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Dose-dependent Regional Cerebral Blood Flow Changes during Remifentanil Infusion in Humans

A Positron Emission Tomography Study

Klaus J. Wagner, M.D., Frode Willoch, M.D.,† Eberhard F. Kochs, M.D.,‡ Thomas Siessmeier, M.D.,† Thomas R. Tölle, M.D.,§ Markus Schwaiger, M.D.,‖ Peter Bartenstein, M.D.#*

Background: **The current study investigated dose-dependent effects of the μ-selective agonist remifentanil on regional cerebral blood flow (rCBF) in volunteers using positron emission tomography (PET).**

Methods: **Ten right-handed male volunteers were included in a ^{15}O-water PET study. Seven underwent three conditions: control (saline), low remifentanil (0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$), and moderate remifentanil (0.15 $\mu g \cdot kg^{-1} \cdot min^{-1}$). The remaining three participated in the low and moderate conditions. A semirandomized study protocol was used with control and remifentanil conditions 3 or more months apart. The order of low and moderate conditions was randomized. Cardiovascular and respiratory parameters were monitored. Categoric comparisons between the control, low, and moderate conditions and a pixelwise correlation analysis across the three conditions were performed ($P < 0.05$, corrected for multiple comparisons) using statistical parametric mapping.**

Results: **Cardiorespiratory parameters were maintained constant over time. At the low remifentanil dose, significant increases in relative rCBF were noted in the lateral prefrontal cortices, inferior parietal cortices, and supplementary motor area. Relative rCBF decreases were observed in the basal mediofrontal cortex, cerebellum, superior temporal lobe, and midbrain gray matter. Moderate doses further increased rCBF in mediofrontal and anterior cingulate cortices, occipital lobe transition, and caudal periventricular grey. Significant decreases were detected in the inferior parietal lobes. These dose-dependent effects of remifentanil on rCBF were confirmed by a correlation analysis.**

Conclusion: **Remifentanil induced dose-dependent changes in relative rCBF in areas involved in pain processing. At moderate doses, rCBF responses were additionally detected in structures known to participate in modulation of vigilance and alertness. Insight into the mechanisms of opioid analgesia within the pain-processing neural network may lead to a better understanding of antinociception and opioid treatment.**

CEREBRAL imaging technologies, including positron emission tomography (PET) and functional magnetic resonance imaging, are increasingly used for noninvasive investigation of drug actions in the human brain *in vivo*. PET has been used in the experimental and clinical setting to obtain information about regional cerebral glucose metabolism and regional cerebral blood flow (rCBF) during anesthesia with volatile[1] and intravenous anesthetics,[2,3] during pain perception,[4–8] in receptor-binding studies,[9,10] and after opioid administration.[11–13]

The primary reason for the use of opioids in anesthesia, as well as in acute and chronic pain management, is their profound analgesic effect. However, opioids may also exert sedative effects. The effects of opioids on cerebral hemodynamics remain controversial; both increases and decreases in CBF, depending on study conditions, model used, species, opioid regimens (supraclinical *vs.* routine dose), and presence of confounding variables (*e.g.*, background anesthetic agents or reduced intracranial compliance), have been described.[14,15] In neuroanesthesia and intensive care, knowledge about the effects of different doses of opioids on CBF in various cortical and subcortical brain areas would be useful.

The PET technique can be used for noninvasive investigations of changes in rCBF after opioid administration. A single dose of fentanyl was used in previous studies to investigate the effects of a μ-selective opioid on brain activity and pain perception with PET.[11,12] Remifentanil is a synthetic opioid that shows classic μ-agonist pharmacologic effects with a rapid onset and peak effect and a short duration of action.[16] The context-sensitive half-time is 3–6 min, and the terminal elimination half-life is 10–20 min.[17] This pharmacokinetic profile is especially advantageous in an experimental setting to administer different dosages in one setting but in a counterbalanced order.

The present study used ^{15}O-water PET to investigate the effects of remifentanil in different doses on relative rCBF in humans.

Materials and Methods

The study was approved by the Ethics Committee of the Faculty of Medicine of the Technical University, Munich, and the radiation protection authorities. In accordance with the Declaration of Helsinki, all subjects gave written informed consent to participate in the study after the experimental procedure and radiation effects had been extensively explained.

* Assistant Professor, ‡ Professor and Chairman, Klinik für Anaesthesiologie, † Assistant Professor, Nuklearmedizinische Klinik und Poliklinik, § Associate Professor, Neurologische Klinik, ‖ Professor and Chairman, # Professor, Klinik für Nuklearmedizin.

