Local Spinal Cord Blood Flow and Glucose Utilization during Spinal Anesthesia with Bupivacaine in Conscious Rats

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The author studied in conscious rats the local spinal blood flow (SCBF) and metabolic effects of intrathecally administered bupivacaine. Fourteen rats received 0.75% bupivacaine, 15 μl, through a chronically implanted lumbar subarachnoid catheter. Twelve control animals were treated identically, except that they received only an equal volume of saline intrathecally. Ten minutes after intrathecal drug injection, either local SCBF or glucose utilization was measured in the lumbar spinal cord of seven experimental and six control animals with the quantitative autoradiographic iodo-125Clantipyrene or 2-14Cdeoxyglucose methods, respectively.

Intrathecal bupivacaine produced a limp tail, absent hindlimb withdrawal to pinch, and 25-30 min of analgesia on the tail-flick test. Mean arterial blood pressure decreased 14% (P < 0.01) after bupivacaine was administered, but there was no change in arteriolar blood gases, pH, or rectal temperature. Subarachnoid bupivacaine reduced both local SCBF and glucose utilization, but the SCBF effect was larger. Local SCBF decreased 27-34% (P < 0.01) in all five spinal gray and three white matter areas measured, and there was little regional variability in the response. The reduction in spinal glucose utilization was regionally selective and less marked. For example, glucose utilization decreased 15% (P < 0.05) and 21% (P < 0.05) in lateral and anterior spinal white matter, respectively, but only decreased approximately 3% in laminae I-III and dorsal white matter (P > 0.1). A trend toward metabolic depression was also evident in laminae VII (−15%, P = 0.06), VII (−13%, P = 0.09), and IV-VI (−11%, P > 0.1). These results indicate that, regardless of whether it acts on the spinal cord itself or on extraspinal cord sites (e.g., spinal roots) to produce anesthesia, intrathecal bupivacaine alters the circulatory and metabolic state of the spinal cord. (Key words: Anesthetics, local; bupivacaine. Anesthetic techniques: spinal. Metabolism: glucose; spinal cord; regional. Spinal cord: blood flow, regional; metabolism, regional; glucose utilization, regional.

Spinal anesthesia is characterized by profound sensory, motor, and sympathetic blockade, which is thought to result from an action of the intrathecally administered local anesthetic on the roots, ganglia, and substance of the spinal cord.1 Although it appears that anesthesia results largely from the root or ganglia effects of the drug,1 there is reason to believe that the circulation and metabolism of the spinal cord might be altered. For example, because of the relationship in the central nervous system between functional activity and metabolism2 or blood flow,3 spinal anesthesia-induced sensory blockade could produce an associated reduction in spinal blood flow and metabolism. A direct spinal cord effect is also possible, however, because intrathecally administered local anesthetics penetrate the substance of the spinal cord4 and are vasodilators.5 Despite its clinical utility, however, studies of the spinal cord blood flow (SCBF) effects of spinal anesthesia are few, and its spinal metabolic effects have never been examined. Moreover, all studies of SCBF during spinal anesthesia have been performed in barbiturate- or halothane-anesthetized animals and, with the exception of a recent report6 indicating that subarachnoid lidocaine does not affect SCBF, the results are preliminary and inconclusive.7-9 Accordingly, the present study was designed to eliminate the influence of general anesthesia and to test the hypothesis that subarachnoid administration of a local anesthetic decreases spinal cord blood flow and metabolism in conscious animals.

Methods

Spinal anesthesia was produced with 0.75% bupivacaine in conscious, male, 350-400 g, Sprague-Dawley rats and local SCBF and glucose utilization measured with quantitative autoradiographic techniques.

