JOURNAL OF MAGNETIC RESONANCE IMAGING 13:325–334 (2001)

Original Research

Modulation of Cerebral Blood Oxygenation by Indomethacin: MRI at Rest and Functional Brain Activation

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The modulation of blood oxygenation level-dependent (BOLD) cerebral MRI contrast by the vasoconstrictive drug indomethacin (i.v. 0.2 mg/kg b.w.) was investigated in 10 healthy young adults without and with functional challenge (repetitive and sustained visual activation). For comparison, isotonic saline (placebo, 20 mL) and acetylsalicylate (i.v. 500 mg) were investigated as well, each in separate sessions using identical protocols. After indomethacin, dynamic T2*-weighted echo-planar MRI at 2.0 T revealed a rapid decrease in MRI signal intensity by 2.1%–2.6% in different gray matter regions ($P \leq 0.001$ compared to placebo), which was not observed for acetylsalicylate and the placebo condition. Regional signal differences were not significant within gray matter, but all gray matter regions differed significantly from the signal decrease of only 1.2% ± 0.7% observed in white matter ($P = 0.001$). For the experimental parameters used, a 1% MRI signal decrease in response to indomethacin was estimated to correlate with a decrease of the cerebral blood flow by about 12 ml/100 g/minute, and an increase of the oxygen extraction fraction by about 15%. Responses to visual activation were not affected by saline or acetylsalicylate, and yielded 5.0%–5.5% BOLD MRI signal increases both before and after drug application. In contrast, indomethacin reduced the initial response strength to 82%–85% of that obtained without the drug. The steady-state response during sustained activation reached only 47% of the corresponding pre-drug level ($P < 0.01$). During repetitive activation the BOLD contrast was reduced to 66% of that observed for control conditions ($P < 0.001$). In conclusion, indomethacin attenuates the vasodilatory force at functional brain activation, indicating different mechanisms governing neurovascular coupling. J. Magn. Reson. Imaging 2001; 13:325–334. © 2001 Wiley-Liss, Inc.

Index terms: cerebral blood flow (CBF); cerebral blood oxygenation (CBO); pharmacologic action; human brain; indomethacin; acetylsalicylate; placebo; magnetic resonance imaging, MRI; brain imaging

Abbreviations: BOLD = blood oxygenation level-dependent, CBO = cerebral blood oxygenation, CNS = central nervous system, EPI = echo-planar imaging, MRI = magnetic resonance imaging, TE = echo time, TR = repetition time

MAGNETIC RESONANCE functional neuroimaging detects changes in cerebral blood oxygenation (CBO) via fluctuations of the absolute concentration of paramagnetic deoxyhemoglobin per voxel. Appropriately sensitized MRI sequences have been shown to provide a sensitive measure of drug-induced changes in vasomotor tone, such as by acetazolamide as vasodilator (1,2) and aminophylline as vasoconstrictor (3). These results may have clinical impact in the application of functional neuroimaging to patients taking pertinent medication and in gaining a better understanding of the mechanisms contributing to the blood oxygenation level-dependent (BOLD) MRI contrast. Indomethacin stirred our particular interest because it is a potent vasoconstrictor known to decrease cerebral blood flow (CBF) without affecting the cerebral metabolic rate of oxygen ($CMRO_2$) (4–7). Similarly to acetylsalicylate, indomethacin acts as a strong inhibitor of prostaglandine synthesis (fatty acid cyclooxygenase inhibitor), which is the reason for its widespread use for antiinflammatory and analgesic purposes (8). However, the mechanisms for its vasoconstrictive action are not well understood. Following administration of indomethacin a reduction of basal CBF by 35% has been reported in human (7,9) and by 40% in baboon (6). This vasoconstrictive potency has been of therapeutic benefit in facilitating the closing of patent ductus arteriosus in infants (10) and in the management of intracranial hypertension (11).

Here indomethacin-induced vasoconstriction provided a pharmacologic model of reduced CBF in humans without the occurrence of alkalosis or cerebral lactate production. We investigated the role of indomethacin in altering CBF autoregulation and central neural reactivity both in the absence of a functional challenge and with the use of robust visual activation paradigms. Ultimately, we hope to contribute further information relating to basic coupling mechanisms underlying the BOLD MRI signal behavior. We therefore specifically addressed the dependence of the resting state BOLD MRI signal strength on vasoconstriction, and investigated modulatory drug effects on the BOLD

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Received May 16, 2000; Accepted September 1, 2000.

responses to repetitive and sustained activation. A preliminary account has been given in abstract form (12).

MATERIALS AND METHODS

Subjects and Drug Application

Following approval by the local ethics committee, and after obtaining informed, written consent 10 healthy volunteers (6 male, 4 female, age range 22–31 years, mean 26 years, mean body weight 80.5 ± 7.5 kg, no ongoing medication) underwent pharmacologic MRI according to an open, randomized parallel group design. While the subjects were being scanned in the magnet either indomethacin (0.2 mg/kg b.w.; Confortid®, Dumex-Alpharma A/S, Kopenhagen, Denmark), acetylsalicylate (0.5 g; Aspisol®, Bayer AG, Leverkusen, Germany), or isotonic saline was administered via an intravenous line previously inserted into the cubital vein. Subjects were not specifically aware of the exact injection time and type of drug given (for protocols see below). They were closely monitored for adverse effects. Peripheral pulse rates and oxygen saturation were recorded continuously.

