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Local Cerebral Blood Flow with Fentanyl-Induced Seizures

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Summary: Local cerebral blood flow (LCBF) was evaluated with the [^{14}C]iodoantipyrine quantitative autoradiographic technique in 29 brain structures in conscious control rats and during fentanyl-induced electroencephalographic (EEG) spike and/or seizure activity and in the postseizure EEG suppression phase. During spike activity, LCBF increased in all structures; the increase reached statistical significance ($p < 0.05$) in the superior colliculus, sensorimotor cortex, and pineal body (+130%, +187%, and +185% from control, respectively). With progressive development of seizure activity, LCBF significantly increased in 24 brain structures (range, +58% to +231% from control). During the postseizure EEG suppression phase, LCBF remained elevated in all structures (+80% to +390% from control). The local cerebrovascular resistance (LCVR) significantly decreased in 10 of 29 structures with the onset of spike activity (range, −24% to −64%), and remained decreased in all brain structures during seizure activity (range, −34% to −67%) and during the EEG suppression phase (range, −24% to −74%). This reduction of LCVR represents a near maximal state of cerebrovasodilation during fentanyl-induced EEG seizure or postseizure suppression activity. The global nature of the LCBF elevation indicates that factors other than local metabolic control are responsible for CBF regulation during local seizure activity. **Key Words:** Autoradiography—Cerebrovascular resistance—Fentanyl—Local cerebral blood flow—Seizures.

High-dose narcotic anesthesia can elicit seizure activity in laboratory animals as well as under clinical conditions (De Castro et al., 1979; Sebel et al., 1981; Bovill et al., 1982; Rao et al., 1982). In a recent report, the increase in brain oxygen uptake due to fentanyl-elicited convulsive activity was not matched by an equivalent compensatory elevation in overall CBF (Carlsson et al., 1982). This finding suggests that cerebral ischemia could result due to uncoupling of the normal relationship of CBF to cerebral metabolic rate (CMR). Quantitative autoradiographic studies of local cerebral metabolic rate for glucose ($LCMR_{glu}$) during fentanyl-induced seizures indicate that a localized and heterogeneous response occurs (Tommasino et al., 1984). In this light, further understanding of the CBF response to narcotic-induced seizures requires study of the localized flow response in various structures and regions of the brain.

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Abbreviations used: CMR, Cerebral metabolic rate; LCBF, local cerebral blood flow; $LCMR_{glu}$, local cerebral metabolic rate for glucose; LCVR, local cerebrovascular resistance.

METHODS

Local cerebral blood flow (LCBF) was measured in 23 Sprague-Dawley rats with the [^{14}C]iodoantipyrine quantitative autoradiographic technique (Reivich et al., 1969; Sakurada et al., 1978). The rats weighed 289 ± 20 g (mean ± SD) and were studied while conscious and during fentanyl administration, resulting in electroencephalographic (EEG) patterns consisting of spike, seizure, and postseizure suppression activity.

Fentanyl-treated animals

The rats were briefly anesthetized with 1.5% halothane and 70% nitrous oxide in oxygen to permit tracheostomy and femoral vessel cannulation of both arteries and veins with PE-50 polyethylene catheters. This vascular access

was used for arterial blood pressure monitoring, venous administration of drugs, infusion of [^{14}C]iodoantipyrine, and rapid intermittent sampling of arterial blood for isotope counting. All incision sites were infiltrated with bupivacaine (0.3 ml of 0.25% solution), and the halothane was discontinued for at least 1 h prior to fentanyl infusion.

Mechanical ventilation was accomplished with a rodent ventilator (Harvard) and facilitated by muscle relaxation obtained with pancuronium bromide (0.2 mg i.v. every 20 min). Heparin (200 IU) was administered to prevent catheter clotting, and rectal temperature was servo-controlled to 37°C with a heating lamp. The electrocardiogram (EKG) and EEG (biparietal needle electrode leads with a gain of 50 μV/cm) were recorded with a Beckman Accutrace® polygraph.

