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Local Cerebral Glucose Utilization in Stimulated Rats Sedated with Thiopental

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Background: **Recent studies have suggested that supraspinal structures are involved in barbiturate-induced enhancement of nociceptive processing. The goal of the study was to determine whether cortical and subcortical regions involved in nociception were relatively activated or depressed by noxious stimulation during infusion of small doses of thiopental.**

Methods: **Local cerebral glucose utilization (LCGU) was measured with the ^{14}C-2-deoxyglucose radioautographic technique in 14 rats. During the LCGU experiment, pressure was applied to the tail every 2 min, and the somatic motor response threshold was recorded. Seven animals received thiopental infusions to produce a steady-state plasma concentration (target concentrations of 10 μg/ml), and seven untreated animals served as controls.**

Results: **A steady-state plasma thiopental concentration (11.1 ± 1.8 to 13.0 ± 2.1 μg/ml) was accompanied by a decrease in the somatic motor response threshold from 277 ± 32 g (before thiopental) to 215 ± 41 g ($P < 0.001$). The somatic motor response threshold remained unchanged in the control group. Average LCGU was 29% less in the thiopental-treated animals than in the untreated controls ($P < 0.001$). In cortical regions associated with nociception, LCGU was relatively increased (+3% ± 14%) during the thiopental infusion in comparison to the visual and auditory cortices (−18% ± 13%; $P < 0.001$). Individual structures that showed relative changes during thiopental infusion included the nucleus accumbens (+17%, $P < 0.05$) and the habenula (−17%, $P < 0.05$). Heterogenous relative changes ($P < 0.05$) in LCGU were observed in the auditory system: auditory cortex (−22%), medial geniculate (−16%), lateral lemniscus (+26%), superior olive (+38%).**

Conclusions: **Noxious stimulation during low-dose thiopental infusions relatively increased LCGU in cortical regions postulated to be responsible for processing of noxious stimuli. Nuclei in the descending pain modulating system were not relatively depressed. (Key words: Anesthetics, intravenous: thiopental. Brain, metabolism.)**

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BASED on evidence from both behavioral studies[1–5] and from single-unit dorsal horn recordings,[6–8] barbiturates enhance nociceptive transmission when the spinal cord is intact.[9] The mechanism of this effect remains controversial.[10] Because barbiturates depress sensitivity to noxious stimulation in spinal cord-injured animals and in *in vitro* preparations,[7,11,12] supraspinal mechanisms may be important in the antianalgesic or hyperalgesic effects of these drugs.[10] To further evaluate the influence of barbiturates on nociceptive transmission, two recent studies[1,13] have characterized the relationships between plasma concentrations of barbiturates and the somatic motor response threshold (SMRT) to tail pressure. At plasma concentrations of thiopental associated with mild-to-moderate sedation, the a steady-state reduction of the motor response threshold correlated with reductions in tail-flick latency.[1] We speculated that noxious stimulation during an infusion of thiopental that reduces the SMRT would cause a relative increase in functional activity in brain regions involved in sensory and affective processing of noxious stimuli,[9] and mesencephalic structures involved in the descending pain modulating system might be preferentially depressed.[10] The current study was undertaken to test the hypothesis that, in comparison to a control state (saline infusion), noxious stimulation during a low-dose infusion of thiopental would produce relative changes in local cerebral glucose utilization (LCGU) in supraspinal brain regions purported to be involved in nociceptive transmission.

Materials and Methods

After approval by the Animal Care Committees of the Montreal Neurological Institute and the University of

Calgary, 14 male Sprague Dawley rats were studied. In these experiments, we prospectively measured LCGU during repeated noxious stimulation in animals receiving sedation with steady-state infusions of thiopental and compared these measurements with concurrent control animals not receiving thiopental.

Preparation for Autoradiographic Studies

We conducted these experiments under the conditions of partial restraint commonly used for autoradiographic studies in the rat.[14] Briefly, after weighing, each animal was anesthetized with 2% halothane in oxygen. Femoral arterial and venous catheters were inserted under direct vision. After application of a thin film of 2% lidocaine jelly to the wound edges, the animal was partially restrained in a plaster cast extending from the ankles to the lower thorax and taped to a lead block. Two hours were allowed for the animals to eliminate the halothane, during which time body temperatures were monitored with a rectal thermometer and maintained at 36–38°C with a heating lamp. Before each study, we evaluated the general health of each animal by visual inspection and with measurements of arterial blood gas tensions and mean arterial pressure to ensure that measurements of these variables were within the normal limits for our laboratory (arterial oxygen tension > 75 mmHg, arterial carbon dioxide tension 30–45 mmHg, *p*H 7.30–7.45, and mean arterial pressure 85–120 mmHg).

