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Epidural Bupivacaine Suppresses Local Glucose Utilization in the Spinal Cord and Brain of Rats

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Using the 2-[^{14}C]deoxyglucose method, the effects of analgesic doses of epidural bupivacaine (300 μg) on local spinal cord glucose utilization (SP-LGU) of the cervical, thoracic, and lumbar regions and local cerebral glucose utilization (BR-LGU) in 38 brain structures were examined in conscious rats. In addition, the effects of intramuscular bupivacaine (300 μg) and the spinal cord transection (T2) were examined to determine whether the induced metabolic changes, if any, are related to the drug's systemic effect and/or deafferentation. Lumbar epidural bupivacaine sufficient to produce analgesia decreased SP-LGU in the thoracic (18–28%) and lumbar (21–29%) spinal cord but not in the cervical cord. Epidural bupivacaine decreased BR-LGU (15–26%) in 35 of 38 structures examined. With intramuscular bupivacaine, SP-LGU remained unchanged in almost all regions, while BR-LGU was significantly decreased (11–23%) in 23 structures. Plasma concentrations of bupivacaine in the epidural and intramuscular groups were comparable. With spinal cord transection alone, SP-LGU significantly decreased with varying degrees depending on the structure examined, but BR-LGU did not decrease in 36 of 38 structures examined. These results indicate that analgesic doses of epidural bupivacaine decrease SP-LGU, probably reflecting decreased neuronal activity of the spinal cord, and that reduced BR-LGU by epidural bupivacaine is most likely due to the drug's systemic effect rather than deafferentation. (Key words: Anesthetics, local: bupivacaine. Anesthetic techniques, epidural. Spinal cord, metabolism: glucose utilization.)

DESPITE EXTENSIVE USE of epidural anesthesia in clinical practice, we are unaware of any report, with the exception of one abstract reported by Lin *et al.*,‡‡ that describes its effects on spinal cord and cerebral metabolism. In the report by Lin *et al.*, epidural lidocaine attenuated the local spinal cord glucose utilization (SP-LGU) response to somatosensory stimulation in rats lightly anesthetized with halothane. Epidural lidocaine also decreased SP-LGU in the structures contralateral to stimulation. However, the sole effects of epidurally administered local anesthetics on spinal cord metabolism may be inconclusive. We therefore examined the effects of epidural bupivacaine on SP-LGU and local cerebral glucose utilization (BR-LGU) in conscious and minimally restrained rats. To determine whether the induced metabolic changes by epidural bupivacaine, if any, are related to the effects of the drug absorbed into systemic circulation and/or deafferentation, we also measured SP-LGU and BR-LGU following intramuscular administration of bupivacaine or spinal cord transection.

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‡‡ Lin DM, Shapiro HM, Shipko EM: Comparison of epidural lidocaine and fentanyl on spinal cord metabolism during sensory stimulation (abstract). ANESTHESIOLOGY 63:A232, 1985.

Materials and Methods

EXPERIMENTAL GROUPS

After approval by the Animal Experimental Committee of Yamaguchi University, the experiments were performed using 39 adult male Wistar rats (weight, 250–325 g) allowed free access to food and water until the time of the experiments. The experimental protocol is illustrated in figure 1. In 29 rats, SP-LGU and BR-LGU were measured. The rats were randomly divided into four groups: epidural bupivacaine group (n = 7), intramuscular bupivacaine group (n = 7), spinal cord transection group (n = 7), and control group (n = 8). In the control group, four rats received epidural saline (40 μl) and four rats received intramuscular saline (40 μl). In the remaining ten rats, the duration of analgesia and the plasma concentrations of bupivacaine were measured after epidural (n = 5) or intramuscular (n = 5) administration of bupivacaine. In all rats given bupivacaine, 300 μg bupivacaine hydrochloride dissolved in 40 μl saline was injected. When bupivacaine was epidurally administered, the injection was followed by a 10-μl saline cannula flush to ensure that all of the drug had been infused. When bupivacaine was intramuscularly administered, the drug was injected into the major gluteal muscle.