Experimental Protocols

To allow an independent assessment of the three drugs, each volunteer underwent three different MRI sessions separated by at least four days. All studies were performed at 2.0 T (Magnetom Vision, Siemens Erlangen, Germany) using the standard circularly polarized head-coil.

BOLD MRI recordings were based on a single-shot, blipped gradient-echo EPI sequence with T2* sensitivity (TR = 2000 msec, mean TE = 54 msec, 70° flip angle, 128 × 128 matrix, 256 × 256 mm^2 field-of-view, 4-mm section thickness) (13,14). Following anatomic imaging (3D FLASH, TR/TE = 15/4 msec, 20° flip angle) dynamic multi-slice EPI recordings were performed in transverse-to-coronal sections, as demonstrated in Fig. 1. Three sections were chosen to provide regional access to the frontotemporal cortex, parietooccipital cortex, calcarine cortex, subcortical gray matter, frontal white matter, and cerebellum. All sections were analyzed for acute drug effects on regional BOLD MRI signal strength. Significance was tested with Student's two-tailed t-test. The central section was also analyzed for the effects of visual stimulation.

Each session consisted of five consecutive BOLD MRI experiments separated by about 2 minutes for image reconstruction and protocol setup: 1) an 8-minute series that included repetitive visual activation, 2) an 8-minute series that included sustained visual activation, 3) a 12-minute series without functional challenge but with drug administration 2 minutes after the onset of scanning, 4) an additional 8-minute series with sustained visual activation, and 5) a final 8-minute series with repetitive visual activation. The last two series started about 12 minutes and 22 minutes after drug injection, i.e., 2 minutes and 12 minutes after the end of the third series.

Visual Activation

Visual activation paradigms included 4-minute periods of repetitive (12 cycles of 10 seconds on/off) or sustained presentations of a reversing checkerboard vs. homogeneous isoluminescent gray light. In either case the stimulation periods were preceded (1 minute) and followed (3 minutes) by gray light, yielding a total duration of 8 minutes for each protocol. The checkerboard stimulus consisted of a circular, radial arrangement of 16 wedges formed by seven to eight black and white segments at equal radial distance. The segments reversed their color 10 times per second, i.e., with a frequency of 5 Hz. Both stimuli had a central red cross as the fixation point. Subjects were instructed to keep their eyes open and maintain attention throughout the scans.

Apart from technical means to minimize motion-induced phase errors by motion-compensating gradient waveforms, avoidance of T1-weighting, comfortable positioning, and head fixation, the resulting image series were visually inspected for movement artifacts using a rapid cine display mode. Detection of gross motion artifacts would have led to exclusion of the series. Fortunately, this was not necessary while taking care to acquaint the volunteers with the experimental setting beforehand. The subsequent analysis of the dynamic MRI data involved a 1-2-1 temporal filter, but no spatial filter and no baseline correction. Stimulus-related responses were identified by cross-correlation of pixel intensity time courses with a box-car reference function resembling the stimulus protocol shifted by 2 seconds to account for hemodynamic latencies. Quantitative maps of correlation coefficients were obtained with a thresholding procedure (error probability $P \leq 0.0001$) that rescales the histogram of correlation coefficients per map with respect to the individual noise distribution, according to the ideas outlined in Ref. 15.

Normalized MRI signal intensity time courses (in percentage of signal change) were obtained from all statistically significantly activated pixels, i.e., from all pixels admitted by the aforementioned analysis.

Monitoring Immediate Drug Effects

MRI monitoring of an immediate drug effect on BOLD MRI signal strength was based on a 12-minute protocol with the respective drug administered as a slow bolus (20 ml, 2-minute duration) starting 2 minutes after the onset of scanning. Data analysis was confined to region-of-interests in the fronto-parietal cortex (upper section in Fig. 1 containing gray and white matter), fronto-temporal cortex (gray matter), centrum semiovale (white matter), subcortical gray matter (basal ganglia), and cerebellum. Mean MRI signal intensity time courses were obtained using dedicated procedures based on IDL (Research Systems Inc., Boulder, CO). Again, the analysis involved a 1-2-1 temporal filter, but no spatial filter and no baseline correction. Therefore, the data were normalized with reference to signal intensity during the initial 2-minute baseline period and analyzed as a percentage of the relative signal change.

