

Fentanyl-induced Seizures Activate Subcortical Brain Metabolism

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Neurophysiologic studies have demonstrated epileptoid activity during high-dose narcotic anesthesia. The authors utilized the ^{14}C -2-deoxyglucose method to evaluate the local cerebral glucose metabolism (I-CMRg) during high-dose fentanyl-induced epileptoid discharges as evaluated by electroencephalography (EEG) in ventilated rats. Fentanyl was administered intravenously at two dose levels ($200\ \mu\text{g}\cdot\text{kg}^{-1}$, $n = 5$; and $400\ \mu\text{g}\cdot\text{kg}^{-1}$, $n = 8$). Seven unanesthetized animals served as controls. During fentanyl administration, the EEG was characterized by the appearance of isolated high voltage ($>100\ \mu\text{V}$) spike and polyspike and wave complexes at a frequency of one every 1-4 s, superimposed on a baseline of reduced frequency and voltage. Isolated ictal discharges (spike or sharp waves at a frequency of 12-20/s) rarely were superimposed upon the spike and polyspike activity.

As a general trend, fentanyl administration induced a significant ($P < 0.05$) decrease of the I-CMRg in the majority of the 37 brain structures surveyed. A clear relationship between I-CMRg and epileptoid activity appeared when the anatomic areas were grouped into functional systems. Cerebral metabolism was globally decreased in the visual and sensorimotor systems (53-78%), in the white matter structures (76-78%), and reticular formation (59-69%) with both fentanyl treatments. The largest deviation from this trend appeared in the limbic system. Here with both treatments, the I-CMRg in the claustrum, septal nucleus, amygdala, and ventral areas of CA1 and CA3 of the hippocampus remained at control values. At the higher fentanyl dosage, there was a more widespread depression of I-CMRg in the rest of the brain, while in the limbic system this effect was reversed, with the I-CMRg returning to control values in the hippocampus (CA1), dentate gyrus, and interpeduncular nucleus.

The relative hypermetabolism in limbic system structures during fentanyl-induced epileptoid activity, coupled with a significant reduction of glucose utilization in the rest of the brain, suggests a role for the limbic system in the genesis of seizure activity during fentanyl administration. (Key words: Analgesics: fentanyl; seizures. Autoradiography. Brain: limbic system; metabolism; seizures. Electroencephalography: fentanyl; seizures.)

WHILE HIGH-DOSE FENTANYL ANESTHESIA is gaining popularity as a safe technique for cardiac anesthesia, recent reports have called attention to possible neuroexcitatory side effects. Seizures and isolated sharp waves have been reported in patients and laboratory animals receiving high doses of fentanyl.¹⁻⁴ Prolonged seizure activity can lead to neuronal death, presumably because metabolite supply becomes inadequate to meet the greatly increased demand.^{5,6} In one recent study, during high-dose, fentanyl-induced seizures in rats, whole brain oxygen uptake increased and this was not matched by a compensatory increase in cerebral blood flow (CBF).⁷ Thus, it is possible that high-dose fentanyl anesthesia resulting seizures could cause ischemia. Neurophysiologic and neuropathologic studies during seizures elicited by other drugs indicate that only certain brain regions participate in the neuroexcitatory stage.⁸⁻¹⁰ Thus, studies of overall brain metabolism and blood flow cannot accurately localize these events or point to areas wherein neuronal loss may occur. The present study was performed to anatomically localize and assess the metabolic response of brain areas involved in seizure activity associated with administration of high doses of fentanyl.

Materials and Methods

I-CMRg was determined in 20 Sprague-Dawley, female rats with the ^{14}C -2-deoxyglucose (DG) autoradiographic method.¹¹ The rats weighed $280 \pm 5\ \text{g}$ (mean \pm SEM), were fed *ad libitum*, and studied while conscious (control, $n = 7$) and after administration of fentanyl ($n = 13$).