EPIDURAL CATHETERIZATION

Lumbar epidural catheterization (PE-10, Becton Dickinson, Sunnyvale, CA) was performed in rats anesthetized with halothane as described by Bahar *et al.*[1] and in our previous report.[2] The catheter was inserted at the L5

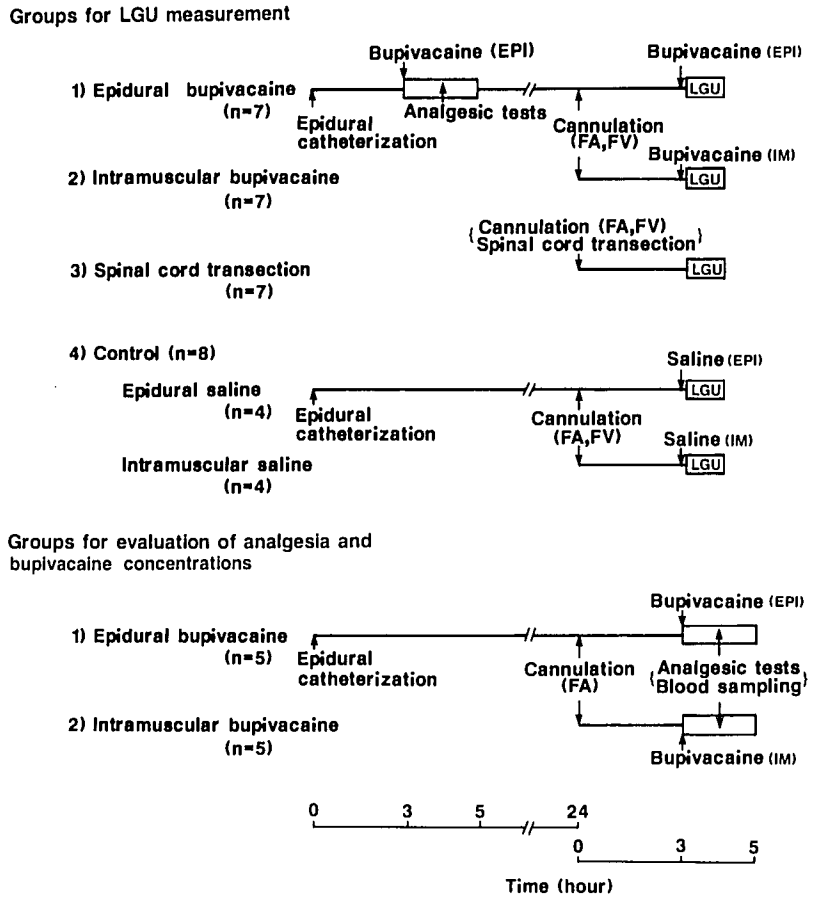

FIG. 1. Experimental protocol. LGU = local glucose utilization; FA = femoral artery; FV = femoral vein; EPI = epidural administration; IM = intramuscular administration.

level and advanced 2 cm cephalad so that its tip was located at the L2 or L3 level. The incisions were closed, and the halothane was discontinued. The rats were returned to their cages, and neurologic function was assessed for the next 24 h. None of the rats developed paralysis, spasticity of the hindlimbs, or abnormal gait during the 24-h observation period.

TESTS FOR ANALGESIA

Analgesia was evaluated by the tail flick (light intensity, 60 W; cutoff time, 20 s) and hot plate (plate temperature, 53° C; cutoff time, 30 s) tests as described by Durant and Yaksh.[3] Response latencies were expressed as the percentage of the maximum possible effect (%MPE).

$$\%\text{MPE} = \frac{\text{postdrug latency} - \text{predrug latency}}{\text{cutoff time} - \text{predrug latency}} \times 100\ \%$$

If rats do not remove their tails and hindlimbs at the preset cutoff time following heat stimulation, postdrug latency is equal to the cutoff time and %MPE becomes 100%. This indicates presence of profound analgesia. If there is no analgesic effect, postdrug latency is equal to the predrug latency and %MPE becomes 0%.