Thiopental was administered with a computer-controlled infusion pump to provide clamping at a plasma target concentration of 10 μg/ml,[15] which has been shown to be associated with a reduction of the SMRT by approximately 30%.[1] The target concentrations were achieved by a bolus and infusion strategy individualized for each rat according to weight. The pharmacokinetic program (STANPUMP) was run with a standard Intel 286 computer driving a Harvard Apparatus Pump 22 (Harvard Apparatus, South Natick, MA). The program used pharmacokinetic modeling to provide real-time predictions of plasma thiopental concentrations.

Measurement of Somatic Motor Response Threshold

A modification of the paw-pressure test[16,17] was used to measure the SMRT to tail pressure. Enhanced nociceptive transmission results in a decrease in the SMRT, while analgesia increases the SMRT. An Analgesy-Meter (Ugo Basile, Milan, Italy) applied a linearly increasing pressure to randomly selected points within the distal 2 cm of the tail, which was supported on a plinth. The end-point (SMRT) was defined as the first movement of the tail that could displace it from the plinth.

The behavioral status of each animal was recorded at the outset of the experiment and just before blood sampling for plasma thiopental concentrations. The behavior status was classified as awake (actively exploring the environment), drowsy (not actively exploring, but easily stimulated by manipulating the head or vibrissae), very drowsy (responds only to vigorous head manipulation), and unresponsive.

The timing of the SMRT measurements and the deoxyglucose injection were based on the program predictions of plasma thiopental levels. Control measurements of the SMRT were made at the beginning of the experiment (initial measurement). The bolus and infusion strategy was begun. Predicted steady-state plasma thiopental concentrations were achieved approximately 5 min later. The SMRT measurements were made when steady-state conditions for plasma thiopental concentrations were predicted by the computer and 3 and 6 min later (three "before 2-deoxyglucose (2-DG) measurements" in each animal). Deoxyglucose was injected 8 min after steady-state thiopental concentrations were predicted. The SMRT measurements were repeated every 2 min during the first 14 min of the 2-DG experiment (seven "during 2-DG measurements" in each animal). Blood samples for plasma thiopental concentration were drawn 2 min ("before 2-DG" value) and 10 min ("during 2-DG" value) after the computer predicted a steady-state plasma thiopental concentration.

Thiopental concentrations in plasma were measured by high performance liquid chromatography with spectrophotometric detection as previously described.[1,18] The total volume of blood samples withdrawn from each animal was approximately 2 ml (15 × 100 μl (2-DG study) and 2 × 250 μl for thiopental measurements). Blood samples were replaced with a volume of normal saline equal to three times the blood sample volume.

Measurement of Local Cerebral Glucose Utilization

LCGU was measured with the autoradiographic 2-DG method of Sokoloff *et al.*[19] The experiment began with the injection of 30 μCi of [^{14}C]DG over 30 s (2-deoxy-d-[1-^{14}C]-glucose-specific activity of 35–40 mCi/mmol, New England Nuclear, Boston, MA). 2-DG was injected 8 min after the STANPUMP program had predicted a

steady-state plasma thiopental concentration. Control animals were treated identically to thiopental-treated animals; the syringe contained saline. Timed arterial sampling for plasma concentrations of [^{14}C]DG and glucose began 15 s after the start of the injection and continued for 45 min. Plasma glucose concentration was measured with a Beckman Glucose Analyzer2 (Beckman Instruments, Brea, CA). Plasma [^{14}C]DG content was measured with a liquid scintillation counter (model 1219, LKB Rackbeta Liquid Scintillation Counter, Allied Scientific, Montreal, Canada) with calibrated [^{14}C] toluene internal standards (New England Nuclear). Animals were killed by decapitation and the brains rapidly removed and frozen in isopentane cooled to −50°C to −60°C by liquid nitrogen vapor. Brains were cut into 20-μm-thick sections in a cryostat (American Optical, Buffalo, NY). Autoradiographs were prepared from the dried brain sections, using calibrated [^{14}C] methylmethacrylate (New England Nuclear) as internal standards for each autoradiograph. The autoradiographic images were analyzed with a microcomputer imaging device (MCID, Imaging Research, St. Catherines, Ontario, Canada).