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Address reprint requests to Dr. Wagner: Klinik für Anaesthesiologie, Klinikum rechts der Isar, Technische Universität München, Ismaninger Strasse 22, D-81675 München, Germany. Address electronic mail to: K.Wagner@lrz.tum.de.

Subjects

Ten right-handed, healthy male volunteers were enrolled in the study. None had a history of neurologic or any other severe disease (American Society of Anesthesiologists physical status 1), and none had a history of drug abuse.

Study Protocol

The volunteers had fasted for at least 6 h before the study. Electrocardiogram and arterial oxygen saturation (Sao_2) were measured and continuously recorded (Capnomac Ultima; Datex, Helsinki, Finland). Noninvasive blood pressure measurements were performed at 5-min intervals (Dinamap 1846 SX; Criticon, Tampa, FL). End-tidal carbon dioxide concentrations were measured using a Capnomac Ultima monitor *via* a catheter placed at the naso-pharyngeal border. Capillary carbon dioxide was measured immediately after every condition of drug administration by blood samples taken from a warm, nonheated finger tip. In a pilot study, remifentanil infusion was increased from 0.025 to 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Significant respiratory depression (< 6 breaths/min) with increases in end-tidal carbon dioxide was observed with more than 0.20 $\mu g \cdot kg^{-1} \cdot min^{-1}$ remifentanil. Therefore, the maximal dose in our study was limited to 0.15 $\mu g \cdot kg^{-1} \cdot min^{-1}$ remifentanil; respiration was only slightly impaired and would be easily counteracted by verbal command. Each volunteer was instructed for respiration by verbal command twice per minute during every condition in our study.

A total of three different conditions of drug administration were investigated: control (saline), low-dose remifentanil (0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$), and moderate-dose remifentanil (0.15 $\mu g \cdot kg^{-1} \cdot min^{-1}$). A semi-randomized study protocol was used to overcome the problem of different dates of data acquisitions and possible residual remifentanil effects: one group of volunteers (n = 3) was first subjected to the control condition, whereas remifentanil measurements were performed 3 or more months after the control condition. In the second group, volunteers (n = 4) were first exposed to the remifentanil measurements and after 3 or more months to the control condition. Three additional volunteers received only the low and moderate doses of remifentanil and did not take part in further investigations. All the reported data are based on results from the seven volunteers (age range, 28–38 yr; mean, 32 years) who underwent all three conditions if not otherwise indicated (statistical results from the entire group are available on request). Statistical analysis was performed with data from the seven remaining subjects.

Each condition was repeated three times, resulting in a total of nine scans for each volunteer (n = 7). Because of its short half-life, remifentanil was delivered by an infusion pump (Combimat 2000; Döring, München, Germany) in a blinded, randomized order with a time interval of more than 30 min between subsequent remifentanil infusion rates. To establish steady state plasma concentrations,[17] remifentanil was administered *via* a separate intravenous line in a left antecubital vein to avoid bolus effects during ^{15}O-water injections. All PET-scanning sessions were scheduled at similar times of the day in a quiet ambient environment. Subjects were instructed to remain in a supine position with their eyes closed and not to move or say anything until prompted for a subjective sedation rating (1–4: 1 = wide awake, 2 = awake, 3 = drowsy, 4 = sedated) after the scan.

Acquisition of Positron Emission Tomography Data

Positron emission tomography measurements were performed using a Siemens 951 R/31 PET scanner (CTI, Knoxville, TN) in a three-dimensional mode with a total axial field of view of 10.5 cm and no interplane dead space. The patients' heads were positioned parallel to the canthomeatal line with the primary sensorimotor cortex covered within the field of view. Attenuation was corrected using a transmission scan (two-dimensional) with an external $^{68}Ge/^{68}Ga$ ring source obtained before the tracer injection. A semibolus of 7 mCi ^{15}O-water was administered intravenously *via* a second intravenous line in a left antecubital vein over 35 s using an infusion pump (Harvard Apparatus SP22, South Natick, MA). The PET scan was initiated when the tracer bolus entered the brain, as indicated by an abrupt increase in the coincidence-counting rate of the tomograph.[18] After correction for randoms, dead time, and scatter, images were three dimensionally reconstructed by filtered back-projection with a Hanning filter (cutoff frequency, 0.4 cycles per projection element), resulting in 31 slices with a 128 × 128 pixel matrix (pixel size, 2.0 mm) and interplane separation of 3.375 mm.