MEASUREMENT OF PLASMA BUPIVACAINE CONCENTRATIONS

Blood samples were obtained from the femoral artery at 10, 30, and 50 min after epidural or intramuscular administration of bupivacaine. Samples were centrifuged, and plasma was separated. The analysis was performed on a capillary column gas chromatograph (GC-7AG, Shimazu Co., Japan) equipped with a flame thermionic detector using mepivacaine hydrochloride as an internal standard. Recovery rate was 101%, and the coefficient of variation was 4%.

ANESTHESIA AND SURGICAL PREPARATION FOR MEASUREMENT OF GLUCOSE UTILIZATION

The rats were anesthetized with 2% halothane, and catheterization of the bilateral femoral arteries and veins was performed. In the rats with an epidural catheter, these procedures were done 24 h after epidural catheterization. In the spinal cord transection group, after arterial and venous cannulation, a laminectomy was performed at T2, the spinal cord was exposed, and the dura was incised under 2% halothane anesthesia. The rats then underwent a complete transection of the cord at T2. Thereafter, all

rats were minimally restrained with a pelvic plaster cast, and heparin (100 U per 0.1 ml) was given intravenously. Halothane was then discontinued, and 3 h were allowed to elapse before the start of drug injection and measurement of glucose utilization. In the spinal cord transection group, before the start of measurement of glucose utilization, motor and sensory blockade of the hindlimbs and tail was confirmed by the pinching and hot plate tests. In this group, continuous phenylephrine infusion (2–8 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was necessary to maintain mean arterial blood pressure (MABP) above 75 mmHg. In all other groups, MABP was maintained above 75 mmHg without phenylephrine. In all groups, Pa_{O_2}, Pa_{CO_2}, *p*H, and hematocrit were maintained within physiologic ranges. Rectal temperature was kept at 37° C by external means.

Measurement of Glucose Utilization

The 2-[^{14}C]deoxyglucose (2-[^{14}C]DG) method[4] was used to measure local glucose utilization. Details are described in our previous reports.[2,5] In the epidural and intramuscular bupivacaine and control groups, 2-[^{14}C]DG was given 5 min after drug injection. Timed arterial blood samples were taken during the 45-min period for plasma glucose and 2-[^{14}C]DG determinations, and thereafter, the rats were killed with an overdose of pentobarbital and decapitated. The brain and spinal cord were then removed. Before removing the brain and spinal cord of the rats given epidural bupivacaine and saline, Evans blue dye (40 μl) was injected through the epidural catheter followed by 10 μl saline cannula flush to estimate the distribution area of the drug. After serial sectioning (20 μm in thickness), the tissue sections were exposed to x-ray film (Kodak SB-5) for 10 days, along with a set of calibrated ^{14}C standards. For determination of local tissue ^{14}C concentrations, a computerized image-processing system (UHG-100 S1, Unique Medical, Japan) was used. The SP-LGU and BR-LGU were calculated from the tissue ^{14}C, plasma glucose, and 2-[^{14}C]DG concentrations using the equations and constants given by Sokoloff *et al.*[4]

Measurements of glucose utilization in the lumbar (L1 or L2) and cervical (C6 or C7) spinal cord were made in nine gray and three white matter regions. In the thoracic spinal cord (T6 or T7), gray matter was divided into eight regions because Rexed lamina VI was not identifiable in this area. Sections of the spinal cord immediately adjacent to those used for autoradiography were stained with hematoxylin and eosin for histologic identification of the spinal cord structures and for comparison of the autoradiograms with an atlas of the rat CNS.[6] Since our autoradiographic method was unable to discriminate lamina I from lamina II, we combined them (laminae I–II). The BR-LGU in 38 regions, including the structures related to pain modulation, were also determined.

Statistics

Statistical differences among groups were tested by one-way analysis of variance. If the *F* statistic of analysis of variance was significant, the least significant difference was applied for the multiple comparisons. $P < 0.05$ was considered statistically significant.