Data Analysis: Local Cerebral Glucose Utilization

Before analysis, regions of interest (ROIs) were defined and identified in a rat stereotactic atlas[20] and used to construct a template for the image analyzer. To test our hypothesis, 19 specific ROIs were defined. On the basis of recent human[21–23] and rat studies[24] forebrain regions representing nociception were chosen in the ventroposterolateral nucleus of the thalamus, in the cingulate gyrus (area 29c, Von Economo classification[25]), and the primary and secondary (association) somatosensory cortices for the hind limb. Brainstem regions selected were those thought to be involved in the bulbospinal endogenous pain modulating system (amygdala periaqueductal gray, nucleus accumbens, nucleus raphe magnus, and nucleus gigantocellularis).[24,26] The habenula was included as part of the mesolimbic antinociceptive loop.[27] For comparison, we selected structures in the visual and auditory systems.

The LCGU values within each ROI were analyzed to determine whether there was any relative change in metabolic activity during hyperalgesia with thiopental. The analysis follows the procedures commonly used for functional brain mapping with positron emission tomography.[21,28] To evaluate the relative changes in the metabolic activity activity associated with thiopental administration, it was first necessary to reduce the intersubject and intergroup variability in global LCGU by scalar normalization of each image [(LCGU in each ROI/mean global LCGU) × 100].[28] Each of the seven animals was randomly paired with a control animal. The state-dependent change in LCGU for each region was calculated as the difference between the thiopental-treated and control animals. To obtain an estimate of the variance of the state-dependent change of LCGU, ΔLCGU was calculated between randomly selected pairs of animals rather than as the difference between the means of each group. Normal distribution of these percentage values was confirmed with the Kolmogorov-Smirnov test. The ΔLCGU values for 19 ROIs were compared with one-way analysis of variance by region. For each ROI, a t statistic was calculated by dividing the mean ΔLCGU in the ROI by the standard error of the mean. The standard error of the mean was determined by dividing the average standard deviation for all of the ROIs by the square root of the number of subjects.[21] Mathematically the t statistic is: $t = \text{mean } \Delta LCGU_i / SEM_{\Delta LCGU}$, where mean Δ $LCGU_i$ is the mean state-dependent change in LCGU in region i, and $SEM_{\Delta LCGU}$ is the standard error of the mean for state-dependent changes in LCGU in all of the ROIs. The effective degrees of freedom were estimated to be equal to (number of subject pairs − 1)(number of separate regions) = (6)(19) = 114.[28] The statistical significance of the t statistic for each region was assessed by comparison with a critical value of t = 3.037 for α = 0.0026, degrees of freedom = 114. The value of α was determined from the Bonferroni correction for 19 comparisons $\alpha = 0.05/19 = 0.0026$.

Values of physiologic variables were analyzed by two-way repeated measures analysis of variance with drug treatment as one factor and time (initial *vs.* final) as the second factor. Individual differences were isolated with the Student-Newman-Keuls test. Statistical significance was inferred when $P < 0.05$. The SMRT values within each treatment group were analyzed by one-way analysis of variance.

Because the study did not include any unstimulated awake and anesthetized animals, we could not directly examine the effects of stimulation and anesthesia. For an indirect evaluation of these issues, we compared the patterns of LCGU in the two groups of animals from this study (stimulated awake and stimulated sedated) with patterns generated from data for three groups of animals studied previously in the same laboratory[29] (awake unstimulated rats (n = 8) and rats anesthetized

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regions,[29] where Z = [LCGU RC
standard deviation for LCGU
of the brain regions responsi
cessing were not evaluated in
pattern analysis, the regions se
regions: visual, auditory, pari
frontal; (2) subcortical regio
mamillary body, medial genic
terior hippocampus, lateral g
eral thalamus, ventral thalam
mus, globus pallidus, and cau
regions: cerebellar cortex, coc
nucleus, superior olive, latera
and inferior colliculus. Z-scor
is followed by Q-component
statistical significance to diffe
This was not possible with the
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Results

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final mean Pa_{CO_2} value was s
mmHg; $P < 0.05$) than the

Table 1. Physiologic Values

Variable
Pa_{CO_2} (mmHg)
Pa_{O_2} (mmHg)
pH
Rectal temperature (°C)
MAP (mmHg)
[Glucose] (mmol · dl^{-1})
Weight (g)