FENTANYL-TREATED ANIMALS

Anesthesia was induced with halothane, 4%, in oxygen. Lidocaine hydrochloride, 1% (0.2 ml total), was infiltrated in all incision sites for local anesthesia. Following tracheostomy, the animals were ventilated with a Harvard® rodent ventilator. Inspired halothane was changed to 1% in oxygen for the remaining part of the surgical proce-

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TABLE 1. Physiologic Conditions during Local Cerebral Glucose Metabolism Measurements

	Control* (n = 7)	Fentanyl* (200 $\mu\text{g} \cdot \text{kg}^{-1}$) (n = 5)	Fentanyl* (400 $\mu\text{g} \cdot \text{kg}^{-1}$) (n = 8)
PaO_2 (mmHg)	116 \pm 6	117 \pm 4	110 \pm 3
PaCO_2 (mmHg)	38.6 \pm 0.9	37.7 \pm 0.6	37.1 \pm 0.3
pH_a	7.45 \pm 0.01	7.42 \pm 0.01	7.42 \pm 0.01
MABP (mmHg)	112 \pm 3	126 \pm 9	122 \pm 7
Plasma glucose (mg/dl)	197 \pm 8	431 \pm 17†	398 \pm 11†

* Values are means \pm SE obtained in the number of animals indicated in parentheses.

† Significantly different from control, $P < 0.001$.

ture. Polyethylene catheters (PE-50) were placed in the left femoral vessels for arterial blood-gas and pH measurements (Radiometer microelectrode system analyzer), arterial blood pressure monitoring, and infusion of drugs and isotope. To permit rapid sampling of arterial blood, an arteriovenous shunt catheter was placed in the right femoral vessels.

Pancuronium bromide (0.2 mg, iv q 20 min) was administered to produce muscle relaxation. Heparin (200 IU iv) was given to prevent clotting of blood in the catheters. Rectal temperature was monitored and servocontrolled to 37° C with a heating lamp. The electrocardiogram (ECG) and electroencephalogram (EEG) were recorded with subcutaneous needle electrodes with a Beckman® Accutrace polygraph. The EEG was recorded from biparietal leads at a gain of 7.5 $\mu\text{V}/\text{mm}$.

Upon completion of the surgical procedure, the halothane administration was discontinued and 60 min elapsed prior to l-CMRg determinations. During this period, the respirator was adjusted to maintain an arterial PCO_2 and PO_2 of 37 \pm 2 mmHg and above 100 mmHg, respectively.

Five rats received 200 $\mu\text{g} \cdot \text{kg}^{-1}$ of fentanyl infused over five minutes, followed by 8 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for 50 min. In eight rats, this fentanyl infusion protocol was doubled. To avoid volume loading, the fentanyl was given following lyophilization and redilution of the drug with 0.9% normal saline to a concentration of 300 $\mu\text{g}/\text{ml}$. During fentanyl administration, fresh heparinized donor blood was given, as required, to maintain mean arterial blood pressure (MABP) above 100 mmHg.

CONTROL GROUP

The conscious group was acclimatized for a ten-day period for at least 4 h/day in a Plexiglas® restraining cage, and this same training cage was utilized during the l-CMRg determination. The anesthesia and surgical protocol was the same as that applied to the fentanyl-treated

animals, except that a tracheostomy and mechanical ventilation were not performed, and the ECG and EEG were not monitored. The animals recovered from anesthesia in the training cage for at least two hours prior to ^{14}C -DG injection. During this stabilization period, they were not disturbed and had access to food and water.

^{14}C -DG AUTORADIOGRAPHY

Ten minutes after starting fentanyl infusion, a pulse of ^{14}C -DG (50 $\mu\text{Ci}/\text{kg}$, New England Nuclear) was injected intravenously, followed by timed collection of arterial blood samples (50–100 μl) over a 45-min period. These samples were used for determination of plasma glucose concentration (Beckman® enzymatic analyzer) and ^{14}C activity (Nuclear-Chicago, Isocap 300). At 45 min the animals were sacrificed by cardiac arrest (saturated potassium chloride intravenously).

The brain was removed rapidly and frozen in 2-methylbutane cooled to -41°C with Freon 22. The brain was sectioned at -20°C in a cryostat (American Optical) and the 20 μ slices rapidly dried on a hot plate (60° C) and subsequently exposed, along with ^{14}C methyl-methacrylate standards, to a single emulsion X-ray film (Kodak SB-5) for 10–12 days. Following film development, optical densities were determined with an autoscanning densitometer (Optronix, P-1000, International Inc.) with an aperture of 200 μ , and all data collected on-line with a Prime computer for calculation of l-CMRg according to the operational equation developed by Sokoloff *et al.* (using a lumped constant of 0.483).¹¹ Brain structures were identified with a stereotaxic brain atlas.¹²

STATISTICAL ANALYSIS

Significant differences between groups, with respect to physiologic variables, were evaluated by one-way analysis of variance (ANOVA, F ratio), followed by Newman-Keuls multiple range test where appropriate. Since the l-CMRg data did not meet the assumption required by the ANOVA method, the non-parametric Kruskal-Wallis analysis of variance was used. Pairwise comparison between groups were assessed by Nemenyi test (unequal sample size).¹³ A P value < 0.05 was considered significant.