Statistical Analysis

For observer-independent determination of changes in rCBF, images were analyzed by statistical parametric mapping (SPM96, Wellcome Department of Cognitive Neurology, Institute of Neurology, University College London, London, United Kingdom). The emission scans were intra-individually realigned before transformation into a standard stereotactic space.[19] As a final preprocessing step, the images were smoothed using an isotropic gaussian kernel (12-mm full width at half-maximum).[20] Analysis of covariance (subject-specific) global normalization was used to adjust for intersubject and interscan variability in tracer count. Categoric comparisons were performed between control *versus* low and low *versus* moderate doses. Further data analysis included a regression analysis (Pearson) of the dose-dependent regional effects of remifentanil on rCBF. Correlation coefficients were transformed to z scores by a Fisher transformation. The resulting foci of significant differences were characterized in terms of peak height (μ, z score) at voxel level

Table 1. Systemic Hemodynamic Parameters, Respiratory Values, and Sedation Score

Parameter	Control (Saline)	Low (0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$)	Moderate (0.15 $\mu g \cdot kg^{-1} \cdot min^{-1}$)
Syst BP (mmHg)	122 ± 6.7	141 ± 22.3	142 ± 22.9
Dia BP (mmHg)	71 ± 4.8	67.7 ± 12.2	68.6 ± 15.1
MABP (mmHg)	88 ± 2.7	88.7 ± 16.4	91 ± 15.8
HR (beats/min)	67 ± 9.0	68.2 ± 6.3	71.4 ± 10.9
Capillary P_{CO_2} (mmHg)	43 ± 1.0	42 ± 1.1	41 ± 1.0
End-tidal CO_2 (mmHg)	42.4 ± 2.1	43.1 ± 4.0	39.8 ± 4.4
Oxygen saturation (%)	97.6 ± 0.8	97.9 ± 2.0	97.7 ± 1.3
Sedation rating	2.2 ± 0.5	3.0 ± 0.6	3.5 ± 0.7

Data are presented as mean ± SD, paired *t* test, $P < 0.05$ only for sedation rating between each condition.

Syst BP = systolic blood pressure; Dia BP = diastolic blood pressure; MABP = mean arterial blood pressure; HR = heart rate; P_{CO_2} = partial pressure of carbon dioxide.

and combined μ and extent (κ, number of voxels) at cluster level. Correction for multiple nonindependent comparisons was performed, and significance level was defined at $P < 0.05$. For predefined brain structures, the corrected threshold (peak height, three-dimensional Hammersmith) was calculated taking into account the volume of search pixels and the smoothness (13.9-mm full width at half-maximum). The predefined structures were selected from brain areas with high opioid receptor binding capability[10] and with previously reported response to a single dose of fentanyl[11]: anterior cingulate cortex, thalamus, anterior striatum, anterior insula, and the periventricular grey of the brainstem, including the periaqueductal grey (PVG). These regions comprised a volume of approximately 60 ml according to the grid system of Talairach, and correspond to a z score of 3.2 ($P = 0.0006$). For all analyses, the cluster extent threshold was set at a minimum of 25 voxels (uniform voxel size of 2 mm), passing the adjusted threshold of $P = 0.0006$. Sedation ratings were analyzed using a two-tailed paired *t* test ($P < 0.05$).

Results

Systemic hemodynamic and respiratory values are presented in table 1. Systolic blood pressure, diastolic blood pressure, mean arterial blood pressure, and heart rate were unchanged within and across the groups (unpaired *t* test, $P > 0.05$). Similarly, respiratory parameters including capillary carbon dioxide, end-tidal carbon dioxide, and oxygen saturation were not different between groups. Subjective sedation ratings indicated a significant increase in sedation from control to low dose ($P = 0.007$) and a further significant increase from the low to moderate condition ($P = 0.01$).

Categoric Comparisons of Regional Cerebral Blood Flow

Control *versus* Low. Results are summarized in table 2 and figure 1. The uncorrected *P* value is < 0.001 for all regions. Accentuated increases in relative rCBF were observed in the right lateral prefrontal cortex and were separable into three clusters at a more stringent threshold of $P = 0.0001$. Increases in the left frontal cortex, in inferior parietal cortices, and in supplementary motor area (SMA) were less pronounced. Marked relative decreases in rCBF were observed in the basal part of the mediofrontal cortex, the cerebellum (vermis and right lateral part), and the rostromedial part of the left superior temporal lobe. The right mesial temporal lobe showed a similar decrease in rCBF slightly below the significance threshold. Within the predefined volume, there was a significant decrease in rCBF in the rostral PVG (z coordinate = −8 to 0; y coordinate = −30 to −20).