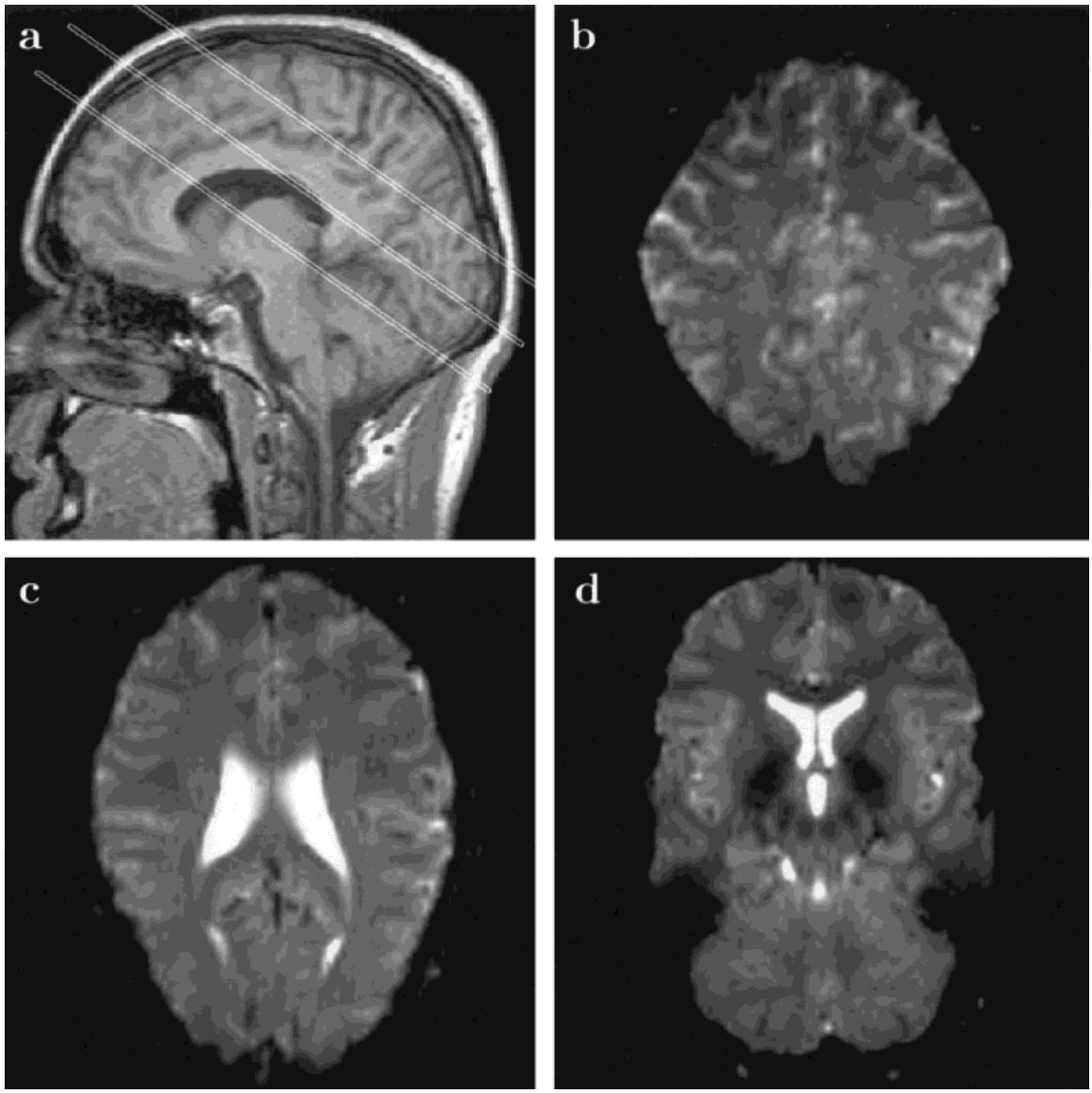

Figure 1. a: Sagittal MR section indicating transverse-to-coronal 4-mm sections and (**b–d**) corresponding single-shot echo-planar images (TR = 2000 msec, mean TE = 54 msec, 2.0 × 2.0 mm^2 in-plane resolution) used for monitoring drug effects in the frontotemporal cortex, parietooccipital cortex, calcarine cortex, basal ganglia, and cerebellum.

RESULTS

As an example, Figure 2 compares activation maps obtained before (coded in shades of red) and after (coded in shades of blue) indomethacin in a single subject for both repetitive (Fig. 2a) and sustained (Fig. 2b) checkerboard stimulation. Activated areas before and after drug application largely overlapped (coded in green) and were also very similar for repetitive and sustained stimulation. The absence of significant differences was confirmed by a quantitative analysis of all subjects and conditions, as summarized in Table 1.

Figure 3 shows mean BOLD MRI signal intensity time courses averaged across subjects before, during, and after administration of indomethacin, acetylsalicylate, and saline, respectively. In contrast to the other two conditions, indomethacin caused an immediate signal decrease within the 2-minute application period. This observation was similar throughout all brain regions and amounted to 2.1% ± 0.6% in the frontoparietal cortex and 2.6% ± 0.5% in the cerebellum (Fig. 3), and (not shown) 1.2% ± 0.7% in white matter (centrum semiovale), 2.5% ± 0.5% in frontotemporal gray matter, and 2.1% ± 1.6% in subcortical gray matter ($P \leq 0.001$ in all cases compared to the saline control). While significant differences were found between gray matter and white matter ($P = 0.001$), no significant differences between regions containing predominantly gray matter could be discerned.