During the stabilization period the ventilator was adjusted to obtain the desired arterial blood gas composition; this was verified by a blood gas determination (Radiometer BMS3-MK2, using 100-μl capillary samples) just prior to fentanyl administration. Nitrous oxide was replaced by 70% nitrogen, and fentanyl was infused at a rate of 10 μg/kg/min to obtain the EEG pattern during which LCBF was measured. Table 1 indicates the fentanyl doses and elapsed infusion times required to obtain the desired EEG configuration. Figure 1 shows the typical EEG patterns that were studied. The following definitions of EEG activity were used: (1) spike, three to five isolated high-voltage discharges per minute superimposed over a lowered frequency; (2) seizure, continuous high-voltage bursts of spike-like discharges (average burst duration, 15 ± 6 s; mean ± SD; (3) suppression, very low-voltage frequency activity with not more than one spike per second occurring after seizure activity. The EEG was continuously monitored during fentanyl infusion, and LCBF was measured as soon as possible after the desired pattern was established. Over the 30-s period of LCBF measurement, animals developing EEG patterns not consistent with our definitions were discarded from further study. Prevailing physiologic conditions were the same for all groups during the LCBF measurement, as indicated in Table 2.

Control group

The conscious group was acclimatized to a Plexiglas restraining cage for at least 4 h/day over a 7-day period, and the same restraining protocol was maintained during LCBF determination. Anesthesia and surgical preparation were the same as for the fentanyl groups, except that tracheostomy was omitted. The EKG and EEG were not recorded, and the animals recovered from anesthesia in the cage for at least 2 h prior to LCBF measurement. During this stabilization period they had free access to food and water.

TABLE 1. *Fentanyl dosage and time required to obtain the desired electroencephalographic pattern*

Parameter	Spike (n = 6)	Seizure (n = 6)	Suppression (n = 5)
Fentanyl total dosage (μg/kg)	89 ± 16	213 ± 83	197 ± 86
Elapsed infusion time (min)	8.4 ± 1.2	18.4 ± 5.7	18.1 ± 7.0

Administration rate, 10 μg kg^{-1} min^{-1}. Values are means ± SD.

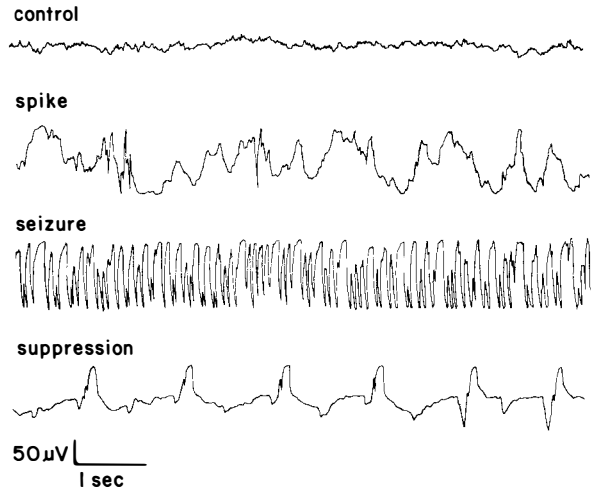

FIG. 1. Representative electroencephalograms (EEG) during the experimental procedure. Control EEG was obtained during 70% N_2O anesthesia, before fentanyl administration. EEG during spike, seizure, and suppression activity were recorded during LCBF measurements.

LCBF quantitative autoradiography

Upon establishment of a characteristic EEG pattern, 75 μCi/kg of [^{14}C]iodoantipyrine (40–60 mCi/mmol in ethanol; New England Nuclear, NEC-712) dispensed in 1.0 ml of normal saline solution (0.9%) was infused at a constant rate for 30 s. During the infusion period, 16–18 arterial blood samples (20 μl) were discontinuously collected from a low, dead-space arteriovenous shunt catheter for determination of arterial isotope activity by liquid scintillation counting (Nuclear-Chicago, ISOCAP 300). The rat was decapitated at the end of the isotope infusion period, and the brain was rapidly removed and frozen in 2-methyl-butane cooled to −41°C with Freon 22.

The brain was sectioned in a cryostat (−20°C), and the 20-μm sections were rapidly dried on a hot plate (60°C) and subsequently exposed, along with six [^{14}C]methyl methacrylate calibrated standards, to a single-emulsion X-ray film (Kodak SB-5) for 11 days. Following film development, optical densities were determined with an auto-scanning densitometer (Optronics, P-1000, International, Inc.) with an aperture of 200 μm, and all data were collected on-line with a Prime computer for calculation of LCBF according to the equation of Reivich et al. (1969), as modified by Sakurada et al. (1978).