Low *versus* Moderate. Results are summarized in table 3 and figure 2. The uncorrected *P* value is < 0.001 for all regions. From low to moderate remifentanil doses, increases in relative rCBF were dominant in the mediofrontal and anterior cingulate cortices simultaneous to increases in an occipital area comprising the lingula and the transition zone between posterior cingulate cortex, precuneus, and cuneus. Furthermore, an increase in relative rCBF was identified in the caudal PVG (z coordinate = −16 to −8; y coordinate = −20 to −30). A reduction in relative rCBF was observed bilaterally in the inferior parietal lobes.

Including the data of the three volunteers who underwent only low and moderate conditions in the analysis provided consistent results. The mediofrontal and anterior cingulate cortices as well as the occipital transition area clearly passed the probability threshold. The cluster in the PVG extended into the thalamus (z score = 4.91, x, y, z coordinates = 10, −20, 6). Reductions in relative rCBF in parietal cortices were also observed.

Correlation Analysis

Results are summarized in table 4 and figure 3. Significant positive correlations between remifentanil doses and relative rCBF were found in the left medial prefrontal gyrus, including the rostral part of the perigeniculate part of the anterior cingulate gyrus, the right lateral prefrontal cortex, the cuneus–cingulate transition, the

Table 2. Categorical Comparison of rCBF: Control *versus* Low

Region	BA	Coordinates (x/y/z)	Peak *z* Value	Corrected *P* Value	Cluster Extension	Cluster Level
Increases						
Right LPFC	44/45	60/20/18	5.96	< 0.001	4,381	< 0.001
	8	24/44/40	5.81	< 0.001		
	45	60/24/8	5.75	< 0.001		
Left premotor	6	−30/−4/46	5.45	0.001	1,067	< 0.001
Left LPFC	10	−26/50/20	4.54	0.045	117	0.055
Right LPi	39	30/−54/36	4.52	0.047	540	0.002
Left LPi	39	−32/−60/36	5.43	0.001	853	< 0.001
SMA	6	2/0/62	4.33	0.097	390	0.007
Decreases						
GFm	11	−4/38/−14	5.19	0.002	268	0.005
Left GTs	34/38	−40/8/−14	5.00	0.006	158	0.110
Cerebellum		−6/−52/−18	4.63	0.030	68	0.040
		46/−70/−20	5.10	0.063	98	0.007
PVG		2/−28/0	3.61	0.705*	25	0.693

The probabilistic threshold used to identify the regions was $P = 0.0006$ for peak *z* value and 25 voxels for cluster extension. Cluster extensions are in number of voxels (uniform voxel size of 2 mm). Uncorrected and corrected *P* values (for multiple comparisons, $P < 0.05$) correspond to the peak *z* values. *P* values at cluster level are corrected for multiple comparison and thresholded at $P < 0.05$.

* Result is significant corrected for multiple corrections within the volume of predefined structures (threshold, $z = 3.2$) but not for whole brain volume.

BA = Brodmann area; LPFC = lateral prefrontal cortex; LPi = inferior parietal lobe; SMA = supplementary motor area; GFm = medial frontal gyrus; GTs = superior temporal gyrus; PVG = periventricular grey.

lingula, and the right medial temporal gyrus. The only significant negative relation indicating a reduction in rCBF across the three dosage levels of remifentanil was observed in the fusiforme gyrus.

Discussion

The current study investigated dose-dependent changes in relative rCBF in different brain areas after administration of the μ-selective opioid agonist remifentanil in healthy volunteers. Main findings were alterations of relative rCBF within structures involved in pain processing and dose-dependent changes in structures previously described to participate in modulation of vigilance and alertness.