Results

The Duration of Analgesia by Epidural Bupivacaine and Plasma Concentrations of Bupivacaine

The results of tail flick and hot plate tests (expressed as %MPE) in rats given bupivacaine epidurally or intramuscularly are shown in figure 2. Although the intensity of analgesia was declining, analgesia persisted throughout the entire period of glucose utilization measurement. Motor blockade by epidural bupivacaine as judged by muscle flaccidity (not quantitatively evaluated) was vari-

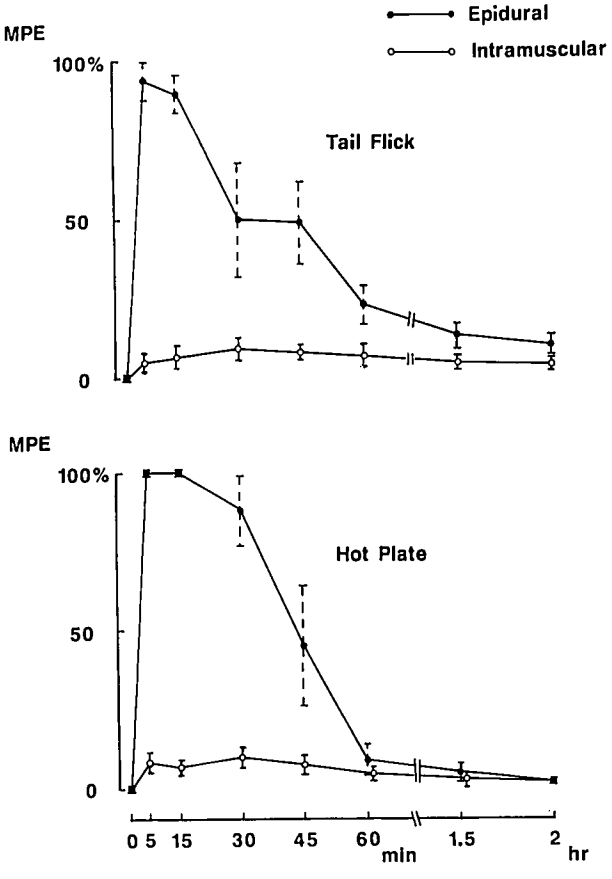

FIG. 2. Time course of percentage of the maximum possible effect (MPE) on the tail flick and hot plate tests after the administration of epidural or intramuscular bupivacaine (300 μg). Time 0 is the time at which bupivacaine was administered. Each point represents the mean ± SE of five rats.

able. Intramuscular bupivacaine did not produce analgesia (%MPE < 20%).

Plasma concentrations of bupivacaine at 10, 30, and 50 min after injection were 0.46 ± 0.05, 0.24 ± 0.02, and 0.20 ± 0.01 μg/ml (mean ± SE) in the intramuscular group, respectively; in the epidural group, they were 0.39 ± 0.06, 0.17 ± 0.03, and 0.10 ± 0.01 μg/ml, respectively. There were no significant differences in bupivacaine concentrations at 10 and 30 min after injection between the groups. At 50 min, bupivacaine concentration in the intramuscular group was significantly higher than that in the epidural group.

Glucose Utilization in the Spinal Cord and Brain

In the rats used for the measurement of SP-LGU and BR-LGU, time course of analgesia after the administration of epidural bupivacaine (evaluated 24 h before the measurement of glucose utilization) was almost identical to that in the rats used for the measurement of the duration of analgesia and plasma concentrations of bupivacaine. Evans blue dye given at the end of experiments was distributed into the lumbar and thoracic spinal cord and not in the cervical spinal cord. Within the control group, there were no significant differences in physiologic variables and glucose utilization between the rats given saline either epidurally or intramuscularly. Therefore, we combined these values and regarded them as the control values.

The physiologic variables in the control, epidural bupivacaine, intramuscular bupivacaine, and spinal cord transection groups are shown in table 1. In the epidural bupivacaine and spinal cord transection groups, MABP was significantly decreased compared to that in the control group. However, hypotension of this degree would not be expected to affect glucose utilization. The plasma glucose concentration in the spinal cord transection group was significantly less than that of the control group, but within the physiologic ranges and acceptable for applying the current method for measurement of glucose utilization.[7] All other physiologic variables were not different among the groups and were all within the physiologic ranges.