Results

PHYSIOLOGIC CONDITIONS

As indicated in table 1, the physiologic conditions existing during l-CMRg measurements in fentanyl-treated rats and in the control group were generally similar. Only plasma glucose, representing the average of four samples collected during the experimental period, significantly increased during fentanyl-induced seizure activity. There

were no significant differences between the two fentanyl-treated groups.

ELECTROENCEPHALOGRAPHIC PATTERNS

High doses of fentanyl induced EEG epileptoid activity in all treated animals.¹⁴ Typical EEG patterns during fentanyl administration are shown in figure 1. Usually, a period of slow wave activity appeared soon after fentanyl administration. The vast majority of the EEG excitation was characterized by the abrupt onset of isolated, high voltage ($>100 \mu\text{V}$) spikes at a frequency of one every 1–4 s (fig. 1*B*) and/or polyspike and wave complexes at a frequency of one every 1–2 s (fig. 1*C*). Ictal discharges occurred rarely and were recognized as brief episodes of high-voltage spike and sharp waves (frequency = 12–20/s), lasting less than 3 s, and followed by resumption of the pre-ictal EEG activity (non-progressive type, fig. 1*D*), or lasting from 6.5 to 37 s and followed by episodes of post-ictal depression of 0.5- to 15.5-s duration (progressive type, fig. 1*E* and 1*F*). During the entire 55-min period of fentanyl administration, the longest cumulative period of ictal and post-ictal activity (burst and depression) represented less than 5% of all the EEG activity, and in most instances was considerably less. There was no apparent

relationship between the two fentanyl treatments and the EEG pattern, and the appearance of isolated ictal discharges was evenly divided between the two groups of treated animals.

LOCAL CEREBRAL GLUCOSE UTILIZATION

Representative brain autoradiograms for control and fentanyl-treated animals are shown in figure 2, and provide a map of some specific areas activated during high-dose, fentanyl-induced seizure activity. Table 2 lists the l-CMRg values in 37 brain structures grouped into functional systems, for the three groups of rats (see discussion relating to semiquantitative interpretation of the data). As a general trend, fentanyl administration caused a significant decrease of the cerebral metabolism in the majority of the structures surveyed. Both fentanyl treatments significantly decreased the l-CMRg in all the structures belonging to the visual and sensorimotor systems (53 to 78% decrease from control), in the myelinated fiber tracts (78% to 87% decrease), and reticular formation (59 to 69% decrease). Some differences between the two groups of treated animals were found in the inferior colliculus and lateral lemniscus (auditory system), caudate-putamen, and globus pallidus (extrapyramidal system) and in the frontal