The rCBF responses to remifentanil are within the widespread network associated with pain processing,[5] demonstrating predominant effects in the opioid receptor–dense medial pain system.[9] These findings are in agreement with the common clinical observation of a reduced intensity and emotional response to pain (medial pain system) but unaffected localization of a painful stimuli (lateral pain system) after synthetic opioid administration. In the current study, the anterior cingulate cortex was involved significantly at moderate doses (fig. 2). A positive response after increasing doses was con-

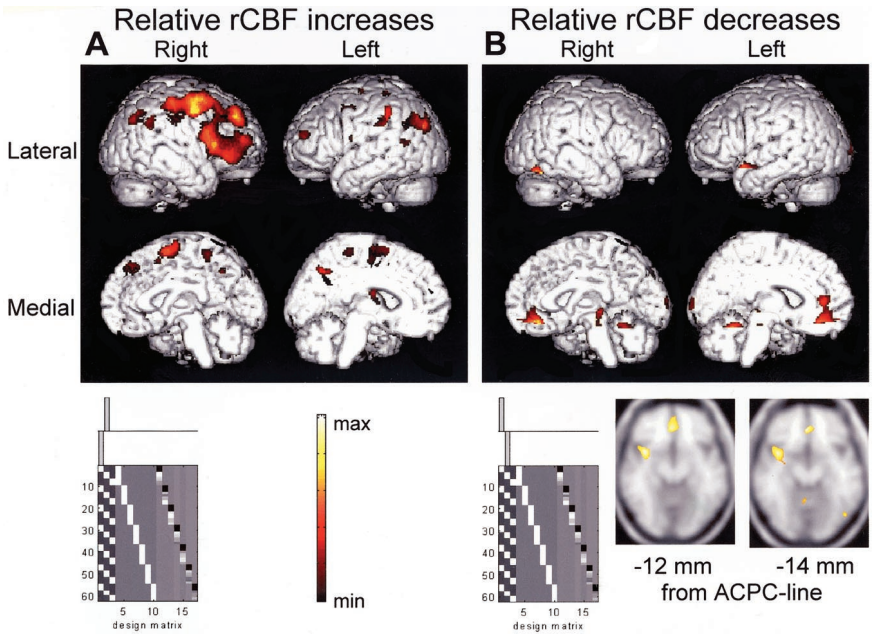

Fig. 1. Relative regional cerebral blood flow (rCBF) increases (*A*) and decreases (*B*) comparing control and low-dose conditions. (*Top*) The relative rCBF increases (*A*) to the left and decreases (*B*) to the right are displayed on a magnetic resonance image surface rendering. The rCBF decreases are complemented with transaxial slices at the level of the superior temoral gyrus to illustrate changes not observed on the surface projections. (*Bottom*) The design matrices of the general linear model used to partition the data (seven blocks corresponding to seven subjects, and seven blocks consisting of nine effects with global activity as covariate of no interest). Threshold was set at $P = 0.0006$ for peak *z* values and a minimum of 25 voxels in extension. Color code identifies rCBF increases (from minimum to maximum scores) or decreases (from minimum to maximum scores) during the low dose in comparison to control (values in table 2). ACPC = anterior commissure posterior commissure.

Table 3. Categorical Comparison of rCBF: Low *versus* Moderate

Region	BA	Coordinates (x/y/z)	Peak *z* Value	Corrected *P* Value	Cluster Extension	Cluster Level
Increases						
ACC/GFm	24/32/10	−10/42/10	6.35	< 0.001	2,078	< 0.001
Cuneus/PCC/Lingula	18/19/31	26/−90/24	5.57	< 0.001	3,295	< 0.001
		12/−72/18	5.55	< 0.001		
		−18/−60/0	5.32	0.001		
PVG		4/−26/−14	4.09	0.219*	55	0.240
ACC	24	−4/8/34	4.04	0.254*	314	0.014
Decreases						
Left LPi	40	−58/−40/50	5.27	0.002	420	0.004
Right LPi	40	58/−48/50	5.23	0.002	434	0.005

The probabilistic threshold used to identify the regions was $P = 0.0006$ for peak z value and 25 voxels for cluster extension. Cluster extensions are in number of voxels (uniform voxel size of 2 mm). Uncorrected and corrected P values (for multiple comparisons, $P < 0.05$) correspond to the peak z values. P values at cluster level are corrected for multiple comparison and thresholded at $P < 0.05$.

* Result is significant corrected for multiple corrections within the volume of predefined structures (threshold, $z = 3.2$) but not for whole brain volume.