The global indomethacin-induced signal decrease reflects an increase of the absolute deoxyhemoglobin concentration throughout the cerebral vasculature. It represents an indirect measure of vasoconstriction and ensuing CBF decrease. Of note, whereas no robust changes in heart rate were found for acetylsalicylate

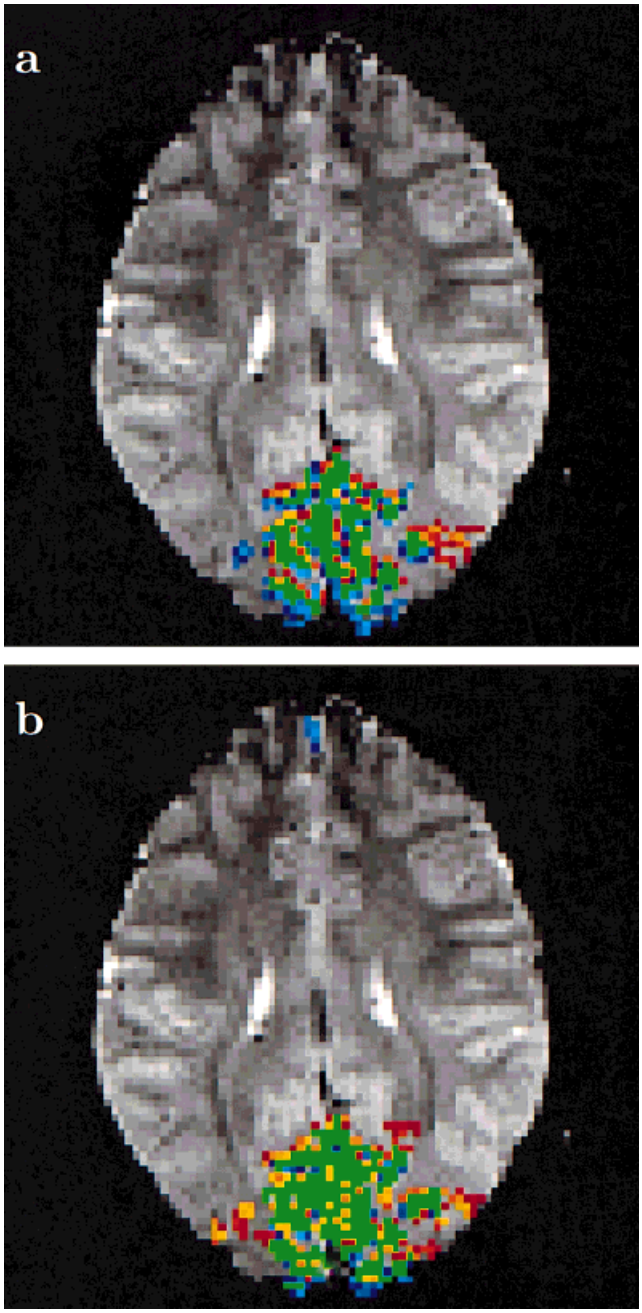

Figure 2. Activation maps of a single subject for (**a**) repetitive and (**b**) sustained stimulation with activated pixels before indomethacin administration coded in shades of red (yellow denoting highest significance) and afterwards coded in shades of blue (deep blue denoting highest significance). Overlap between pre- and post-drug activation is displayed in green.

and saline at 67 ± 12 beats/minute, there was a transient mean decrease of 6 beats/minute for about 3–5 minutes after indomethacin administration. Peripheral oxygen saturation remained essentially unchanged.

Figures 4 and 5 summarize the drug effects on functional responses to sustained and repetitive visual activation, respectively. They depict normalized BOLD MRI signal intensity time courses averaged across subjects before and after indomethacin, acetylsalicylate, and saline.

Table 1
Activated Pixels (mean ± SD) for Repetitive and Sustained Visual Activation Before and After Drug Administration

Drug	Repetitive stimulation[a]		Sustained stimulation[b]	
	Before	After[c]	Before	After[c]
Indomethacin	182 ± 59	139 ± 68	189 ± 148	109 ± 88
Acetylsalicylate	160 ± 82	202 ± 68	171 ± 47	231 ± 143
Saline	175 ± 99	199 ± 93	233 ± 108	135 ± 112

[a] $n = 10$.
[b] $n = 8$.
[c] Differences are statistically not significant ($P > 0.05$, two-sided paired t-test).

Based on the spatial congruence found in pertinent activation maps (compare Fig. 2 and Table 1), post-drug results of the volunteers were obtained from the same individual clusters of pixels activated before drug application. Whereas both acetylsalicylate and saline showed invariant BOLD MRI responses before and after drug action, indomethacin caused a striking decrease of response magnitude for both sustained and repetitive stimulation. First, indomethacin attenuated the initial positive BOLD response to visual activation to only 85% (sustained protocols) and 82% (repetitive protocols) of the respective pre-drug response strengths. Second, the temporal response evolution to sustained activation exhibited a subsequent decline to a plateau value of only 47% of the corresponding steady-state response obtained without indomethacin (compare Fig. 4a and b). Third, the functional contrast obtained during repetitive activation, i.e., the peak-to-peak difference between functional states, reached only 66% of the corresponding pre-drug signal differences (compare Fig. 5a and b). Pertinent results are quantified for all drugs in Table 2. Although the measurements displayed a small signal intensity drift, the pre- and post-stimulation baseline periods of 1 and 3 minutes, respectively, were long enough to properly account for this variation during the quantitative analysis.

DISCUSSION

Positive BOLD effects that present as MRI signal increases upon brain activation are commonly understood as a state of hyperoxygenation resulting from vasodilation, i.e., the reduction of deoxyhemoglobin by enhanced delivery of oxyhemoglobin in excess of elevated oxygen consumption, resulting in enhanced production of deoxyhemoglobin (16). In contrast, the mechanisms that give rise to the post-stimulation "undershoot" (an effective deoxygenation and relative BOLD MRI signal decrease) are less well defined in humans. They have been proposed to mainly reflect a delayed increase of cerebral blood volume (CBV) in animal studies (17). The complex interplay of these diverging signal contributions is responsible for the particular temporal response profiles elicited by repetitive and sustained stimulation paradigms. Selective pharmacologic effects may therefore help to detect specific dependencies.