EEG patterns during fentanyl administration

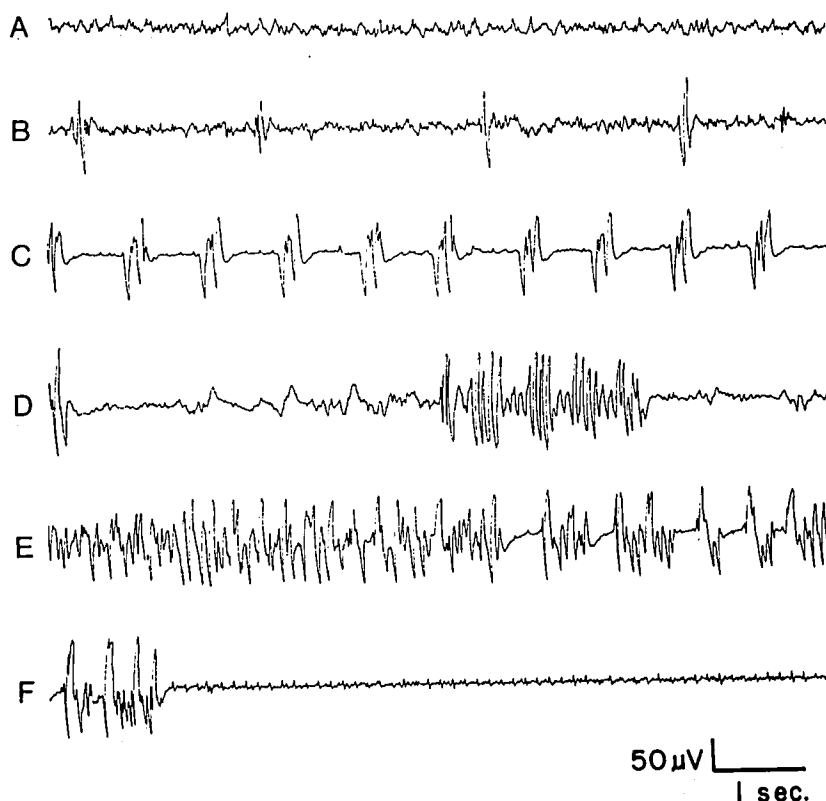


FIG. 1. Representative electroencephalographic (EEG) patterns during administration of high doses of fentanyl in the rat. See text for further elaboration. A: before starting fentanyl administration (70% N_2O :30% O_2); B: isolated spike; C: spike and wave complexes; D: isolated ictal discharges; E: isolated ictal discharges; and F: post-ictal EEG depression.