The SP-LGU and BR-LGU values are shown in tables 2 and 3. Epidural bupivacaine produced a significant decrease of SP-LGU in all Rexed laminae and white matter regions of the thoracic (18–28%) and lumbar (21–29%) spinal cord with little regional variability. Epidural bupivacaine also produced a significant decrease of BR-LGU (15–26%) in 35 of 38 structures examined. In the intramuscular bupivacaine group, however, SP-LGU remained unchanged in almost all regions examined but BR-LGU decreased significantly (11–23%) in 23 structures. With intramuscular bupivacaine, BR-LGU in six structures (table 3) was significantly higher (15–23%) than that with epidural bupivacaine. In the spinal cord transection group, BR-LGU did not decrease significantly except in the frontal cortex (10%) and cuneate nucleus (21%), while SP-LGU decreased significantly in the dorsal white matter regions (22–33%) in all spinal cord, laminae I–V (14–22%) and lateral white matter region (18%) in the lower thoracic cord, and laminae I–II, III (15–17%), and lateral ventral white matter regions (20–21%) in the lumbar cord.

Discussion

The current study demonstrates that epidural bupivacaine in a dose sufficient to produce analgesia decreases glucose utilization in the spinal cord and brain. The SP-LGU and BR-LGU values in the control group are comparable with those in our previous report[2] and those reported by Crosby *et al.*[8] The decrease in SP-LGU with epidural bupivacaine was observed in both gray and white matter regions of the thoracic and lumbar spinal cord where the drug was assumed to be distributed (judged, although not proved, by the Evans blue dye distribution). Since there was no significant change in the cervical spinal cord metabolism, the decreased SP-LGU

Table 1. Physiologic Variables

	Control* Saline 40 μl (n = 8)	Epidural Bupivacaine 300 μg/40 μl (n = 7)	Intramuscular Bupivacaine 300 μg/40 μl (n = 7)	Spinal Cord Transection (n = 7)
Temperature (° C)	37.1 ± 0.1	36.9 ± 0.1	36.8 ± 0.1	37.0 ± 0.03
MABP (mmHg)	108 ± 4	91 ± 5†	115 ± 2‡	81 ± 2†§
Pa_{O_2} (mmHg)	99 ± 3	102 ± 7	93 ± 6	87 ± 6
Pa_{CO_2} (mmHg)	42 ± 2	42 ± 1	41 ± 1	42 ± 3
*p*H	7.40 ± 0.02	7.44 ± 0.01	7.42 ± 0.01	7.43 ± 0.01
Hematocrit (%)	41 ± 1	40 ± 2	43 ± 1	43 ± 1
Plasma glucose (mg/dl)	195 ± 11	171 ± 11	175 ± 12	145 ± 6†

Values are mean ± SE.
* Epidural saline (n = 4) and intramuscular saline (n = 4).
† Significantly different from the control group ($P < 0.05$).
‡ Significantly different from the epidural bupivacaine group ($P < 0.05$).
§ Significantly different from the intramuscular bupivacaine group ($P < 0.05$).