Values are mean ± SD for 7 animals. Anir
* $P < 0.05$ by ANOVA *versus* initial values
Pa_{CO_2}, Pa_{O_2} = arterial tensions of carbon
beginning and end, respectively, of the 2-[

to the first failure to respond to tail-clamp with either pentobarbital (n = 5) or isoflurane (n = 3)). The pattern of LCGU in each of these five groups was characterized by calculating a Z value for each of 26 brain regions,[29] where Z = [LCGU ROI − mean global LCGU]/standard deviation for LCGU in all regions].[28,30] Many of the brain regions responsible for nociceptive processing were not evaluated in the previous study.[29] For pattern analysis, the regions selected were: (1) cortical regions: visual, auditory, parietal, sensory/motor, and frontal; (2) subcortical regions: superior colliculus, mamillary body, medial geniculate, dentate gyrus, anterior hippocampus, lateral geniculate, amygdala, lateral thalamus, ventral thalamus, habenula, hypothalamus, globus pallidus, and caudate; and (3) brainstem regions: cerebellar cortex, cochlear nucleus, vestibular nucleus, superior olive, lateral lemniscus, pontine gray, and inferior colliculus. Z-score pattern analysis usually is followed by Q-component factor analysis to assign statistical significance to differences in the patterns.[30] This was not possible with the small number of subjects in the current studies, so the significance of the patterns calculated remains unresolved.

Results

The effects of noxious stimulation and thiopental infusion on the measured physiologic variables are summarized in table 1. There were no significant differences between initial values determined in the control and thiopental-treated animals. In the control group, the final mean Pa_{CO_2} value was significantly less (37 ± 2 mmHg; $P < 0.05$) than the initial values (41 ± 2 mmHg) and the final blood glucose value (8.3 ± 0.95 mmol/dl) significantly greater than initial values (6.9 ± 0.94 mmol/dl). Thiopental infusion caused a respiratory acidosis: the Pa_{CO_2} increased from 40 ± 2 to 48 ± 4 mmHg ($P < 0.05$), and the *p*H decreased from 7.43 ± 0.01 to 7.35 ± 0.02 ($P < 0.05$). Rectal temperature fell in the thiopental treated animals, from 36.7 ± 0.7°C to 35.4 ± 1.2°C ($P < 0.05$).

The infusion strategy provided plasma thiopental concentrations within the target range of 10–15 μg/ml throughout the period of noxious stimulation and nociceptive threshold measurements. Plasma thiopental concentrations before and during the 2-DG study were 11.1 ± 1.8 and 13.0 ± 2.1 μg/ml, respectively (table 2). The initial SMRT values were similar in the control and thiopental-treated groups. The thiopental infusion decreased the SMRT from 277 ± 32 to 215 ± 25 g before the 2-DG injection, and this reduction was maintained throughout the first 20 min of the 2-DG experiment (215 ± 41 g, $P < 0.001$). The SMRT did not change in the control group ($P = 0.68$). All of the animals in the thiopental group showed a behavioral effect from the thiopental. Three animals were classified as "drowsy" and four were "very drowsy."

The results of the 2-DG measurements are summarized in table 3. The global mean LCGU in thiopental-treated animals (60 ± 9 $\mu mol \cdot 100\ g^{-1} \cdot min^{-1}$) was significantly less than in the control group (85 ± 5 $\mu mol \cdot 100\ g^{-1} \cdot min^{-1}$; $P < 0.001$). The regional differences in normalized LCGU were confirmed to be normally distributed by the Kolmogorov-Smirnov test (K-S distance = 0.06, $P = 0.052$). Analysis of the ΔLCGU values by analysis of variance revealed that

Table 1. Physiologic Values

Variable	Control (n = 7)		Thiopental Treated (n = 7)	
	Initial	Final	Initial	Final
Pa_{CO_2} (mmHg)	41 ± 2	37 ± 2*	40 ± 2	48 ± 4*
Pa_{O_2} (mmHg)	85 ± 7	98 ± 10	92 ± 7	98 ± 5
*p*H	7.43 ± 0.01	7.43 ± 0.01	7.43 ± 0.01	7.35 ± 0.02*
Rectal temperature (°C)	36.5 ± 0.5	36.6 ± 0.4	36.7 ± 0.7	35.4 ± 1.2*
MAP (mmHg)	127 ± 8	127 ± 16	128 ± 4	127 ± 17
[Glucose] ($mmol \cdot dl^{-1}$)	6.8 ± 0.94	8.3 ± 0.95*	7.6 ± 1.0	7.4 ± 0.5
Weight (g)	335 ± 22		316 ± 20	

Values are mean ± SD for 7 animals. Animals were weighed before catheter insertions.