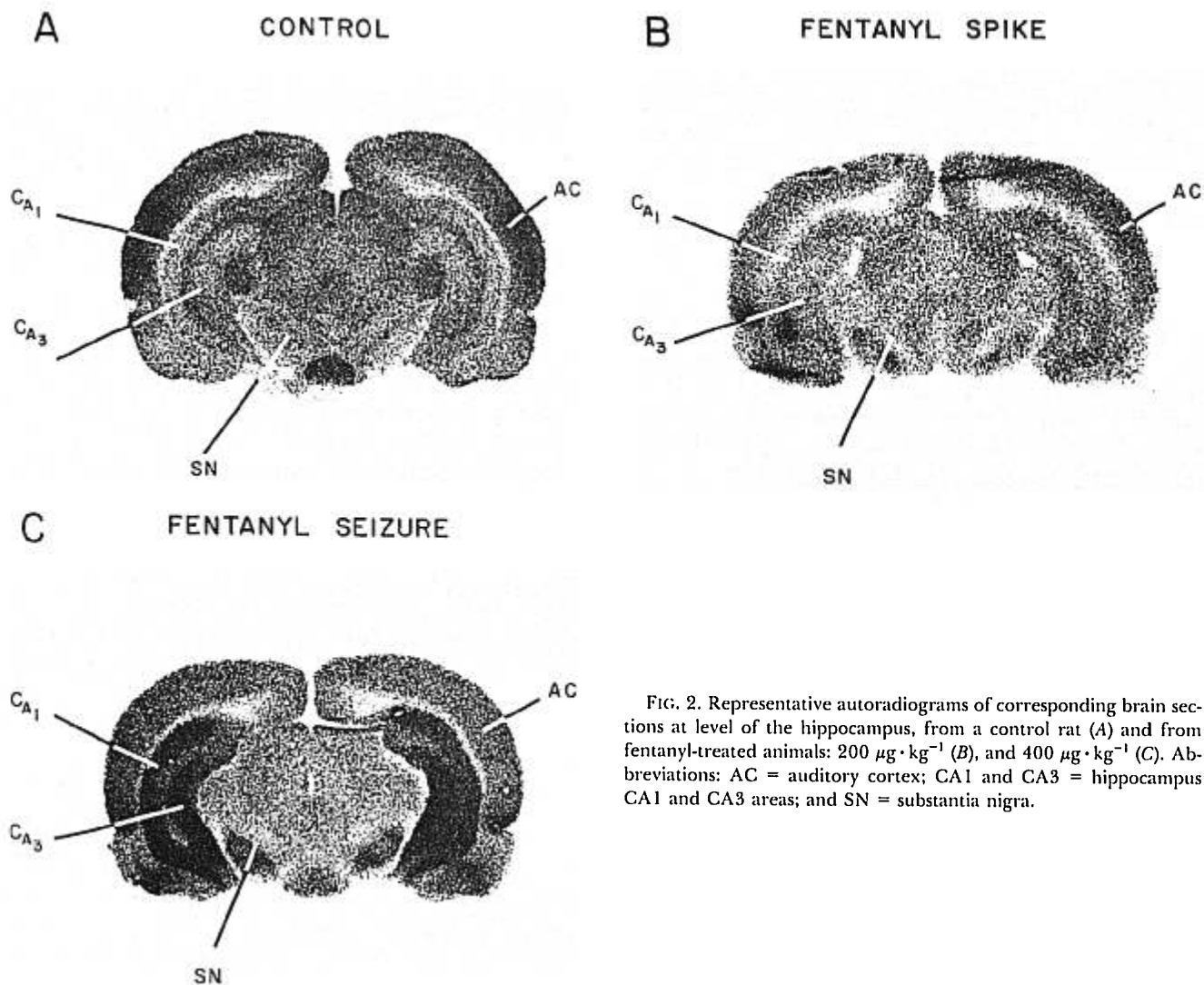


FIG. 2. Representative autoradiograms of corresponding brain sections at level of the hippocampus, from a control rat (A) and from fentanyl-treated animals: $200 \mu\text{g} \cdot \text{kg}^{-1}$ (B), and $400 \mu\text{g} \cdot \text{kg}^{-1}$ (C). Abbreviations: AC = auditory cortex; CA1 and CA3 = hippocampus CA1 and CA3 areas; and SN = substantia nigra.

cortex. In these structures the metabolism remained at control values in the animals receiving $200 \mu\text{g} \cdot \text{kg}^{-1}$ of fentanyl, and was decreased significantly when the dosage was doubled (table 2 and fig. 3). The largest deviation from this trend, *i.e.*, depressed metabolism after fentanyl administration, was apparent in the limbic system. The l-CMRg in the claustrum, septal nucleus, amygdala, and ventral areas of the CA1 and CA3 of the hippocampus, remained at control values with both fentanyl treatments. Furthermore, while increasing the dosage of the fentanyl resulted in a more widespread depression of the metabolic rate in non-limbic structures, this effect was reversed in the limbic system, with the metabolism returning to control values in the hippocampus (CA1), dentate gyrus (CA3), and interpeduncular nucleus (fig. 4). Indeed, the metabolism in the ventral areas of CA1 and CA3 of the hippocampus was increased significantly when compared with the lower dosage of fentanyl (fig. 4). The only extra-

limbic system structure without a significant metabolic change after fentanyl administration, was the pineal body.

Discussion

^{14}C -DEOXYGLUCOSE METHOD AND SEIZURES

The ^{14}C -DG method has been applied extensively to produce functional neuroanatomic maps of the local metabolic activity accompanying seizures.^{8-10,15-20} However, difficulties arise when attempts are made to strictly quantitate the l-CMRg response during seizures. In our experiment, quantitation difficulties arise in defining steady-state conditions and in knowing the influence of brain glucose content upon the lumped constant (LC).¹¹ Epileptic activity may not represent a steady state and this could violate certain assumptions of the ^{14}C -DG method.¹¹ However, in our study, fentanyl administration resulted

TABLE 2. Local Cerebral Glucose Utilization during Fentanyl Treatment in Rats ($\mu\text{mol} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$)