TABLE 2. *Physiological conditions for control and fentanyl-treated animals during local cerebral blood flow measurements*

Parameter	Control (n = 6)	Spike (n = 6)	Seizure (n = 6)	Suppression (n = 5)
$P_{a}O_2$ (mm Hg)	109 ± 18	109 ± 13	108 ± 13	116 ± 15
$P_{a}CO_2$ (mm Hg)	36.7 ± 2.9	36.5 ± 2.4	36.0 ± 2.0	37.5 ± 2.3
pH_a	7.40 ± 0.03	7.41 ± 0.04	7.41 ± 0.04	7.41 ± 0.04
MABP (mm Hg)	128 ± 12	131 ± 9	139 ± 11	147 ± 9
Hct (%)	42 ± 1	45 ± 1	45 ± 2	44 ± 3

Values are means ± SD. No significant differences were found between groups. MABP, mean arterial blood pressure; Hct, hematocrit.

Statistical analysis

Differences between groups, with respect to physiologic parameters, were evaluated by one-way analysis of variance (ANOVA, F ratio), followed by the Newman-Keuls test where appropriate (Zar, 1974). Since the LCBF could not be assumed to be normally distributed, differences between groups were tested for by the Kruskal-Wallis analysis of variance, and pairwise comparisons between groups were assessed by the Nemenyi test (unequal sample size) (Miller, 1966). A p value less than 0.05 was considered significant.

RESULTS

Typical autoradiograms obtained during the different EEG stages evoked by fentanyl administration are shown in Fig. 2. LCBF was measured in 29 brain structures and areas; these results are tabulated in Table 3, which is arranged according to brain functional systems. For illustrative purposes, Fig. 3A indicates the percent changes in LCBF from the control state in 11 areas. In many structures there was a trend for LCBF to become progressively elevated, parallel with the sequentially emerging EEG changes associated with fentanyl administration. During spike activity, LCBF increased in all structures; however, this elevation was statistically significant only in the superior colliculus, sensorimotor cortex, and pineal body. The LCBF increases in these structures averaged 130%, 187%, and 185% from control, respectively. With onset of seizures LCBF was significantly increased in all but five structures. Throughout the brain, the seizure-related LCBF increase ranged from 58% from control in the superior colliculus to a high of 231% in the hypothalamus. During postseizure EEG suppression, LCBF remained elevated in all structures. This change ranged from 80% in the cerebellar white matter to over 350% in the septal nucleus, hippocampus, and hypothalamic areas. A modest change in the structure distribution of statistically significant increases from control occurred. In the suppression phase the LCBF in six structures, although elevated, was not significantly different from control values. Also, no significant differences (Nemenyi test) were noted among the spike, seizure, and suppression groups.

The mean arterial blood pressure increased from control values by 3, 11, and 19 mm Hg for the spike, seizure, and suppression groups, respectively. To normalize the influence of these arterial pressure increases on LCBF, the local cerebrovascular resistance (LCVR) was calculated (Table 4), and the LCVR of representative structures, expressed as percent change from control, are shown in Fig. 3B. With the onset of spike activity the LCVR decreased in all surveyed structures; however, the decrease was significant only in 10 of 29 structures surveyed. As the EEG pattern progressed to seizures, only the auditory, visual, and sensorimotor cortices and the superior collicus did not register a significant reduction in LCVR. During EEG post-