* $P < 0.05$ by ANOVA *versus* initial values within the group.

Pa_{CO_2}, Pa_{O_2} = arterial tensions of carbon dioxide and oxygen, respectively; [Glucose] = plasma glucose concentration; Initial and final = sampling times at the beginning and end, respectively, of the 2-DG experiment.

Table 2. Somatic Motor Response Threshold Values

	Initial Measurement	Before 2-DG Measurement	During 2-DG Measurement	Within Group Analysis (ANOVA)
SMRT control group (7 animals)	247 ± 26	237 ± 33	235 ± 34	F = 0.386 *P* = 0.68
SMRT thiopental treated group (7 animals)	277 ± 32	215 ± 25*	215 ± 41*	F = 8.21 *P* = 0.003
Plasma thiopental concentration ($\mu g \cdot ml^{-1}$)		11.1 ± 1.8	13.0 ± 2.1	

Values are mean ± SD. SMRT = measurements of the somatic motor response threshold.

* Significant ($P < 0.05$) difference from the initial measurement.

there were significant differences among the regions ($F = 6.043$, $P < 0.001$). The state-dependent changes in LCGU in cortical regions postulated to be involved in nociception (primary somatosensory cortex, secondary somatosensory cortex, and cingulate cortex; $+3.4 \pm 14\%$) were significantly different from the visual and auditory cortex ($-18 \pm 13\%$, $P = 0.012$). Although there were significant changes in two structures in the mesolimbic antinociceptive loop, the nucleus accumbens and the habenular nucleus, the structures involved in the descending pain modulating system (periaqueductal gray and nucleus raphe magnus) did not show significant state-dependent differences.

Figure 1 shows the pattern of LCGU in 26 brain regions. The value Z quantifies, in units of standard deviation, the difference between the mean LCGU for the structure and the global mean LCGU across all structures. Thus, in this analysis, none of the structures in the cortical or brainstem regions was more than approximately 1.5 standard deviation units away from the global mean in any of the treatment groups. In the cortical and subcortical regions, there appear to be two consistent patterns. The animals subjected to tail pressure, with or without a thiopental infusion, demonstrate a pattern of regional LCGU variability similar to unstimulated normal control rats. The animals at surgical levels of anesthesia with pentobarbital or isoflurane show patterns in which LCGU variability appears to be less than in the unanesthetized groups. The brainstem structures showed much greater variability in all groups studied, and we cannot discern any simple patterns in these structures.

Discussion

The main findings of this study were that, during a thiopental infusion that decreased the SMRT to tail pressure by 23% ($P < 0.001$), global LCGU decreased by 29% ($P < 0.001$), and LCGU in cortical regions postulated to be involved in nociceptive processing was increased relative to the other cortical regions studied ($P = 0.012$). Thus the results support the hypothesis that cortical processing of noxious stimuli was increased (relative to other cortical sensory regions) during thiopental infusions that reduce the SMRT. However, this may have been the result of enhanced nociceptive processing rather than the cause. Our initial hope was that the results would demonstrate a consistent pattern in ΔLCGU throughout the cell assemblies that are hypothesized to be involved in pain perception. Specifically, we anticipated that the study would show increased of LCGU in sensory regions involved in both the affective and the discriminative aspects of pain perception, coupled with depression of LCGU in the brainstem nuclei involved in the descending pain modulating system. Such findings would be consistent with current hypotheses concerning the mechanisms of barbiturate-induced hyperalgesia.[10] However, the results of the current study do not conform to such a pattern and fail to support selective depression of the periaqueductal gray and the nucleus raphe magnus as a mechanism for the reduction in the SMRT observed.