	Control* (n = 7)	Fentanyl* (200 $\mu\text{g} \cdot \text{kg}^{-1}$) (n = 5)	Fentanyl* (400 $\mu\text{g} \cdot \text{kg}^{-1}$) (n = 8)
Auditory system			
Cortex	94 \pm 4	35 \pm 6†	36 \pm 5‡
Medial geniculate	80 \pm 5	15 \pm 3‡	19 \pm 4‡
Inferior colliculus	140 \pm 6	71 \pm 6	63 \pm 7‡
Olivary body	118 \pm 8	48 \pm 4‡	64 \pm 7†
Cochlear nucleus	114 \pm 4	59 \pm 4†	61 \pm 11† (n = 7)
Lateral lemniscus	54 \pm 3	34 \pm 9	22 \pm 4‡ (n = 7)
Visual system			
Cortex	75 \pm 3	30 \pm 6†	28 \pm 2‡
Lateral geniculate	54 \pm 4	12 \pm 3‡	16 \pm 3†
Superior colliculus	73 \pm 5	27 \pm 6‡	31 \pm 3‡
Sensorimotor system			
Sensorimotor cortex	80 \pm 3	35 \pm 7‡	33 \pm 3‡
Thalamus, ventrolateral nucleus	77 \pm 7	22 \pm 3‡	23 \pm 3‡
Thalamus, dorsomedial nucleus	77 \pm 4	23 \pm 4†	24 \pm 3‡
Periventricular gray	53 \pm 4	17 \pm 5‡	21 \pm 2‡
Cerebellar gray	45 \pm 1	19 \pm 3‡	21 \pm 2‡
Extrapyramidal system			
Caudate-putamen	79 \pm 3	32 \pm 6	25 \pm 2‡
Globus pallidus	41 \pm 5	14 \pm 4	8 \pm 2§
Substantia nigra	50 \pm 5	19 \pm 2‡	24 \pm 5†
Limbic system			
Caudate	59 \pm 3	44 \pm 11	50 \pm 11
Nucleus accumbens	63 \pm 2	23 \pm 4†	20 \pm 3‡
Septal nucleus	54 \pm 2	37 \pm 7	53 \pm 10
Cingulate gyrus	89 \pm 4	36 \pm 8†	32 \pm 6‡
Piriform cortex	76 \pm 4	26 \pm 2†	26 \pm 3‡
Amygdala	48 \pm 4	31 \pm 6	41 \pm 7
Habenula	89 \pm 2	44 \pm 5‡	50 \pm 4†
Hypothalamus	42 \pm 3	18 \pm 3‡	19 \pm 3‡
Ammon's horn	53 \pm 3	24 \pm 3‡	30 \pm 4†
Hippocampus (CA1)	57 \pm 4	27 \pm 4†	51 \pm 8
Dentate gyrus (CA3)	54 \pm 4	25 \pm 5†	57 \pm 12
Hippocampus: ventral areas CA1 and CA3	60 \pm 4	28 \pm 4	73 \pm 13¶
Entorhinal cortex	52 \pm 2	18 \pm 5‡	22 \pm 3†
Interpeduncular nucleus	98 \pm 6 (n = 6)	37 \pm 6‡	47 \pm 5
Myelinated fiber tracts			
Corpus callosum	25 \pm 3	6 \pm 2†	5 \pm 1‡
Internal capsule	23 \pm 2	5 \pm 3‡	3 \pm 0.5‡
Cerebellar white	24 \pm 3	4 \pm 1‡	5 \pm 1†
Cerebral association area			
Frontal cortex	77 \pm 3	37 \pm 4	27 \pm 4‡
Reticular formation	42 \pm 2	13 \pm 4‡	17 \pm 2‡
Pineal body	58 \pm 4	51 \pm 11 (n = 4)	40 \pm 3 (n = 6)

* Values are means \pm SE obtained in numbers of animals indicated in parentheses.

Significantly different from control: † $P < 0.05$; ‡ $P < 0.01$, § $P < 0.001$; or between fentanyl treated groups: ¶ $P < 0.05$.

in a predominant EEG "steady state" of spike and wave activity which began before ^{14}C -DG administration, and continued for the 45-min experimental interval. In about half of the rats, this "steady state" was interrupted by brief periods (less than 5% of the time of the ^{14}C -DG measurement) of seizure bursts and/or burst suppression activity. Thus, "steady-state" conditions prevailed insofar as is possible when neuroexcitatory states are studied with the ^{14}C -DG method. Greater quantitation problems arise

with the LC used in the calculation of l-CMRg.¹¹ The LC has been shown to change when brain tissue glucose content is altered beyond normal ranges as occurs with seizures.^{17,21,22} These glucose changes are unknown during fentanyl-induced seizure activity and, thus, our results are only semiquantitative.