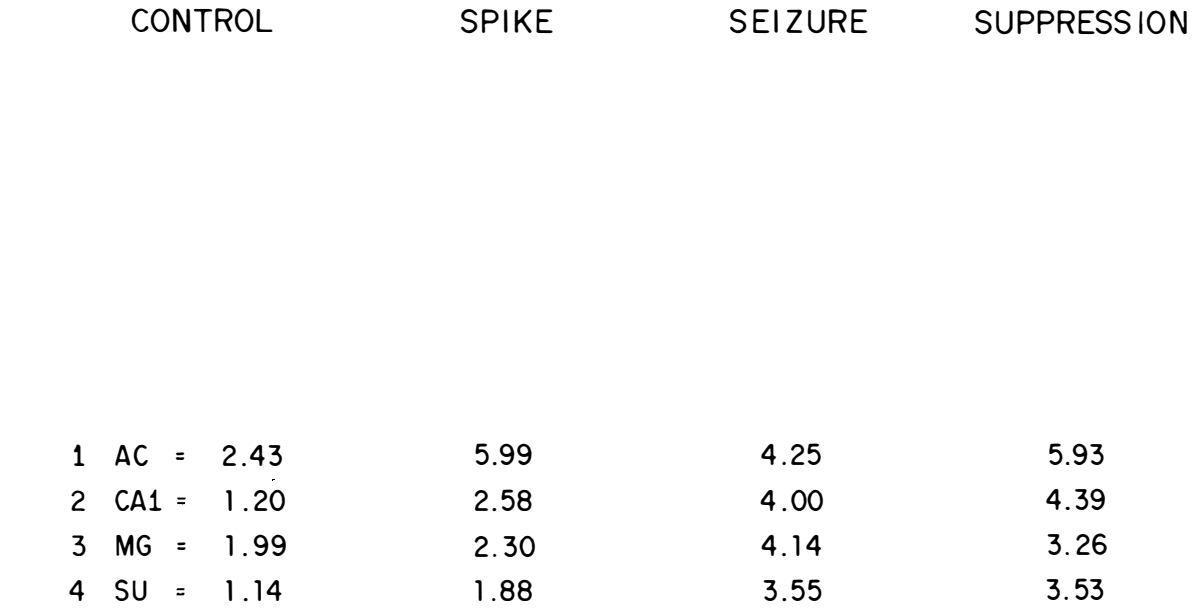

FIG. 2. Representative autoradiograms of corresponding brain sections at the level of the hippocampus from a control rat and during fentanyl-induced spike or seizure or postseizure suppression EEG activity. The local cerebral blood flow values (ml g^{-1} min^{-1}) were measured in the animals' brains shown above. AC, auditory cortex; MG, medial geniculate; SU, substantia nigra; CA1, hippocampus.

TABLE 3. *Local cerebral blood flow (ml g^{-1} min^{-1}) during high doses of fentanyl in rats*

Region	Control (n = 6)	Spike (n = 6)	Seizure (n = 6)	Suppression (n = 5)
Auditory system				
Cortex	2.15 ± 0.43	4.01 ± 1.51	3.53 ± 0.72	4.06 ± 1.38
Medial geniculate	1.60 ± 0.32	2.64 ± 0.73	2.82 ± 0.81	3.47 ± 0.82[b]
Inferior colliculus	2.15 ± 0.36	4.77 ± 1.06	4.88 ± 1.12[a]	5.29 ± 1.10[a]
Visual system				
Cortex	1.61 ± 0.43	3.25 ± 0.78	3.16 ± 1.08	3.60 ± 1.16[a]
Lateral geniculate	1.25 ± 0.37	2.35 ± 0.91	3.80 ± 1.65[a]	2.73 ± 0.90
Superior colliculus	1.44 ± 0.42	3.31 ± 1.21[a]	2.28 ± 0.44	3.32 ± 1.23[a]
Sensorimotor system				
Sensorimotor cortex	1.59 ± 0.32	4.56 ± 2.08[a]	3.94 ± 1.65	4.59 ± 1.63[a]
Thalamus				
Ventral nucleus	1.48 ± 0.40	1.88 ± 0.23	3.35 ± 1.01[a]	4.77 ± 2.41[a]
Dorsomedial nucleus	1.43 ± 0.39	1.87 ± 0.37	3.34 ± 1.34[a]	3.17 ± 1.01[a]
Periventricular gray	1.04 ± 0.22	2.13 ± 0.60	2.33 ± 0.52[a]	2.80 ± 1.18[a]
Cerebellar gray	1.05 ± 0.24	2.25 ± 0.59	2.86 ± 1.28[a]	2.60 ± 1.24
Extrapyramidal system				
Caudate-putamen	1.10 ± 0.15	2.36 ± 0.98	2.90 ± 1.14[a]	3.73 ± 1.71[a]
Globus pallidus	0.88 ± 0.14	1.22 ± 0.21	2.19 ± 0.93[a]	2.77 ± 1.61[a]
Substantia nigra	0.92 ± 0.18	2.09 ± 0.77	2.46 ± 0.85[a]	2.77 ± 0.76[a]
Limbic system				
Claustrum	0.94 ± 0.13	1.80 ± 0.66	2.36 ± 1.11[b]	3.09 ± 1.76[a]
Septal nucleus	1.11 ± 0.25	1.98 ± 0.41	3.43 ± 0.82[a]	5.44 ± 1.94[b]
Piriform cortex	0.87 ± 0.15	1.51 ± 0.27	1.95 ± 0.79[a]	2.27 ± 1.05[a]
Amygdala	0.85 ± 0.15	1.42 ± 0.35	2.52 ± 1.46[a]	3.48 ± 1.59[b]
Hypothalamus	0.95 ± 0.26	1.49 ± 0.24	3.15 ± 0.97[b]	4.34 ± 1.92[b]
Hippocampus (CA1)	1.11 ± 0.27	2.54 ± 0.59	3.63 ± 0.91[a]	4.16 ± 1.59[b]
Dentate gyrus (CA3)	1.03 ± 0.25	2.10 ± 0.41	3.11 ± 0.87[a]	3.87 ± 2.46[a]
Ventral area (CA1–CA3)	1.23 ± 0.37	3.22 ± 0.70	4.01 ± 1.04[a]	5.58 ± 1.70[b]
Interpeduncular nucleus	1.54 ± 0.38	3.30 ± 0.90	3.67 ± 0.97[a]	3.81 ± 2.04
Myelinated fiber tracts				
Corpus callosum	0.53 ± 0.10	0.97 ± 0.41	1.06 ± 0.30[a]	1.00 ± 0.35
Internal capsule	0.49 ± 0.08	0.81 ± 0.13	1.07 ± 0.28[a]	1.13 ± 0.44[a]
Cerebellar white	0.55 ± 0.04	0.89 ± 0.34	0.99 ± 0.14[b]	0.99 ± 0.47
Cerebral association area				
Frontal cortex	1.50 ± 0.24	3.94 ± 1.67	4.63 ± 1.95[a]	4.45 ± 1.03[a]
Reticular formation	0.84 ± 0.13	1.74 ± 0.33	2.11 ± 0.49[a]	2.07 ± 0.72[a]
Pineal body	0.98 ± 0.27	2.79 ± 0.69[c]	2.84 ± 0.97[c]	3.11 ± 0.32 (n = 3)