TABLE 2. Local Spinal Cord Glucose Utilization

	Control* Saline 40 μl (n = 8)	Epidural Bupivacaine 300 μg/40 μl (n = 7)	Intramuscular Bupivacaine 300 μg/40 μl (n = 7)	Spinal Cord Transection (n = 7)
Cervical spinal cord				
Gray matter				
I–II	31 ± 1	28 ± 1	32 ± 1	29 ± 2
III	35 ± 1	31 ± 1	35 ± 1	34 ± 2
IV	39 ± 2	34 ± 2	39 ± 1	40 ± 2
V	41 ± 2	36 ± 2	42 ± 2	43 ± 2
VI	42 ± 2	37 ± 2	44 ± 1‡	44 ± 2‡
VII	41 ± 2	37 ± 2	43 ± 1‡	44 ± 1‡
VIII	37 ± 2	34 ± 2	40 ± 1	39 ± 1
IX	37 ± 2	33 ± 2	39 ± 1	39 ± 1
X	41 ± 2	38 ± 2	45 ± 2	43 ± 2
White matter				
Dorsal	18 ± 1	15 ± 1	19 ± 1‡	14 ± 1†
Lateral	20 ± 1	18 ± 1	21 ± 1	17 ± 1
Ventral	20 ± 1	19 ± 2	23 ± 1	18 ± 1
Thoracic spinal cord				
Gray matter				
I–II	32 ± 1	24 ± 1†	27 ± 2†	25 ± 1†
III	35 ± 1	27 ± 1†	32 ± 2‡	29 ± 1†
IV	35 ± 1	26 ± 1†	33 ± 1‡	30 ± 1†
V	37 ± 2	29 ± 2†	34 ± 1‡	32 ± 1†
VII	37 ± 2	30 ± 2†	36 ± 1‡	37 ± 2‡
VIII	36 ± 2	29 ± 2†	36 ± 1‡	37 ± 3‡
IX	32 ± 2	25 ± 1†	30 ± 1‡	30 ± 2‡
X	40 ± 2	32 ± 2†	39 ± 2‡	37 ± 2‡
White matter				
Dorsal	18 ± 1	13 ± 2†	17 ± 0.4‡	12 ± 1†
Lateral	17 ± 1	14 ± 1†	16 ± 1‡	14 ± 1†
Ventral	20 ± 1	15 ± 1†	19 ± 0.4‡	17 ± 1
Lumbar spinal cord				
Gray matter				
I–II	35 ± 1	26 ± 1†	32 ± 2‡	29 ± 2†
III	39 ± 1	29 ± 1†	36 ± 2‡	33 ± 2†
IV	42 ± 2	33 ± 2†	41 ± 2‡	39 ± 2‡
V	44 ± 2	33 ± 2†	44 ± 2‡	41 ± 2‡
VI	45 ± 2	35 ± 2†	45 ± 2‡	43 ± 2‡
VII	45 ± 3	35 ± 2†	45 ± 2‡	43 ± 2‡
VIII	45 ± 3	34 ± 1†	43 ± 2‡	41 ± 2‡
IX	41 ± 2	32 ± 1†	41 ± 2‡	38 ± 1‡
X	49 ± 3	38 ± 1†	47 ± 3‡	48 ± 3‡
White matter				
Dorsal	21 ± 1	15 ± 1†	20 ± 1‡	15 ± 1†
Lateral	24 ± 1	19 ± 1†	23 ± 1‡	19 ± 1†
Ventral	25 ± 1	19 ± 1†	24 ± 1‡	20 ± 1†

Values are mean ± SE ($\mu mol \cdot 100\ g^{-1} \cdot min^{-1}$).
* Epidural saline (n = 4) and intramuscular saline (n = 4).
† Significantly different from the control group ($P < 0.05$).
‡ Significantly different from the epidural bupivacaine group ($P < 0.05$).

in the lumbar and thoracic spinal cord with epidural bupivacaine could be attributed to local anesthetic blockade. It is unlikely that bupivacaine absorbed into the systemic circulation affected spinal cord metabolism because intramuscular bupivacaine had no effect on SP-LGU despite the fact that the plasma concentrations of bupivacaine with intramuscular use were comparable with those with epidural administration.

The results from this study agree in part with those previously reported by Lin *et al.*‡‡ The original design of their study was to examine the effect of epidural lidocaine on evoked metabolic response in the spinal cord to the peripheral stimulation in rats lightly anesthetized with halothane (0.5–0.6%). Although the authors stated that the reduction of SP-LGU was minimal, their results showed that epidural lidocaine (2%, 40 μl) significantly decreased SP-LGU (4–26%) in the lumbar spinal cord (both gray and white matter) contralateral to somatosensory stimulation. Although there are differences in the experimental protocols and drugs used between their