BA = Brodmann area; ACC = anterior cingulate cortex; GFm = medial frontal gyrus; PCC = posterior cingulate cortex; PVG = periventricular grey; LPi = inferior parietal lobe.

firmed in the correlation analysis (fig. 3). The anterior cingulate cortex is a main target of opioid receptor–binding substances and is the region most frequently reported to be activated in pain studies.[5] It has extensive connections with the prefrontal cortex, medial thalamic nuclei, amygdala, and periventricular grey, and part of it projects to autonomic brainstem motor nuclei. The anterior cingulate cortex regulates autonomic and endocrine functions and is involved in emotional learning, emotional assessment of internal and external stimuli,[21] and encoding of the degree of pain unpleasantness and pain threshold.[4] The lateral prefrontal cortex was already activated at lower doses and did not show any further significant response when remifentanil infusion was increased. This brain area is involved in the cognitive evaluation of somatosensory stimuli and attention[6] and has been related to pain coping strategies.[7,8] The PVG was recruited with increasing opioidergic stimulation. Descending input from the limbic forebrain and diencephalon with ascending nociceptive afferents[22] are integrated in the PVG, which also controls nociceptive transmission at the level of the spinal cord.[23] Electrical stimulation of the PVG has been shown to exert analgesia related to the release of endogenous opioids.[24] This emphasizes the relevance of the present rCBF responses in the PVG and its participation in opioidergic analgesia. The positive correlation between rCBF and remifentanil doses in the temporal cortex is in agreement with earlier studies, indicating an involvement of the temporal lobe in endogenous opioid neurotransmission by changes in opioid receptor binding[25] and increased glucose metabolism in the temporal lobe in humans and monkeys during fentanyl and remifentanil administration.[26] However, exogenous auditory stimuli, such as the verbal

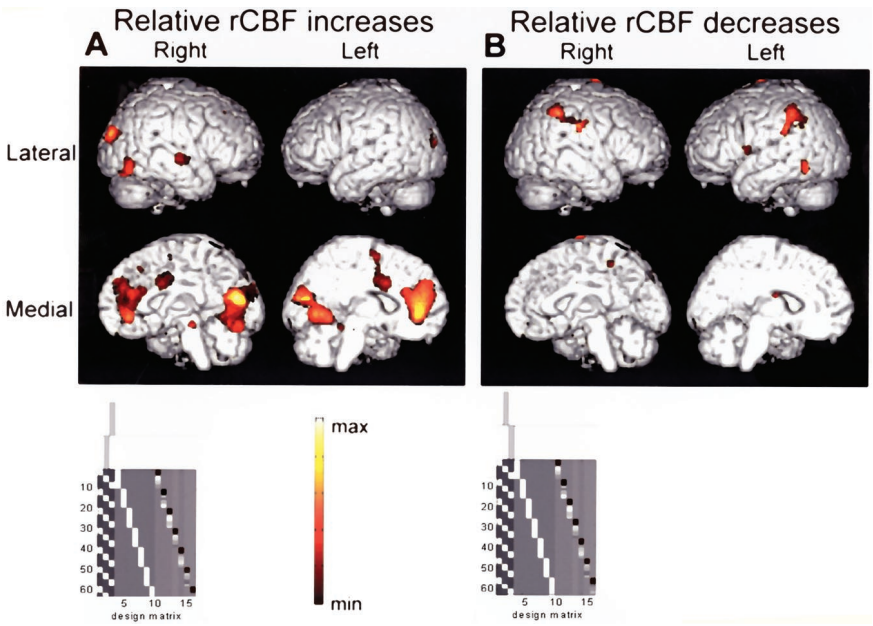

Fig. 2. Relative regional cerebral blood flow (rCBF) increases (*A*) and decreases (*B*) comparing low and moderate conditions. (*Top*) The relative rCBF increases (*A*) to the left and decreases (*B*) to the right displayed on a magnetic resonance image surface rendering. (*Bottom*) The design matrices of the general linear model used to partition the data (seven blocks corresponding to seven subjects, and seven blocks consisting of nine effects with global activity as covariate of no interest). Threshold was set at $P = 0.0006$ for peak z values and a minimum of 25 voxels in extension. Color code identifies rCBF increases (from minimum to maximum scores) or decreases (from minimum to maximum scores) during the low dose in comparison to control (values in table 3).

Table 4. Correlation Analysis Across Control, Low, and Moderate

Region	BA	Coordinates (x/y/z)	Peak *z* Value	Corrected *P* Value	Cluster Extension	Cluster Level
Positive						
Cuneus/PCC	19/31	14/−72/16	5.66	< 0.001	1,756	< 0.001
Right LPFC	8	18/30/46	5.25	0.002	575	0.002
Lingula	18/19	−18/−66/2	4.94	0.007	1,109	< 0.001
		−14/−52/−2	4.72	0.020		
SMA	6	−4/−2/62	4.81	0.013	1,180	< 0.001
ACC/GFm	24/32/10	−12/44/26	4.74	0.018	1,377	< 0.001
Right GTm	21	66/−6/−6	4.68	0.023	240	0.032
Negative						
Fusiforme	37	−52/−54/−16	4.69	0.022	239	0.031

The probabilistic threshold used to identify the regions was $P = 0.0006$ for peak *z* value and 25 voxels for cluster extension. Cluster extensions are in number of voxels (uniform voxel size of 2 mm). Uncorrected and corrected *P* values (for multiple comparisons, $P < 0.05$) correspond to the peak *z* values. *P* values at cluster level are corrected for multiple comparison and thresholded at $P < 0.05$.