Values are means ± SD obtained in numbers of animals in parentheses.

Significance determined using Kruskal-Wallis analysis of variance and Nemenyi test where appropriate: [a]$p < 0.05$, [b]$p < 0.01$, [c]$p < 0.001$ from control.

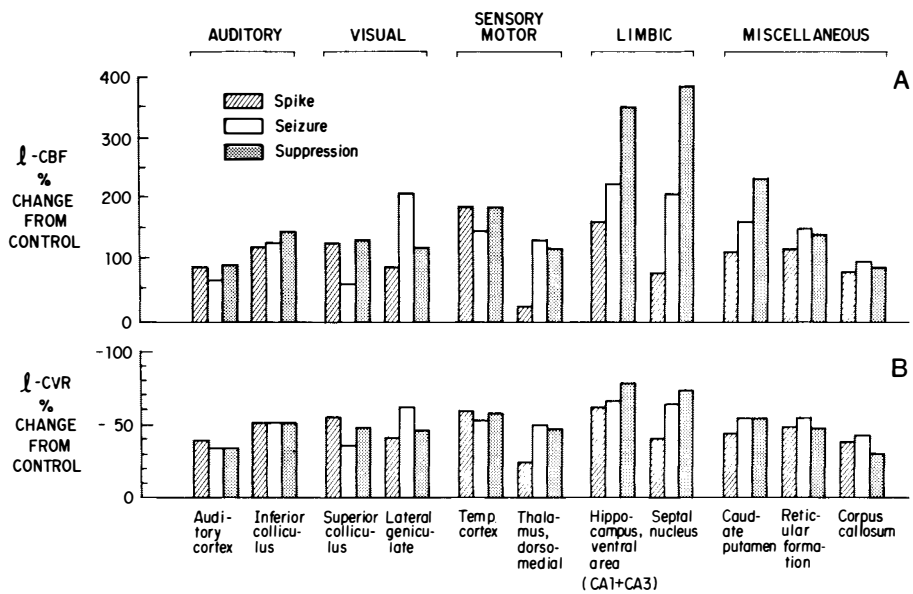

FIG. 3. Percent change from control of **(A)** local cerebral blood flow (l-CBF) and **(B)** local cerebrovascular resistance (l-CVR) of representative brain structures. (See Tables 3 and 4 for statistical differences between groups.)

TABLE 4. *Local cerebrovascular resistance (mm Hg/ml 100 g^{-1} min^{-1}) in control and high-dose, fentanyl-treated rats*