Precise indications of neurophysiologic function cannot be drawn from ^{14}C -DG autoradiography studies alone. Absence of a change in l-CMRg in a particular structure

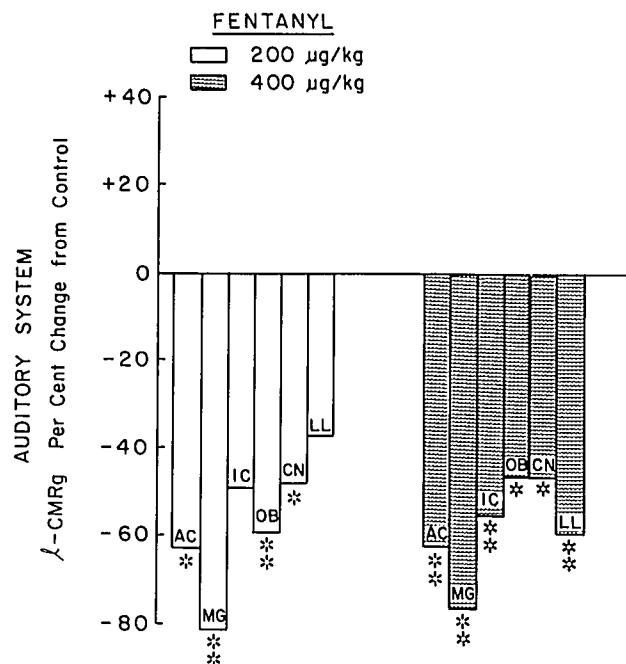


FIG. 3. Auditory system: local cerebral glucose metabolism (l-CMRg) during fentanyl-induced seizure activity (expressed as per cent change from control). Abbreviations: AC = auditory cortex; MG = medial geniculate; IC = inferior colliculus; OB = olivary body; CN = cochlear nucleus; and LL = lateral lemniscus. Significantly different from control: * = $P < 0.05$; ** = $P < 0.01$.

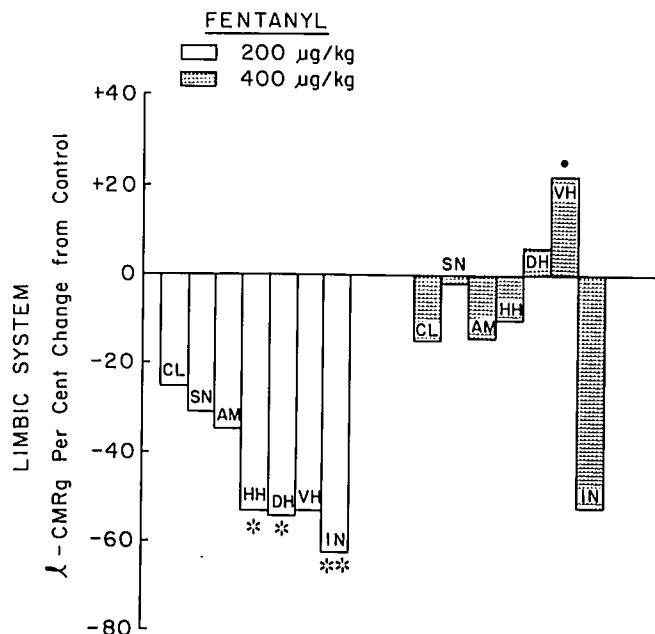


FIG. 4. Limbic system: local cerebral glucose metabolism (l-CMRg) during fentanyl-induced seizure activity (expressed as per cent change from control). Abbreviations: CL = claustrum; SN = septal nucleus; AM = amygdala; HH = hippocampus CA1; DH = dentate gyrus CA3; VH = ventral areas of CA1 and CA3 of the hippocampus; and IN = interpeduncular nucleus. Significantly different from control: * = $P < 0.05$; ** = $P < 0.01$; or between fentanyl-treated groups: * = $P < 0.05$.

or region of the brain does not rule out its functional participation in a neurophysiologic event. Also, increased ^{14}C -DG uptake does not differentiate between primary or secondary activation of the involved structure.^{8,15} However, absence of a change in certain areas of the brain, while other areas change, can create imbalances in highly integrated brain functional systems as various inhibitory and/or facilitory relationships are altered.