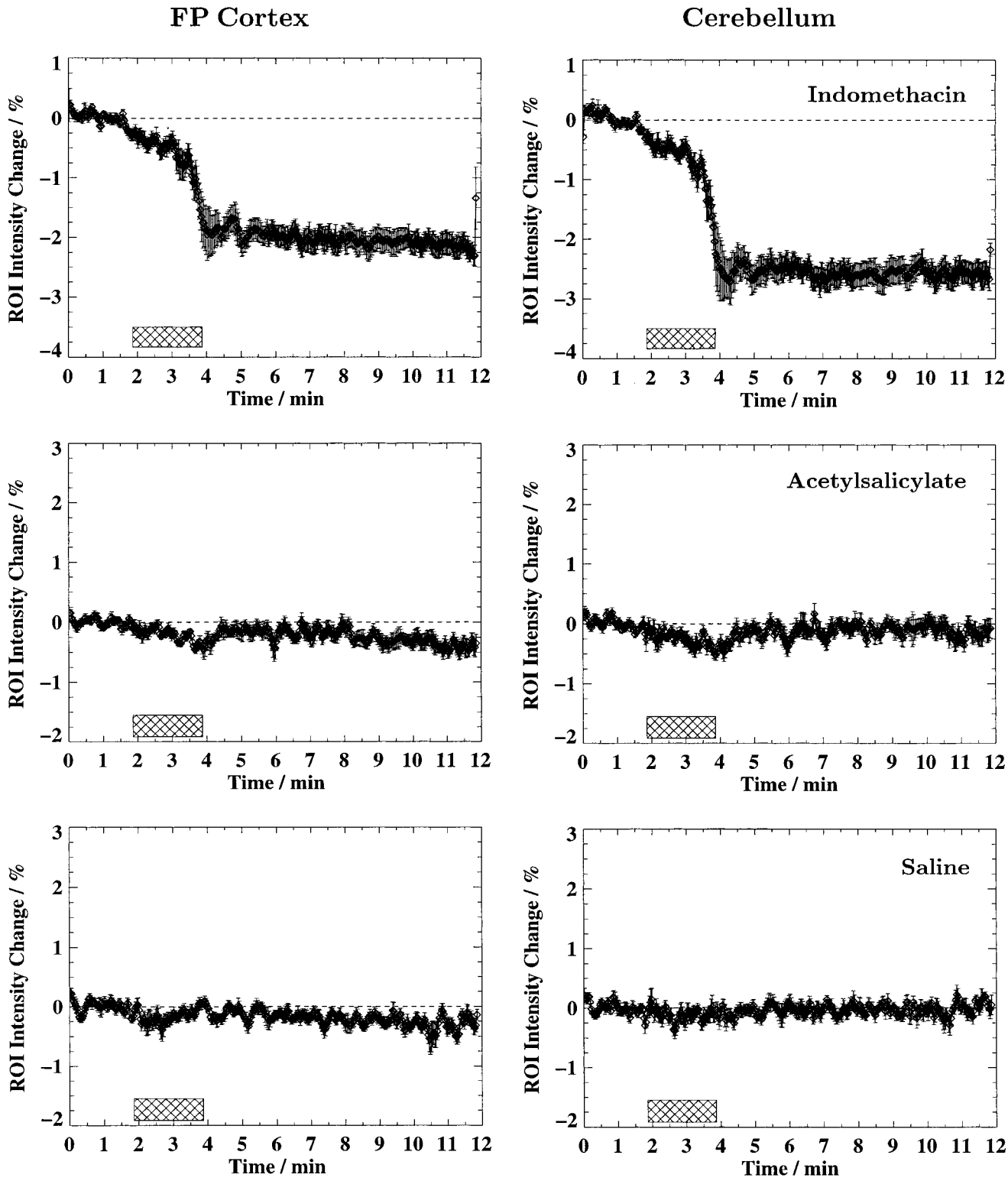

Figure 3. Normalized BOLD MRI signal intensity time courses (averaged across subjects) depicting drug effects in (**left**) frontoparietal cortex and (**right**) cerebellum: (**top**) indomethacin, (**middle**) acetylsalicylate, and (**bottom**) saline. The 2-minute period of drug administration is indicated (hatched bar). Vertical lines represent the standard error of the mean.

Acetylsalicylate

Interestingly, the application of acetylsalicylate yielded results similar to those obtained for the placebo condition. Acetylsalicylate did not significantly change the BOLD MRI signal at rest nor did it cause alterations of the response pattern or functional contrast in response to visual activation. The present findings provided no evidence for a change of the net CBO at rest and did not