Region	Control (n = 6)	Spike (n = 6)	Seizure (n = 6)	Suppression (n = 5)
Auditory system				
Cortex	0.61 ± 0.09	0.37 ± 0.15[a]	0.40 ± 0.06	0.40 ± 0.14
Medial geniculate	0.83 ± 0.23	0.53 ± 0.14	0.52 ± 0.10[a]	0.44 ± 0.13[a]
Inferior colliculus	0.61 ± 0.13	0.29 ± 0.08[a]	0.29 ± 0.07[a]	0.29 ± 0.07[a]
Visual system				
Cortex	0.84 ± 0.21	0.42 ± 0.10[a]	0.47 ± 0.12	0.46 ± 0.19
Lateral geniculate	1.11 ± 0.37	0.64 ± 0.28	0.41 ± 0.15[a]	0.60 ± 0.26
Superior colliculus	0.97 ± 0.34	0.44 ± 0.15[a]	0.62 ± 0.08	0.50 ± 0.21
Sensorimotor system				
Sensorimotor cortex	0.84 ± 0.22	0.34 ± 0.16[a]	0.40 ± 0.15	0.35 ± 0.15[a]
Thalamus				
Ventral nucleus	0.93 ± 0.29	0.71 ± 0.13	0.43 ± 0.12[a]	0.42 ± 0.27
Dorsomedial nucleus	0.97 ± 0.32	0.73 ± 0.19	0.48 ± 0.20[a]	0.51 ± 0.18
Periventricular gray	1.29 ± 0.35	0.65 ± 0.17[a]	0.62 ± 0.12[a]	0.61 ± 0.27[a]
Cerebellar gray	1.27 ± 0.33	0.62 ± 0.18	0.58 ± 0.25[a]	0.69 ± 0.38
Extrapyramidal system				
Caudate-putamen	1.17 ± 0.14	0.64 ± 0.23	0.53 ± 0.16[a]	0.53 ± 0.39[a]
Globus pallidus	1.50 ± 0.28	1.11 ± 0.25	0.72 ± 0.27[a]	0.79 ± 0.57
Substantia nigra	1.42 ± 0.25	0.70 ± 0.25[a]	0.62 ± 0.19[a]	0.57 ± 0.20[a]
Limbic system				
Claustrum	1.39 ± 0.26	0.80 ± 0.22	0.69 ± 0.28[a]	0.69 ± 0.52[a]
Septal nucleus[b]	1.19 ± 0.25	0.69 ± 0.15	0.42 ± 0.09[a]	0.31 ± 0.14[a]
Piriform cortex	1.52 ± 0.31	0.89 ± 0.15	0.81 ± 0.31[a]	0.83 ± 0.53
Amygdala	1.55 ± 0.32	0.97 ± 0.23	0.72 ± 0.38[a]	0.54 ± 0.33[a]
Hypothalamus[b]	1.43 ± 0.41	0.90 ± 0.19	0.47 ± 0.14[a]	0.42 ± 0.25[a]
Hippocampus (CA1)	1.21 ± 0.31	0.55 ± 0.16	0.40 ± 0.10[a]	0.41 ± 0.20[a]
Dentate gyrus (CA3)	1.31 ± 0.37	0.65 ± 0.15	0.47 ± 0.13[a]	0.61 ± 0.47[a]
Ventral area (CA1–CA3)	1.12 ± 0.35	0.42 ± 0.10	0.37 ± 0.09[a]	0.29 ± 0.11[a]
Interpeduncular nucleus	0.87 ± 0.23	0.43 ± 0.15[a]	0.40 ± 0.10[a]	0.49 ± 0.27
Myelinated fiber tracts				
Corpus callosum	2.48 ± 0.57	1.54 ± 0.56	1.38 ± 0.34[a]	1.71 ± 0.95
Internal capsule	2.72 ± 0.66	1.66 ± 0.32	1.35 ± 0.31[a]	1.57 ± 0.91[a]
Cerebellar white	2.35 ± 0.29	1.61 ± 0.42	1.42 ± 0.18[a]	1.79 ± 0.86
Cerebral association area				
Frontal cortex	0.87 ± 0.17	0.38 ± 0.15[a]	0.35 ± 0.14[a]	0.34 ± 0.08[a]
Reticular formation	1.54 ± 0.22	0.78 ± 0.20	0.69 ± 0.15[a]	0.80 ± 0.37[a]
Pineal body	1.39 ± 0.38	0.50 ± 0.15[a]	0.54 ± 0.21[a]	0.46 ± 0.07 (n = 3)

Values are means ± SD. Kruskal-Wallis analysis of variance and Nemenyi test where appropriate: [a]significantly different from control at $p < 0.05$; [b]spike group is significantly different from seizure and suppression groups at $p < 0.05$.

ictal suppression, the LCVR decrease remained significant in the majority of the brain structures (16 of 29 structures). There were no differences in the LCVR changes between the spike, seizure, and suppression states (Table 4). Thus, in the great majority of surveyed structures, localized subcortical spiking activity was sufficient to elicit a major and generalized reduction in LCVR, which did not further change during subcortical seizures or EEG suppression.