ΔLCGU during the thiopental infusion was significantly different in two of the mesolimbic nuclei involved in antinociception, the nucleus accumbens (+17%) and the habenular nucleus (−17%), and in structures in the auditory system. The relative increase in the nucleus accumbens is not likely to be responsible for the decrease in the SMRT because activation of this nucleus is thought to have antinociceptive effects.[27] The likely effect of a relative depression of the habenula on nociception is not clear to us. The pattern of changes within the auditory system was not consistent. The auditory cortex and medial geniculate were relatively de-

Table 3. Local Cerebral Glucose Uti

Forebrain	8
S1	10
Cingulate cortex	9
S2	8
Thalamus, VPL nucleus	
Brainstem nuclei	
Periaqueductal gray	
Nucleus accumbens	
Nucleus raphe magnus	
Nucleus gigantocellularis	
Amygdala	
Habenula	1
Visual system	
Visual cortex	
Lateral geniculate body	
Superior colliculus	
Auditory system	
Auditory cortex	1
Medial geniculate body	1
Inferior colliculus	1
Lateral lemniscus	1
Superior olive	1
Cochlear nucleus	1

LCGU values are μmol · 100 g⁻¹ · min⁻¹, me
animal] × 100; ΔLCGU = state-dependent
nterval for the mean difference; S1 and S2
*P < 0.05.

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olive showed a relative increa
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of thiopental were heterogen
and subcortical systems subse
The SMRT to tail pressure v
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fects of thiopental on the SM
evidence to show that descen
systems do not influence the c
required to abolish the SMRT.
at much higher anesthetic c
used in the current study. For
of thiopental infusion, unresp
ulation usually occurs at plasm
tions greater than 25–30 μg/m
state are still responsive to ta

Table 3. Local Cerebral Glucose Utilization in 19 Regions of Interest

	Mean LCGU		Normalized LCGU (%)			
	Control (n = 7)	Thiopental (n = 7)	Control (n = 7)	Thiopental (n = 7)	ΔLCGU (%) (CI)	*t*-Statistic
Forebrain						
S1	84 ± 9	64 ± 9	98 ± 9	106 ± 6	8 (7)	1.48
Cingulate cortex	101 ± 10	73 ± 14	118 ± 9	120 ± 14	3 (18)	0.499
S2	92 ± 9	65 ± 11	108 ± 9	107 ± 5	0 (11)	0.061
Thalamus, VPL nucleus	81 ± 8	53 ± 8	95 ± 11	88 ± 5	−7 (9)	−1.233
Brainstem nuclei						
Periaqueductal gray	65 ± 6	42 ± 8	76 ± 9	70 ± 11	−6 (12)	−1.140
Nucleus accumbens	67 ± 8	57 ± 10	78 ± 6	95 ± 15	17 (15)	3.210*
Nucleus raphe magnus	57 ± 7	40 ± 11	67 ± 7	67 ± 15	0 (11)	0.029
Nucleus gigantocellularis	47 ± 5	40 ± 6	55 ± 6	65 ± 5	10 (8)	1.874
Amygdala	48 ± 6	40 ± 9	56 ± 6	65 ± 8	9 (10)	1.651
Habenula	101 ± 11	61 ± 9	118 ± 9	101 ± 7	−17 (5)	−3.165*
Visual system						
Visual cortex	98 ± 8	61 ± 8	114 ± 7	100 ± 8	−14 (13)	−2.585
Lateral geniculate body	76 ± 8	49 ± 8	89 ± 6	80 ± 7	−8 (10)	−1.512
Superior colliculus	80 ± 8	47 ± 10	93 ± 6	78 ± 16	−15 (11)	−2.886
Auditory system						
Auditory cortex	133 ± 2	82 ± 16	156 ± 7	134 ± 9	−22 (10)	−4.127*
Medial geniculate body	109 ± 3	68 ± 14	127 ± 7	111 ± 10	−16 (9)	−3.074*
Inferior colliculus	152 ± 12	103 ± 15	178 ± 11	171 ± 22	−7 (28)	−1.345
Lateral lemniscus	109 ± 9	93 ± 14	128 ± 7	154 ± 13	26 (15)	4.878*
Superior olive	123 ± 13	110 ± 18	143 ± 13	182 ± 24	38 (29)	7.168*
Cochlear nucleus	102 ± 13	79 ± 16	119 ± 10	130 ± 18	10 (18)	1.901

LCGU values are $\mu mol \cdot 100\ g^{-1} \cdot min^{-1}$, mean ± SD. n represents the number of animals. Normalized LCGU (%) = [LCGU in each region/global LCGU for each animal] × 100; ΔLCGU = state-dependent difference in normalized LCGU values between the thiopental-treated and the control animals; CI = 95% confidence interval for the mean difference; S1 and S2 = primary and secondary somatosensory cortices, respectively.