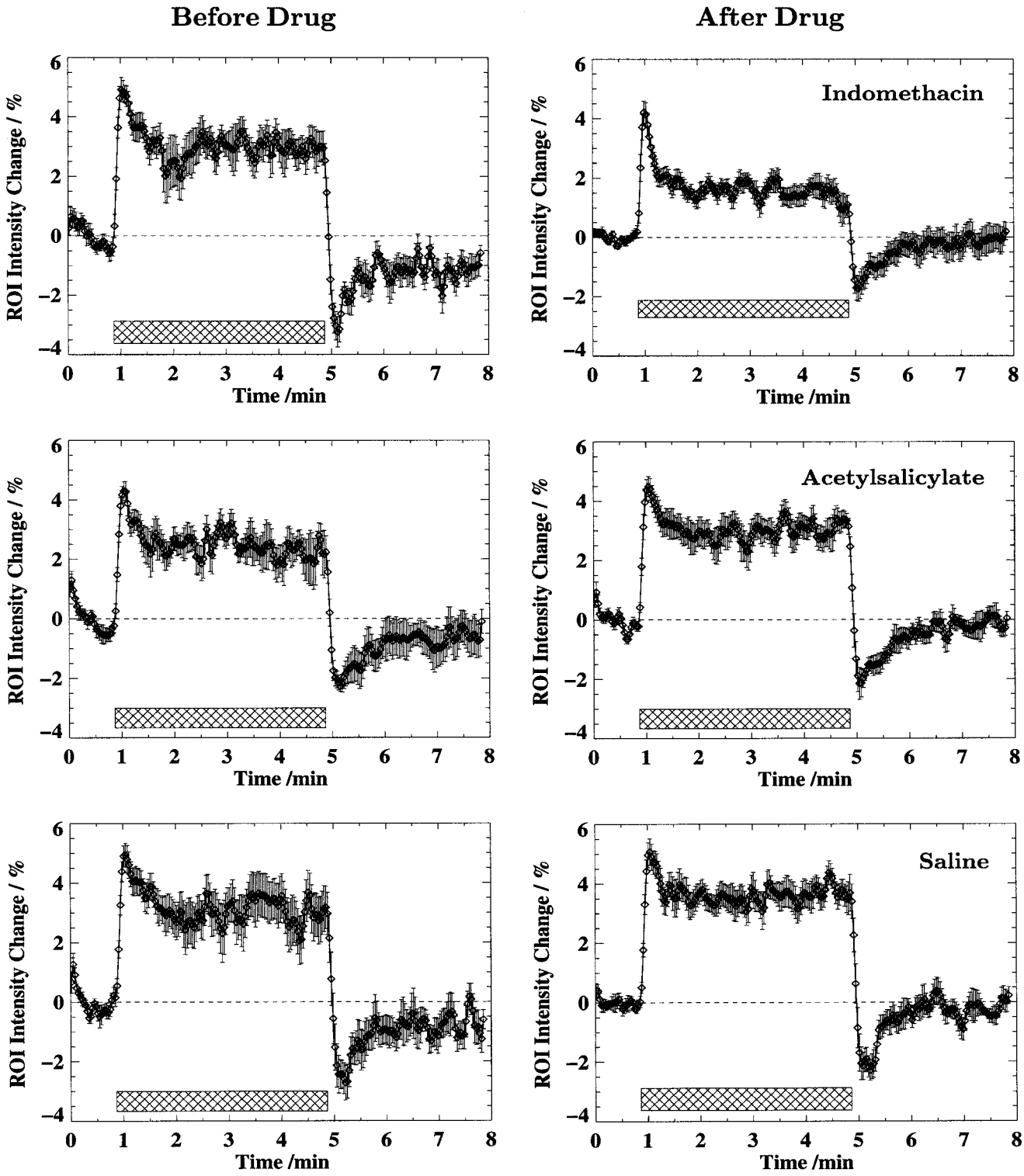

Figure 4. Normalized BOLD MRI signal intensity time courses (averaged across subjects) for sustained activation of visual cortex (**left**) before and (**right**) after administration of (**top**) indomethacin, (**middle**) acetylsalicylate, and (**bottom**) saline. For each subject the post-drug time courses were derived from the same cluster of pixels activated before drug application. The 4-minute period of sustained stimulation is indicated (hatched bar). Vertical lines represent the standard error of the mean.

indicate a change in reactivity or responsiveness to a functional challenge.

The "neutral" behavior of acetylsalicylate was somewhat surprising because a large increase in cerebral oxygen consumption has been reported in baboons after 50–200 mg/kg of salicylate (18). The difference may be due to the smaller doses used here. However, it could also be caused by two antagonistic properties reported for sodium salicylate: a constriction of cerebral blood vessels (possibly by an inhibi-