DISCUSSION

The present study reveals that subcortical neurophysiological excitation due to high doses of fentanyl is accompanied by a one- to over threefold increase in LCBF. These results are in agreement with numerous other studies of the overall CBF response to seizures elicited by a variety of stimuli (Plum et al., 1968; Plum and Duffy, 1975; Meldrum and Nilsson, 1976). However, they expand our understanding of CBF control during seizures in several ways. While narcotic-induced seizures are generated subcortically (Tommasino et al., 1984), the LCBF response is much more widespread and includes structures throughout the brain. Also, this generalized LCBF response occurs very quickly, i.e., within the first few spikes elicited by fentanyl.

However, our findings are in apparent conflict with those of Carlsson et al. (1982), who found about a 40% decrease in total CBF in rats during seizures caused by high doses of fentanyl. While many explanations could be posed to interpret the different results obtained in Carlsson's laboratory and ours, we feel that the two groups performed similar experiments, and that differences in the CBF measurement method and fentanyl dose and administration rates may be responsible for the di-

vergent results. Despite utilization of different CBF measurement techniques, Carlsson's control CBF levels (reflecting mainly cortical blood flow) were the same as our unweighted average for all cortical LCBF values under the same anesthetic conditions (unpublished observations). However, as our LCBF measurements require only 30 s to perform, we were able to concentrate our studies during EEG activity, which consisted mainly of burst activity during the seizure state. The duration of the burst activity averaged 50–70% of the flow determination period in our study. In Carlsson's experiments the CBF measurements required at least 15 min, and therefore reflected an average of burst-suppression activity, which is weighted substantially more toward suppression, since this type of activity predominates when very high doses of fentanyl are administered. Against this explanation of the differences between these experiments is the fact that we established that the immediate postictal suppression period is characterized by maintenance of extremely high LCBF values. However, when seizures are prolonged over 2 h, there is evidence that a state of hypoperfusion can develop (Ingvar and Siesjö, 1982). In this light, our studies, performed at the onset of seizure activity demonstrating early high flows, may not be inconsistent with Carlsson's report of low flows following a longer period of seizure activity.

Another factor requires consideration in explaining the differences between these two studies. Our protocol was empirically designed to maximize seizure incidence at the lowest possible fentanyl dose. In Carlsson's study, seizures occurred as an incidental finding after a period of fentanyl loading followed by a maintenance infusion (Carlsson et al., 1982). While Carlsson's total fentanyl dose was two to three times greater than that employed in our experiments, we postulate that the seizures occurred as blood levels of fentanyl were declining in his rats. Unfortunately, fentanyl blood levels were not measured in either study.

The findings of both studies may be unified by a discussion of the factors responsible for the genesis of seizures by narcotics. Currently these seizures are thought to occur when an imbalance between inhibitory and facilitatory influences on the hippocampal area of the limbic system develops (Schwartzkroin and Wyler, 1981; Siesjö, 1981). Narcotic-induced seizures emerge as these agents initially depress inhibitory circuits that normally act to check the tendency of the hippocampus to spontaneously discharge (Linseman and Corrigall, 1982). In this situation, as the blood level of a narcotic increases, its depressant action on the brain becomes more manifest and convulsions cease. Our rats had seizures during fentanyl induction, whereas Carlsson's rats had seizures during emergence from deep fentanyl anesthesia. Other examples of anesthetics with dose-dependent bimodal neuroexcitatory and depressant actions include enflurane and lidocaine (Winters et al., 1972; de Jong, 1977; Myers and Shapiro, 1979; Ingvar and Shapiro, 1981).

During fentanyl-induced spike and seizure activity, LCVR was significantly decreased in a majority of brain structures. In accord with the findings of many laboratories, this resistance reduction presumably represents compensation for elevated metabolism (Plum et al., 1968; Howse et al., 1974; Plum and Duffy, 1975). In our studies, the LCVR reduction was maintained during the postseizure EEG suppression phase, indicating that the usually coupled relationship among brain function, EEG activity, cerebral metabolism, and brain blood flow is disturbed. This high flow state could be interpreted as a reactive hyperemia due to inadequate CBF compensation during seizures. On the other hand, although the inter- or postictal period is characterized by EEG suppression, cerebral metabolism could be extremely high, due to the need to reestablish ionic gradients prior to resumption of EEG activity. In this case, maintenance of high CBF in the early suppression period might indicate an appropriate matching of metabolic requirements and flow.