BA = Brodmann area; PCC = posterior cingulate cortex; LPFC = lateral prefrontal cortex; SMA = supplementary motor area; ACC = anterior cingulate cortex; GFm = medial frontal gyrus; GTm = medial temporal gyrus.

command for respiration, may have induced the observed increases in rCBF close to the primary auditory cortex.[27] Based on the fundamental relation of stimulus frequency and activation level, it is improbable that a significant auditory activation measurable by PET can be induced by a single short verbal command during the 50-s acquisition period.[28] However, it cannot be completely ruled out that attention may be modified by verbal commands.

A marked increase in relative rCBF during opioid administration was observed in the transition zone of the medial part of the occipital lobe, which has not been reported previously. Rainville *et al.*[29] identified a specific pattern of cerebral activation associated with an experimental induced hypnotic state. The change from restful awake to a state with general relaxation, automatic responding, and slight disorientation in time corresponded to increases in occipital rCBF and an increase in occipital delta activity in the electroencephalogram. Likewise, conditions with altered states of consciousness, such as meditation[30] and sleep,[31] are associated with an rCBF increase in the same brain area and may be related to the sedation and decreased arousal common to these states.

The sites of action of opioids in the human brain were first described by Jones *et al.*[13] in a case report using morphine for a patient suffering chronic pain from a carcinoma. Firestone *et al.*[11] later examined the rCBF responses to a single dose of fentanyl in healthy subjects with similar results to our study using remifentanil. Adler *et al.*[12] investigated the interaction of repeated boli of fentanyl and painful stimuli on rCBF. These results were only partly consistent with their previous report[11] and our data. The differences probably reflect the residual effects of warm and painful stimuli applied simultaneously with fentanyl. Repeated boli of fentanyl are unlikely to provide a steady state opioid plasma level as

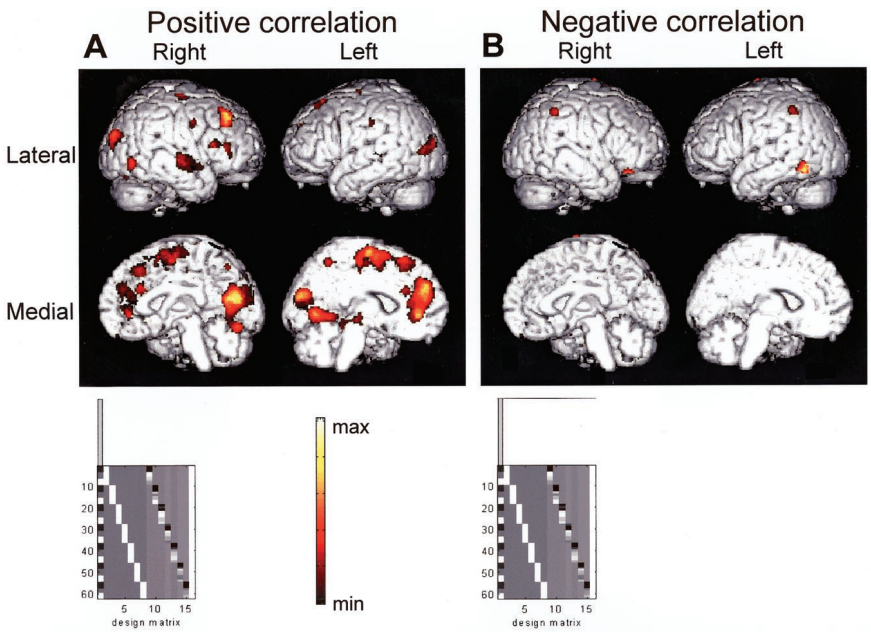

Fig. 3. Positive (*A*) and negative (*B*) correlations between relative regional cerebral blood flow (rCBF) and remifentanil doses. (*Top*) The significant positive (*A*) and negative (*B*) correlations displayed on a magnetic resonance image surface rendering. (*Bottom*) The design matrices of the general linear model used to partition the data (seven blocks corresponding to seven subjects, and seven blocks consisting of nine effects with global activity as covariate of no interest). Threshold was set at $P = 0.0006$ for peak *z* values and a minimum of 25 voxels in extension. Color code identifies positive (from minimum to maximum scores) and negative (from minimum to maximum scores) correlations between relative rCBF and remifentanil doses across all individuals and conditions (values in table 4).