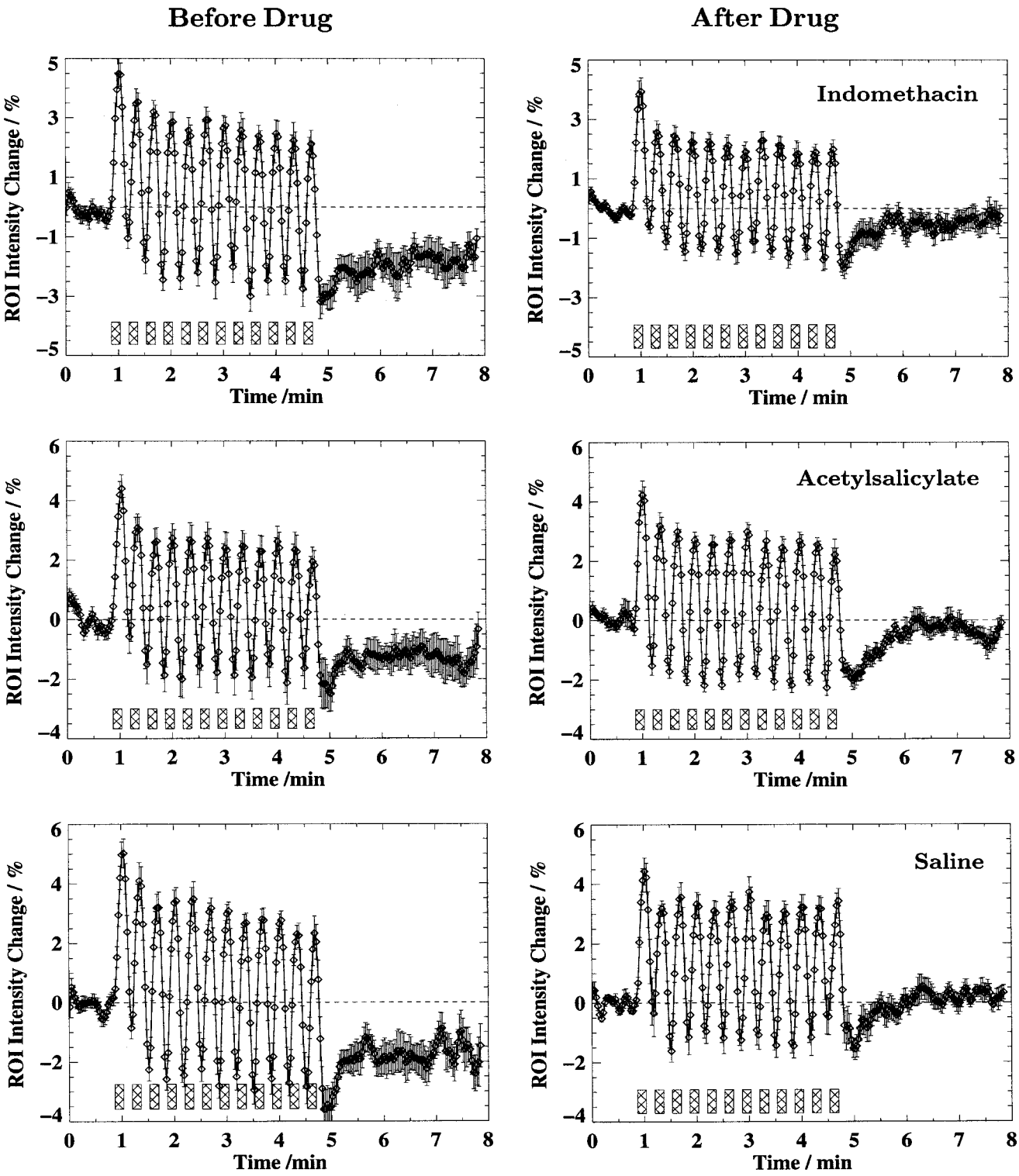

Figure 5. Normalized BOLD MRI signal intensity time courses (averaged across subjects) for repetitive activation of visual cortex (**left**) before and (**right**) after administration of (**top**) indomethacin, (**middle**) acetylsalicylate, and (**bottom**) saline. For each subject the post-drug time courses were derived from the same cluster of pixels activated before drug application. The 4-minute period of repetitive stimulation is indicated (12 cycles of 10 seconds on/off, hatched bars). Vertical lines represent the standard error of the mean.

tion of prostaglandin synthesis) and a vasodilation secondary to increased brain metabolism via central stimulation. For example, 20 minutes (60 minutes) after the administration of 65 mg/kg aspirin in newborn piglets CBF and $CMRO_2$ increased by 16%–22% (20%–32%) and 23% ± 2% (26% ± 3%), respectively (19). Being of similar magnitude, the opposite contributions in terms of deoxyhemoglobin content might cancel each other such that no net BOLD MRI effect could be measured.

Table 2
Normalized BOLD MRI Response Strengths (in Percent, Mean ± SD) for Repetitive and Sustained Visual Activation Before and After Drug Administration

Drug	Repetitive stimulation[a] functional contrast		Sustained stimulation[b] steady-state response	
	Before	After	Before	After
Indomethacin	4.76 ± 0.95	3.12 ± 0.77**	3.45 ± 1.16	1.63 ± 1.02*
Acetylsalicylate	4.68 ± 1.43	4.24 ± 1.16	2.90 ± 0.99	3.02 ± 1.21
Saline	4.59 ± 1.50	4.41 ± 1.32	3.70 ± 1.90	3.94 ± 1.08

[a] $n = 10$.
[b] $n = 8$.
*$P < 0.01$; **$P < 0.001$ (two-sided paired t-test).

Cerebrovascular Effects of Indomethacin

In contrast to saline and acetylsalicylate, the immediate BOLD MRI signal decrease induced by therapeutic doses of indomethacin reflects a corresponding reduction of the net CBO. It comes as no surprise that this effect is more accentuated in well vascularized gray matter than it is in white matter. Similar BOLD differences have been reported at vasodilation (1), and at vasoconstriction using aminophylline (3) or hypocapnea (20). The temporal evolution of the indomethacin effect is in excellent agreement with the dynamic changes in CBF previously observed after indomethacin (21). Because $CMRO_2$ has been reported to remain unchanged under these conditions (4,7,9,22), the present MRI findings imply that vasoconstriction and decreased CBF lead to a larger oxygen extraction (OE) at rest. The reported concomitant decrease in CBV of 10%–15% (23) seems to be of minor importance as it would lower the total hemoglobin content per voxel and, hence, increase rather than decrease the BOLD MRI signal intensity. Therefore, without a putative CBV contribution the present net decrease might have been even greater.