TABLE 3. Local Cerebral Glucose Utilization

	Control* Saline 40 μl (n = 8)	Epidural Bupivacaine 300 μg/40 μl (n = 7)	Intramuscular Bupivacaine 300 μg/40 μl (n = 7)	Spinal Cord Transection (n = 7)
Somatosensory cortex				
Whole area	88 ± 3	68 ± 3†	75 ± 3†	83 ± 4‡
Hindlimb projection area	84 ± 3	64 ± 4†	69 ± 3†	76 ± 3‡
Thalamus				
Mediodorsal nucleus	90 ± 5	70 ± 3†	78 ± 3†	83 ± 4‡
Ventrobasal complex	81 ± 3	65 ± 3†	71 ± 3	81 ± 4‡
Auditory system				
Cortex	101 ± 5	75 ± 4†	83 ± 6†	96 ± 8‡
Medial geniculate nucleus	85 ± 4	64 ± 4†	76 ± 5	86 ± 7‡
Inferior colliculus	106 ± 5	80 ± 7†	91 ± 4	94 ± 7
Visual system				
Cortex	79 ± 3	60 ± 3†	62 ± 2†	72 ± 4‡
Lateral geniculate nucleus	73 ± 3	56 ± 2†	66 ± 4‡	71 ± 3‡
Superior colliculus	71 ± 2	53 ± 2†	60 ± 3†	70 ± 5‡
Frontal cortex	88 ± 2	67 ± 3†	69 ± 2†	79 ± 4†‡
Limbic system				
Septal nucleus	55 ± 2	42 ± 3†	43 ± 2†	51 ± 2‡
Accumbens nucleus	75 ± 3	64 ± 4	64 ± 1	71 ± 4
Hypothalamus	56 ± 2	42 ± 2†	47 ± 2†	51 ± 2‡
Amygdala	73 ± 4	56 ± 3†	62 ± 3†	75 ± 4‡
Hippocampal formation				
CA1	59 ± 2	47 ± 2†	51 ± 2†	60 ± 3‡
CA3	60 ± 2	47 ± 3†	53 ± 2†	60 ± 3‡
Dentate gyrus	59 ± 2	46 ± 1†	53 ± 2‡	58 ± 3‡
Entorhinal cortex	70 ± 3	56 ± 3†	55 ± 3†	66 ± 4‡
Medial habenular nucleus	65 ± 2	53 ± 3†	61 ± 2‡	60 ± 3
Lateral habenular nucleus				
Medial region	79 ± 2	64 ± 3†	75 ± 3‡	76 ± 3‡
Lateral region	92 ± 3	71 ± 3†	82 ± 2†‡	86 ± 3‡
Interpeduncular nucleus	79 ± 3	65 ± 3†	68 ± 3†	75 ± 4‡
Mammillary complex	82 ± 3	65 ± 2†	72 ± 4	87 ± 7‡
Extrapyramidal system				
Caudate putamen	91 ± 2	69 ± 4†	72 ± 3†	82 ± 4‡
Substantia nigra	64 ± 3	50 ± 3†	55 ± 2	65 ± 5‡
Central gray	61 ± 2	45 ± 3†	49 ± 2†	56 ± 3‡
Dorsal raphe nucleus	66 ± 3	53 ± 3†	59 ± 2	66 ± 4‡
Median raphe nucleus	73 ± 3	56 ± 3†	63 ± 2†	72 ± 4‡
Raphe magnus nucleus	43 ± 3	34 ± 3	36 ± 1	41 ± 3
Locus coeruleus	56 ± 2	45 ± 2†	47 ± 2†	58 ± 2‡
Pontine reticular formation	53 ± 2	40 ± 2†	44 ± 1†	50 ± 2‡
Gigantocellular reticular nucleus	51 ± 2	40 ± 2†	42 ± 1†	47 ± 2‡
Paragigantocellular reticular nucleus	53 ± 3	42 ± 3	48 ± 1	50 ± 3
Dorsal column nuclei				
Cuneate nucleus	80 ± 6	61 ± 3†	67 ± 4	63 ± 4†
Gracile nucleus	56 ± 2	43 ± 2†	53 ± 4‡	49 ± 3
Corpus callosum	35 ± 3	29 ± 2†	27 ± 1†	34 ± 2
Cerebellar gray	52 ± 2	40 ± 2†	43 ± 2†	49 ± 3‡

Values are mean ± SE ($\mu mol \cdot 100\ g^{-1} \cdot min^{-1}$).
* Epidural saline (n = 4) and intramuscular saline (n = 4).
† Significantly different from the control group ($P < 0.05$).
‡ Significantly different from the epidural bupivacaine group ($P < 0.05$).

study and ours, it appears that epidural local anesthetics, when given in a sufficient dose to produce analgesia, decrease SP-LGU in both gray and white matter regions.