* $P < 0.05$.

pressed, and the lateral lemniscus and the superior olive showed a relative increase in activity. These data suggest that the functional effects of hyperalgesic doses of thiopental were heterogeneous within the auditory and subcortical systems subserving nociception.

The SMRT to tail pressure was used to quantify the response to the noxious stimulus in this study because this measure of nociception can be measured easily under the conditions required for autoradiography and because our laboratory previously determined the effects of thiopental on the SMRT.[1] Rampil[31] presented evidence to show that descending cortical and bulbar systems do not influence the concentration of isoflurane required to abolish the SMRT. This result was obtained at much higher anesthetic concentrations than those used in the current study. For example, in our model of thiopental infusion, unresponsiveness to head stimulation usually occurs at plasma thiopental concentrations greater than 25–30 μg/ml, and the animals in this state are still responsive to tail-clamp.[1] When administering barbiturates or isoflurane, anesthetic depth has a major influence on LCGU throughout the brain.[29] Surgical anesthesia with pentobarbital or isoflurane was associated with a 50% decrease in global LCGU[29] in comparison to the 29% decrease observed in the current study with thiopental. The Z value patterns presented in figure 1 suggest that surgical anesthesia with either pentobarbital or isoflurane is associated with a reduction in LCGU variability, probably due to the large decrease in glucose metabolism throughout the brain. In contrast, the pattern for thiopental remains similar to that for the unstimulated awake controls. Cleland *et al.*[9] suggest that supraspinal mechanisms are important in barbiturate-induced enhancement of nociceptive transmission, including effects on the SMRT. Thus we believe that, although the SMRT may be a spinal cord reflex, it may be a useful marker to identify states of enhanced nociceptive transmission. In the current study, we have used functional brain mapping with LCGU to simultaneously examine many of the brain

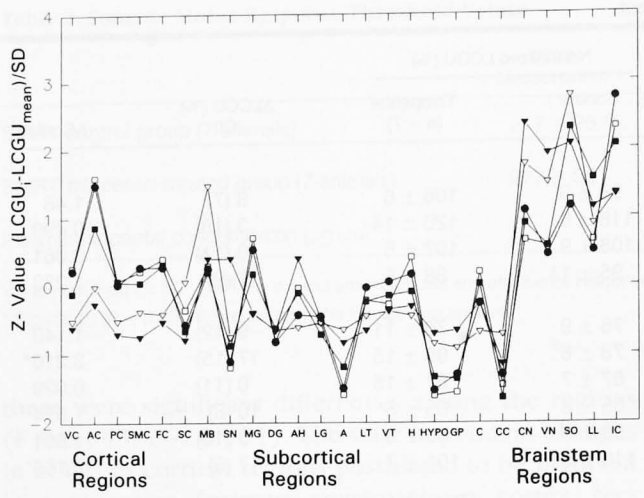

Fig. 1. Patterns of local cerebral glucose utilization (LCGU) in unstimulated animals (filled circles = unanaesthetized; empty triangles = anesthetized with isoflurane; filled triangles = anesthetized with pentobarbital) and in animals with repeated tail stimulation (empty squares = unanesthetized; filled squares = sedated with thiopental). LCGUi = LCGU in the region of interest, i.

regions involved in nociception. LCGU has been used previously to identify focal activation of brain regions by physiologic and experimental stimuli.[28,32] During stimulation of peripheral nerves, LCGU increased around the afferent synaptic terminals, not in the cell bodies of the dorsal root ganglion.[33] The investigators proposed that, at the cellular level, the increase in LCGU was related to increased activity of synaptic Na^+-K^+-ATPase required to restore ionic gradients after each action potential. If this result applies generally, then an increase in LCGU in a structure means that input to that structure is increased, without specifying whether that input is excitatory or inhibitory. In the current study this would imply, for example, that the increase in LCGU in the nucleus accumbens (+17%) reflected an increase in afferent input to that nucleus.