Because indomethacin (like hypocapnea) has been found to reduce CBF in healthy young adults from a resting state level of 50–65 ml/100 g brain tissue/minute (24) to 60% or 30–38 ml/100 g/minute (25), such alteration is likely to be quantitatively correlated with the indomethacin-induced BOLD MRI signal change. Accordingly, a 40% CBF decrease should roughly correspond to the observed 2% signal decrease. In other words, assuming a constant oxygen consumption at rest (here defined as gray light exposure), a 1% signal decrease under the chosen experimental conditions would refer to a CBF reduction by about 12 ml/100 g/minute.

According to Ogawa et al (26) the change of the oxygen extraction fraction after indomethacin may be estimated from the relative change of the relaxation rate 1/T2* and the fractional changes of CBF and CBV:

$$\frac{\Delta OE}{OE} \cong \frac{\Delta(1/T2^*)}{(1/T2^*)} + \frac{\Delta CBF}{CBF} - \frac{\Delta CBV}{CBV}$$

Assuming a constant oxygen consumption (4,5), a 40% CBF decrease (25), a 10%–15% CBV decrease (23), and taking into account that the 2% signal decrease after indomethacin translates into a similarly small change of $\Delta(1/T2^*)/(1/T2^*)$, the resulting oxygen extraction fraction must be enhanced by about 30%. Of note, this finding reveals a remarkable reserve capacity for the utilization of the oxygen supply under indomethacin-induced vasoconstriction.

Modulation of BOLD MRI Responses to Functional Activation

Despite pronounced vasoconstriction after indomethacin, visual activation elicited a positive BOLD MRI response with only a mild reduction of the initial signal strength. This signal increase demonstrates a still effective physiologic response to neurostimulation under indomethacin—at least with respect to the underlying dominant CBF increase. In contrast, the observation of a subsequent attenuation of the response strength to both sustained and repetitive stimulation indicates a pronounced modulation of the neurovascular coupling, which links changes in brain activity to the hemodynamically mediated and MRI-detectable changes in functional BOLD contrast.

Of note, indomethacin, which reduces the resting state BOLD MRI signal intensity by about 2%, allows for a positive steady-state response strength of 2% during sustained visual activation. Phenomenologically at least, the response reaches an absolute BOLD MRI signal intensity similar to that without the drug at rest. Thus, by applying the CBF "calibration" for the immediate drug effect (see previous section), and by assuming that the indomethacin-induced vasoconstriction is compensated for by the activation-induced CBF increase, the sustained functional challenge would afford a CBF increase of 25–30 ml/100 g/min. In fact, under indomethacin the neurovascular activation largely feeds upon the same oxygen tension as in the resting state without vasoconstriction.

It has been reported that under hypocapnia-induced vasoconstriction the photic activation of visual cortex under normocapnia completely disappeared (25). While the BOLD decrease with hypocapnia appears to be even more pronounced than with indomethacin, it is not clear whether this result is confounded by residual motion and diversion of the subjects' attention from the stimulation caused by the requirement to hyperventilate and lie still.

Hypoxia has been shown to represent a strong force for offsetting the indomethacin-driven contraction

mechanism (27). For example, moderate hypoxia (inhalation of 17% oxygen) caused the indomethacin-depressed CBF to rise from 38 to 57 ml/100 g/minute, and hypercapnia (inhalation of 2%–4% carbon dioxide) increased the CBF to 55 ml/100 g/minute. The ability to almost quantitatively abolish mutual changes in CBF strongly suggests that a similar mechanism and/or mediator is responsible for the underlying vasoreactivity. In contrast, neurofunctional stimulation as used here was unable to regain steady-state BOLD MRI response strengths to visual activation as observed before indomethacin application. Apart from a decreased pre-stimulation baseline, repetitive and sustained stimulation reached only 66% and 47% of the pre-drug functional contrast. These findings suggest that the vasoconstrictive action of indomethacin and the vasodilative response to a functional challenge are likely to be governed by multiple mechanisms.

Proposed mechanisms for the indomethacin-induced cerebral vasoconstriction include the inhibition of prostacyclin synthesis (4) or of 5.6 epoxy-eicosatrienoic acid (5.6 EET) via the epoxygenase pathway (28), an enhanced secretion of endothelins (the circulating levels of which have been shown to double with indomethacin (29)), a blockade of the prostanoid synthesis (30), and a nonprostaglandin-mediated mechanism (31). Although no direct contribution to this ongoing discussion can be derived from the present data, it is interesting to note that the CBF response to whisker stimulation in chloralose-anesthetized rats has been found to be reduced by 40% after adenosine receptor blockade with the use of topical theophylline, and by 58% after adding a blocker of nitric oxide (NO) synthase (31). With regard to effect magnitudes, therefore, our observations of indomethacin-reduced (though still marked) functional responses suggest that if NO is the key mediator of neurovascular coupling, then it is superior to the indomethacin mechanism for vasoconstriction and should be more effective than the putative mediators noted above.

ACKNOWLEDGMENTS

We thank Martin Ingvar from the Department of Clinical Neuroscience at the Karolinska Institutet, Stockholm, Sweden, for stimulating discussions and generous support.

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