD) in the posterior cerebral arteries (PCA) before and after indomethacin therapy. The measure of neuronal activity was assessed by visual-evoked-potential (VEP) in the control phase as well as after administration of indomethacin. To answer the question whether another widely used, non-selective NSAID has a different effect on neurovascular coupling, visually evoked flow velocity changes in PCAs and visual-evoked-potentials were also investigated before and under the effect of naproxen.

2. Subjects and methods

Fifteen young healthy adults (8 males, 7 females) between 20 and 35 years of age (mean age: 25 ± 4 years) were included in the study. The study was approved by the local ethics committee, and each volunteer gave written, informed consent. Cerebrovascular risk factors, history of migraine, coronary and peripheral artery diseases were screened and subjects with risk factors were excluded. The included subjects did not take any medicine regularly. The study protocol included routine clinical laboratory tests, serum lipids, and inflammatory markers. Blood was drawn after an overnight fast between 8 and 9 a.m., after the TCD examination. All volunteers underwent a complete neurological examination.

The functional TCD tests were performed in a quiet room at about 23 °C while the subjects were sitting comfortably. All volunteers had abstained from caffeine overnight before the study. Blood pressure was measured noninvasively before the TCD examination and at the end of the experiment. TCD examinations were always performed by the same examiners (L.O., K.SZ.).

3. Functional TCD study

Two 2-MHz probes were mounted by an individually fitted headband. In all cases, the P2 segment of the PCA was insonated on both sides at a depth of 58 mm. Peak systolic and end diastolic blood flow velocities were recorded with a Multidop T2 Doppler device (DWL, Überlingen, Germany). The reason for the separated evaluation of peak systolic and end diastolic blood flow velocities was that these indices are known to show different time courses in dynamic blood flow regulation. Being less influenced by Doppler artefacts [33], the peak systolic velocity index was used. The other reason for using peak systolic flow velocities in the present study was that this flow parameter reflected the dynamic flow regulation most appropriately [34].

As a stimulation paradigm, we used a news magazine with emotionally neutral text that the volunteers could read freely. This "reading" test had been previously validated against a checkerboard stimulation paradigm [35]. The stimulation protocol consisted of 10 cycles with a resting phase of 20 s and a stimulation phase of 40 s for each cycle. During the resting periods, volunteers were instructed to close their eyes; during the stimulation phases, they read silently. Changes between phases were signaled acoustically with a tone. After a short time delay at the beginning of the visual stimulation cerebral blood flow velocity increased rapidly, overshot and then stabilized at a constant but lower level.

Beat-to-beat intervals of cerebral blood flow velocity data were interpolated linearly with a "virtual" time resolution of 50 ms for averaging procedures. Within each person, flow velocity data of ten cycles were averaged. To ensure independence from the insonation angle and to allow comparisons between volunteers, absolute data were transformed into relative changes of cerebral blood flow velocity in relation to baseline. Baseline was calculated from the blood flow velocity averaged for a time span of 5 s at the end of the resting phase, before the beginning of the stimulation phase. Relative flow velocities were expressed in % of baseline. To analyze the maximum increase of relative flow velocity changes, the highest of the values obtained during the stimulation phase was taken from each subject.

Pulsatility index (PI) was calculated during the whole experiment using the following equation: PI = (peak systolic flow velocity − end diastolic flow velocity) / mean flow velocity [36]. PI at the resting phase was used for statistical analysis, and calculated from the PI averaged for a time span of 5 s at the end of the resting phase, before the beginning of the stimulation phase.

Besides visually evoked flow velocities, visual-evoked-potentials (VEP) were also investigated over the occipital cortex (Neuropack, Nihon Kohden Corporation, Tokyo, Japan) and amplitudes and latencies of P100 waves were calculated.

After the control examination, 3 × 25 mg indomethacin was given orally to the same volunteers (n = 15) for 2 days, after which the visually evoked flow test and the examination of visual-evoked-potentials were repeated. Four weeks later, the same protocol was performed in the same subjects after administration of 2 × 550 mg naproxen for 2 consecutive days (Fig. 1).

4. Statistical analysis

Data were expressed as means ± standard deviation (SD). Tests for normal distribution were performed, and the homogeneity of the variances was checked by an F test. Results of bilateral measurements were averaged within one subject.

Repeated measures ANOVA with Greenhouse–Geisser adjustments for the degrees of freedom was applied to compare absolute and relative changes of visually evoked cerebral blood flow velocities during the stimulation period between the control, indomethacin and naproxen phases. Paired *t*-test was used to compare the pulse rate, systolic and diastolic blood pressures, resting flow velocity and pulsatility index, maximum relative flow velocity change, and amplitude and latency of the visual-evoked-potentials (P100 wave) between the control and NSAIDs phases. When statistical significance was detected, Scheffe's post hoc test was performed. A difference of $p < 0.05$ was considered statistically significant.

5. Results

Data from all volunteers were used for evaluation. Baseline characteristics of the subjects can be found in Table 1. Blood pressure, pulse rate, and parameters of the visual-evoked-potentials (amplitude and latency of P100 wave) were similar in the control, indomethacin and naproxen phases (Table 1). The resting peak systolic flow velocity was significantly lower after administration of either naproxen or indomethacin than in the control phase ($p < 0.01$; Table 1). Both NSAIDs increased the pulsatility index compared to the control period ($p < 0.01$; Table 1).

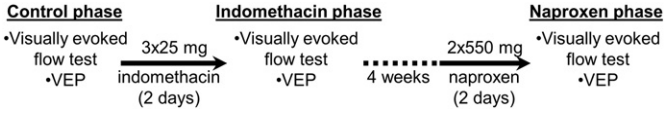

Fig. 1. At first, the visually evoked flow response and visual-evoked-potentials (VEP) were tested without medication (control phase). After the control examination, 3 × 25 mg indomethacin was given orally to the same volunteers (n = 15) for 2 days, after which the visually evoked flow test and examination of visual-evoked-potentials were repeated. Four weeks later, the same protocol was performed in the same subjects after administration of 2 × 550 mg naproxen for 2 consecutive days.