The results in the current study do not support the hypothesis that the hyperalgesic effects of thiopental result from enhancement of processing throughout the primary somatosensory pathway. The most that can be said from this study is that cortical regions proposed to be involved in nociceptive processing were relatively activated during hyperalgesia in comparison to other cortical regions, which were relatively depressed. Because both groups of animals received noxious stimulation of an intensity adjusted to the threshold of response, this relative increase in LCGU may represent enhanced cortical nociceptive processing during hyperalgesia. However, these results also may be explained simply by a relatively greater depression of unstimulated pathways by thiopental, with retained signal transmission and activation of the cortical projection of the primary somatosensory pathway.[32]

The physiologic changes caused by the thiopental infusion (decrease in rectal temperature and respiratory acidosis) were expected, because it was not practical to either servocontrol body temperature or to ventilate the lungs of sedated animals. Because the temperature coefficient Q_{10}, between 37°C and 27°C, is 2.2–2.4,[34] the temperature drop of 1.2°C likely decreased global LCGU by approximately 8%. Although the increase in Pa_{CO_2} from 40 ± 2 to 48 ± 4 mmHg in the thiopental group would be likely to increase cerebral blood flow, we are not aware of any evidence that changes of this magnitude would influence LCGU. The effects of these physiologic changes on LCGU would influence global LCGU and, therefore, would have been minimized by the normalization procedures. We are not aware of any evidence that focal changes in LCGU result from changes in body temperature or Pa_{CO_2} in this range.

It is difficult to assess the risk of a type II error in this study, because it is not clear what difference in LCGU we should expect and it is difficult to determine the power of the study to detect a pattern of LCGU change among several brain regions. The study is too small to detect isolated cortical LCGU increases of 9–11% associated with unilateral femoral nerve stimulation[32] (for a *t* test with a difference of 10%, SD 14%, $\alpha = 0.05$, $\beta = 0.80$, then n = 32 in each of the two groups). In contrast, in a study of chronic femoral nerve constriction, cortical LCGU increased 50–100%.[24] The current study has adequate power to detect isolated LCGU changes of 23% (for an unpaired *t* test with seven subjects in each group, SDΔLCGU = 14%, $\alpha = 0.05$, $\beta = 0.813$).

This study design has several important limitations that may be responsible for the failure to demonstrate specific enhancement of cell assemblies responsible for forebrain nociceptive processing. For cortical regions, we did not establish the exact location of the primary somatosensory cortex for the tail with an innocuous stimulus, such as vibration. Although we used the standard atlas locations, the activation may be sufficiently focal that this method could have missed an activation that was present.[32] This limitation does not apply to the anatomic locations of the subcortical and brainstem nuclei, which were identified easily on the

autoradiographs. Despite our efforts to minimize extraneous stimulation, during the 45 min of the LCGU measurement, the rats may have received unintentional visual, auditory, and tactile stimuli. Although the control animals were treated in the same fashion, this nonspecific stimulation may have contributed to variance in the measurements that made isolation of focal activation more difficult. We chose to stimulate the tail because this can be done without moving or disturbing the animal. Fore-paw or hind-paw stimulation usually requires that the animal be lightly restrained in a towel.[16] The choice of the tail unfortunately precluded side-to-side comparison of LCGU in each animal, a technique that may have been helpful in identification of small focal regions of activation.

In summary, the results of this study suggest that the cerebral functional effects of sedative concentrations of thiopental are heterogeneous. The distribution of metabolic changes does not support the hypothesis that enhanced nociceptive transmission is due to activation of the primary nociceptive pathways or selective depression of brainstem pain modulating nuclei. The results of this study require confirmation, particularly in experiments using stimulation paradigms in awake animals that can demonstrate activation of the primary somatosensory cortex.

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Does Early Pos
Endotoxin-indu

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Background: It is well known
lung injury, resulting in adult res
Lidocaine pretreatment has recen
endotoxin-induced lung injury in
rent study was to determine wh
ment with intravenous lidocaine
injury induced by endotoxin in
Methods: Thirty-two male ane
domly assigned to receive one o
each group): infusion of saline (
with lidocaine treatment (group
coli endotoxin (100 $\mu g \cdot kg^{-1}$ ov
lidocaine treatment (group E-S), o
lidocaine treatment (group E-L).
infusion of endotoxin (groups E
S-S and S-L), the animals receive
by continuous infusion of li
$mg \cdot kg^{-1} \cdot h^{-1}$ in groups S-L and E
E-S). The rabbits' lungs were ve
dynamics, peripheral leukocyte
terial O_2 tension (Pa_{O_2}) were rec
period (6 h). After the observat
fraction of bronchoalveolar lava
trations of activated complemen
cytokines, and arachidonic aci
measured and analyzed. The rat
weight (W/D weight ratio) and
BALF were analyzed as indexes o
pridina luciferin analogue–dep
(representing O_2^- production) b
the pulmonary artery and light
lung were compared among the

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