LIMBIC SEIZURES AND OPIATE RECEPTORS

These experiments point to the involvement of the subcortically located limbic system in either the genesis and/or propagation of neuroexcitation due to high doses of fentanyl. While the general influence of fentanyl is to reduce l-CMRg in the majority of brain structures, the tendency of limbic system structures to remain at control or slightly higher metabolic levels, has functional neurophysiologic implications.^{10,15} This metabolic redistribution is characteristic of "limbic seizure" models,^{9,10,16} as contrasted with models of "generalized seizures" that show increased glucose utilization throughout most of the brain, including the neocortex.^{9,17,18}

A wealth of neurophysiologic data indicates that the limbic system is very sensitive to a variety of stimuli that can lead to self-sustaining repetitive discharges.^{9,23} The pyramidal cells of the hippocampus possess innate epileptogenic properties, which are normally inhibited by GABA-ergic interneurons.^{9,24,25} Autoradiographic studies of opiate receptor localization reveal a very dense population of opiate receptors in the limbic system and other closely related subcortical structures.²⁶ Within the hippocampal complex, opiate receptor distribution is greater in the CA1 area proper when compared with the CA3 area of the dentate gyrus.²⁷ Accordingly, electrophysiologic evidence shows differential hippocampal responses (area CA1 > CA3) to large doses of morphine.²⁸ Electrophysiologic studies support the concept that morphine causes disinhibition of the pyramidal cells of the hippocampus leading to seizure discharges.²⁸ Other mechanisms for opiate potentiation of limbic seizures include augmented release of excitatory neurotransmitters or facilitation of coupling between excitatory postsynaptic potentials and somatic spike-generating sites.²³ Opioid peptides possess epileptogenic properties similar to narcotics which can be blocked by naloxone.²⁹ These studies add further proof that seizures can result from interactions of opiate receptors with various agonist compounds.

Other anesthetic agents with neuroexcitatory properties (enflurane, lidocaine, and ketamine) also cause increased limbic system uptake of ^{14}C -DG.^{16,19,30,31} Because of evidence indicating that progressive increases in neuroexcitatory stimuli result in a dose-related change (usually recruitment of additional structures) in the distribution of ^{14}C -DG uptake in subcortical and cortical structures,¹⁰

a strict anatomic comparison of different drugs is not possible until dose-response data are available. However, utilization of local metabolic and electrophysiologic data together can improve our understanding of the central nervous system effects of drugs. A further example of this approach is seen when the generalized seizure state elicited by fentanyl and bicuculline are compared metabolically.^{9,17} Almost negative image patterns of I-CMRg activity can be seen in the cortex, subcortex, and other brain structures. This is an indication of the different mechanisms involved in epileptogenesis with these two agents.

CLINICAL IMPLICATIONS

Very high doses of narcotics have long been associated with the development of seizures. Therefore, it is not surprising that fentanyl, when given in sufficient doses to rats, elicits seizures. Despite species and dose differences, the possibility that this phenomenon could involve humans remains. The likelihood of inducing seizures in patients increases with introduction of more potent narcotics. Unfortunately, recent reports attributing seizures to fentanyl, during induction of anesthesia, do not provide enough details to clearly make their point.^{2,3} As we await further details concerning a possible relationship of fentanyl to seizure activity, certain low risk steps can be suggested to improve the safety of high-dose narcotic anesthesia. Anticonvulsant premedications may be considered, although case reports indicate that normal doses of benzodiazepines did not prevent seizures purported to be due to high doses of fentanyl.^{2,3} Varying rates of narcotic administration, as well as higher doses of benzodiazepines, may avoid seizures. Other, more specific anticonvulsant premedication also may be helpful, and I-CMRg studies showing their action foci could help in selecting agents for evaluation.³¹ When fentanyl is used in high doses, sudden shifts toward respiratory alkalosis should be avoided, as they may potentiate seizure activity due to an increase of the non-ionized lipophilic proportion of the drug encouraging increased brain uptake.³²

While the present study has localized sites of relatively high brain metabolic activity during fentanyl-induced seizures, it cannot predict the pathologic consequences of prolonged subcortical epileptic activity. It has long been recognized that limbic structures are highly vulnerable to neuronal death during prolonged seizure.^{9,10,17,25,33,34} However, histopathologic analysis and studies of the degree of local cerebral blood flow compensation are required to further define the potential clinical impact of high doses of fentanyl-induced seizures. In the interim, from an academic standpoint, it seems prudent that EEG monitoring be employed, where possible, during high-dose fentanyl anesthesia in patients who receive muscle relaxants early in the induction sequence. In humans,

limbic seizures are notoriously difficult to detect with standard scalp electrode placements, and more specialized EEG electrode arrays may be required.³⁵ Such monitoring could confirm or reject the hypothesis that fentanyl could cause seizures in humans.

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