we could expect in our study. Adler *et al.*[12] used a very low significance level ($P < 0.01$, $z > 2.5$), whereas we used stricter thresholds with correction for multiple comparisons, which explains some of the different results (see Statistical Analysis, lowest threshold for *a priori* defined areas: $k \geq 25$ voxels, $P < 0.0006$, $z > 3.2$).

The observed pattern of rCBF changes most likely reflects the agonist actions of remifentanil on neuron-located presynaptic or postsynaptic opioid receptors,[32] resulting in an increased synaptic energy demand independent of the excitatory or inhibitory function of the neuron.[33] Opioid receptor stimulation is generally believed to suppress brain activity,[34] which results in a reduced rCBF. However, net changes in rCBF reflect local and remote synaptic activity as well as interaction with other cell assemblies. A direct action of remifentanil on opioid receptors on cells of the cerebrovascular bed is another possible explanation for the observed alterations in rCBF. Activation of different opioid receptor subtypes by morphine may result in changes of cerebral vascular resistance.[35] A variety of factors (*e.g.*, adenosine, nitric oxide, cardiorespiratory parameters) are known to profoundly influence CBF.[36] In the current study, no significant systemic cardiovascular changes occurred during low and moderate remifentanil infusion (table 2). Thus, these factors are unlikely to be responsible for the observed relative rCBF changes. Probably the most important reason for stable systemic hemodynamics was the constant infusion rate of remifentanil instead of a bolus administration.[37] Because changes in arterial carbon dioxide partial pressure ($Paco_2$) can substantially alter rCBF, volunteers' normocapnia (table 2) was maintained by identical verbal command for respiration during every condition investigated. Corfield *et al.*[38] detected limbic system activation during carbon dioxide breathing similar to the activation observed in our study. Their results likely reflect motor-related influences on breathing or uncomfortable sensations associated with carbon dioxide values of up to 50 mmHg. We relied on real-time capnography in addition to capillary blood gas monitoring to ensure $Paco_2$ concentrations within the physiologic range. On the premises of a relatively constant tidal volume and a constant alveolar dead space, there is a consistent correlation between end-tidal carbon dioxide and $Paco_2$.[39] Factors that can alter the end-tidal carbon dioxide–$Paco_2$ relation (*e.g.*, chest wall rigidity, artificial ventilatory support) were not present in our study. From this we conclude that alterations in $Paco_2$ were not a reason for potential changes in global CBF and were unlikely responsible for the observed alterations in relative rCBF. Kofke *et al.*[26] demonstrated an absolute increase in brain activity in the temporal lobe after opioid administration, supporting our interpretation that the relative increases in rCBF reflect an absolute increase in rCBF. Finally, even if CBF was globally reduced, brain regions with a relative increase would still be at least "relatively resistant" to the global effects and *vice versa*.

According to a pilot study, 0.15 $\mu g \cdot kg^{-1} \cdot min^{-1}$ remifentanil was used, which provides moderate intraoperative analgesia in a variety of clinical settings.[40,41] Pharmacodynamic opioid effects observed in the present study (table 1) correspond with mood effects and side effects obtained in other studies of healthy volunteers using full and partial μ-agonist opioids, *e.g.*, fentanyl and morphine.[42,43] The semi-randomized study protocol (see Methods) may affect our results but avoids carryover effects and was necessary because psychomotor effects still may be apparent 60 min after termination of remifentanil infusion.[44] The dose–response curve of remifentanil beyond the given doses is of interest because high doses of opioids may not actually produce more analgesia but can produce epileptiform activity and neuropathologic lesions.[45] Defining this therapeutic window may result in an efficient use of opioids and indicate the necessity of administration of other anesthetics or vasoactive drugs to reduce risks of overdosage and delayed recovery.

In conclusion, this study identifies regional specific changes of relative rCBF after intravenous administration of remifentanil. The study provides the first human data on the rCBF response pattern to different doses of an opioid. The rCBF responses to remifentanil share a common network with pain-processing brain areas. Further investigation is needed to verify if increasing doses of other μ-agonists act in the same way.

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