Cerebral effects of epidural analgesia may be related to the exposure of the brain to local anesthetics by means of vascular absorption and/or diffusion up to the cerebrospinal fluid[9] and also related to the deprivation of afferent input.[10] In the current study, BR-LGU decreased after both epidural and intramuscular bupivacaine, with the decrease being observed in many structures whether or not they were related to pain modulation. Furthermore, the plasma concentrations of bupivacaine obtained in the epidural and intramuscular groups were comparable. The results, therefore, indicate that bupivacaine absorbed into the systemic circulation from the epidural space affected cerebral metabolism. One may infer that

deafferentation may have partly contributed to the reduction in BR-LGU, because in six of 38 structures, BR-LGU in the epidural bupivacaine group was lower than that in the intramuscular bupivacaine group. To test this possibility, we examined BR-LGU changes after transection of the spinal cord, which provides complete blockade of both ascending and descending neural transmission, and found no significant changes in BR-LGU in 36 of 38 structures examined. Lin *et al.*§§ reported that intrathecal tetracaine caused a decrease in BR-LGU and attenuated the cerebral metabolic responses to unilateral sciatic nerve stimulation. They stated that the widespread decrease in glucose utilization can perhaps be explained by a generalized reduction in neural transmission in the presence of spinal subarachnoid block and halothane (0.5–0.6%) anesthesia. However, the present results indicate that deafferentation does not contribute significantly to the cerebral metabolic depression associated with epidural local anesthetic blockade.

In contrast to its minimal effect on BR-LGU, transection of the spinal cord decreased SP-LGU in varying degrees (14–33%) both in the gray and white matter regions of the spinal cord below transection. The effects of transection of the high spinal cord on SP-LGU deserves comment since we are unaware of any study except one reported by Schwartzman *et al.*[11] They demonstrated in monkeys that 24 h after spinal cord transection at the T10 level, SP-LGU decreased in laminae VI–IX and increased in lamina I in the lumbar region. They attributed the increase in SP-LGU in lamina I in the lumbar spinal cord to loss of descending inhibitory influences and the decrease in the ventral horn to loss of descending facilitatory influences. In the current study, metabolic depression was observed in both gray and white matter regions, and no significant increase in SP-LGU was observed in any structures examined. The differences in the results between Schwartzman's study and ours may be due to the differences of the species, the level of transection, and the time of measurement after transection. Nevertheless, it can be said that normal resting SP-LGU is modified by the neuronal activity of the descending modulatory systems. Lack of significant changes in spinal cord glucose utilization in the intramuscular bupivacaine group suggests that although cerebral metabolism is changed, the decrease either is not associated with changes in the activity of descending modulatory systems or that changes in the activity of these descending systems has little or no effect on spinal cord metabolism.

The effects of intrathecal local anesthetics on SP-LGU appear to be different from those of epidural anesthesia. Crosby[12] reported that SP-LGU did not significantly decrease in the gray matter (the decrease was equivocal; $P = 0.06$) despite profound sensory and motor blockade with intrathecal bupivacaine (0.75%; total, 25 μl). However, he observed a significant reduction of SP-LGU in the lateral and ventral white matter.[12] Currently, it is difficult to comment further on whether the differences in the spinal cord metabolic responses to intrathecal or epidural local anesthetics may indicate a difference in the site of action or may reflect differences in the spinal cord concentration of local anesthetic. Further studies are warranted to elucidate this point.

In summary, epidural bupivacaine decreases both cerebral and spinal cord glucose utilization, but the cerebral metabolic depression is probably due mainly to systemic absorption of bupivacaine.

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