Analysis of the LCBF and LCVR data indicates that most of the increase in flow and decrease in vascular resistance occurred with the onset of spike activity. Thereafter, in a majority of brain structures, LCVR remained relatively constant, while LCBF continued to increase in many brain areas. Such an increase in CBF is passive (no intrinsic active vasodilation) and follows elevation of arterial blood pressure, i.e., CBF autoregulation is altered. In fact, the reduction of LCVR observed in our experiments may represent a near maximal state of cerebral vasodilation. In rats studied under similar conditions, inhalation of carbon dioxide sufficient to produce a P_{aCO_2} of ~80 mm Hg reduced total CVR from a control value of 1.27 to 0.31 mm Hg/ml 100 g^{-1} min^{-1} (Dahlgren et al., 1981). This degree of hypercapnia is known to elicit near maximal cerebrovasodilation, and the LCVR values obtained in our experiments during fentanyl neuroexcitation-suppression are within the same range as those in the hypercapnic rats (Dahlgren et al., 1981). When LCVR is maximally reduced, autoregulation is absent.

The high degree of spatial and temporal resolu-

tion inherent in the autoradiographic LCBF technique employed in the present study may add a new dimension to our comprehension of CBF regulation during seizures. A prior study from this laboratory, on $LCMR_{glu}$ during fentanyl-elicited neuroexcitation, found a heterogeneous local metabolic response (Tommasino et al., 1984). This included depression of cerebral cortical metabolism coupled with a relative hypermetabolism in some structures belonging to the limbic system. The depression of metabolism in the foregoing experiment in the cerebral cortex was ~50%. In our present LCBF study we found an elevation of cortical LCBF of >130% under similar conditions during high-dose fentanyl administration. This uncoupling of the normal cerebral flow–metabolism relationship suggests that factors other than local metabolism and tissue pH control flow during fentanyl seizures (Howse et al., 1974; Astrup et al., 1976; Chapman et al., 1977; Siesjö, 1978). Within certain limbic system structures, local metabolism remained unchanged from control values, while flow again significantly increased (Tommasino et al., 1984). During generalized seizures elicited by bicuculline, Ingvar and Siesjö (1982) noted a similar disproportionate elevation of LCBF when compared to the change in local metabolism in many structures. Since the diffuse hyperemia detected in our experiments was already established following the first few spikes elicited by fentanyl, it is entirely possible that neurogenic influences on the cerebral circulation may control the initial flow elevation. Siesjö (1978) has suggested that such a flow response may be part of a generalized autonomic nervous system response to seizures.

Our study and those performed by others indicate that the magnitude of the metabolic and CBF response to seizures may not be the same for all convulsants (Siesjö, 1978; Blennow et al., 1979). A way of simultaneously examining these flow–metabolism relationships is to calculate the LCBF/$LCMR_{glu}$ ratio. During bicuculline seizures, this ratio increased by 11% in frontal cortex and decreased by 7% in the auditory cortex within 20 min of seizure onset (Ingvar and Siesjö, 1982). Under similar conditions, during the onset of fentanyl seizures, the frontal cortex ratio increased by 772%, while the auditory cortex increased by 272% (combining data from the present experiment and that of Tommasino et al., 1984). In Carlsson's rats, more prolonged seizures induced by fentanyl caused a 64% decrease in the CBF/CMR ratio for oxygen (Carlsson et al., 1982). The foregoing ratios were selected to permit comparison of similar areas of cerebral cortex among the three laboratories. In the cortex our high ratios are a reflection of reduced metabolism and relatively extreme hyperemia. The ratios are lower or decreased with bicuculline seizures because cortical metabolism as well as blood flow increases (Ingvar and Siesjö, 1982). We can suggest no further explanation for the reduction in Carlsson's ratio, other than as discussed above.

Taken alone, Carlsson's ratio can be interpreted to indicate a relative insufficiency of flow compensation for the metabolic demands of fentanyl seizures. The ratio information from the present study indicates hyperperfusion, and extends to all those structures we evaluated. Thus, our LCBF/$LCMR_{glu}$ ratios for fentanyl predict that ischemia should not occur during the onset phase of fentanyl-induced seizures. If Carlsson's findings are substantiated by other studies, then prolonged seizures due to extremely high doses of fentanyl and/or other narcotics should be avoided. In the interim, we suggest that EEG monitoring during high-dose fentanyl anesthesia may be prudent, as the brain areas activated by narcotic seizures are known to be selectively vulnerable to prolonged seizures and hypoxic–ischemic insults (Blennow et al., 1978; Dam, 1982; Atillo et al., 1983). Until the scope and/or clinical significance of this potential problem is better understood, EEG monitoring may help to define the problem as well as guide anticonvulsant therapy.

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