Anesthesia

The spinal subarachnoid space of rats was catheterized according to the method of Yaksh and Rudy.10 During halothane-nitrous oxide anesthesia, the animal’s head was positioned in a stereotactic head-holder and a 15 cm length of polyethylene tubing (PE 10) inserted through a slit in the cisternal membrane. The catheter was advanced 8 cm caudally so that, as demonstrated radiographically,10 its distal tip lay at the rostral portion of the lumbar enlargement. After securing the catheter to the back of the animal’s neck and bringing the proximal tip out through the wound, the incision was closed and anesthesia discontinued. Rats were returned to their cages for 24-72 h, during which period neurologic function was assessed intermittently. Evidence of neurologic dysfunction (e.g., paralysis, spasticity, abnormal gait) prior to experiments or a malpositioned catheter noted at the time of spinal cord removal.

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resulted in exclusion from the study of four of 32 rats. Two additional experiments were omitted because of difficulties during the experiments.

In spite of extensive published experience with this method of administering drugs into the subarachnoid space of the rat,\textsuperscript{10,11} no reports have considered dose requirements for spinal anesthesia. However, on the basis of dye and radiolabeled morphine studies, Yaksh and Rudy\textsuperscript{10} reported that administering volumes of 20 μl or less intrathecally limits spread to 2–3 cm from the catheter tip. In preliminary studies, therefore, the effectiveness of 10–25 μl of preservative-free 0.75% bupivacaine was evaluated. Freely moving animals were observed after intrathecal administration of bupivacaine for hindlimb immobility, a limp tail, and absence of hindlimb withdrawal to a forceps pinch. Having established in this manner that bupivacaine, 15 μl, produced anesthesia confined generally to the hindquarters and tail, analgesia was quantified by the tail-flick response. For this purpose the tail of five partially restrained rats was placed over a slit 1.5 cm from a 150-watt focused projection bulb.\textsuperscript{11} The end-point of the test was removal of the tail; lack of any response by 6 s, after which time tissue damage occurred, was considered a maximal effect and was cause to terminate the trial. The results are expressed as maximum percentage effect (MPE)\textsuperscript{11} according to the formula:

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\text{MPE} = \frac{(\text{postinjection response latency}) - (\text{predrug response latency})}{(\text{cut-off time})} \times 100
\]

where the predrug latency and cut-off times equal 2 and 6 s, respectively. The efficacy of bupivacaine was established in these preliminary studies, and anesthesia was judged to be adequate during the actual experiments when the tail became limp and no attempt was made to withdraw a hindlimb pinched with a forceps.

On the day of experiments, animals with a previously implanted subarachnoid catheter were prepared during about 15 min of 1% halothane–70% nitrous oxide anesthesia with femoral artery and vein catheters. Animals were then partially immobilized with a pelvic plaster cast and allowed at least 3 h to recover from surgery and general anesthesia. Local SCBF and glucose utilization were measured in separate groups of seven experimental animals each. Spinal anesthesia was induced in both groups by administering intrathecally with a microliter syringe (Hamilton Co., Reno, Nevada) 0.75% bupivacaine, 15 μl. Because of the longer duration of the glucose utilization experiments, these animals received an additional 10 μl of drug 25 min after the first dose. Since the internal volume of the subarachnoid catheters was approximately 7 μl, each intrathecal drug injection was followed immediately by a 10 μl saline flush. Twelve control animals (six each for flow or glucose utilization measurement) were treated identically, but, instead of bupivacaine, received only equal volumes of saline intrathecally. Mean arterial blood pressure (MABP), arterial blood gases and pH, and rectal temperature were monitored frequently; temperature was maintained with a heat lamp. Local spinal blood flow and glucose utilization measurements began 10 min after intrathecal drug injection.

**Spinal Metabolism and Blood Flow Measurement**

The 2-[14C]deoxyglucose (2-[14C]DG) method\textsuperscript{12} was used to measure local spinal glucose utilization. Animals received an intravenous bolus of 2-[14C]DG (Amersham, Arlington Heights, Illinois), 125 μCi/kg, and timed arterial blood samples were taken during the 45-min experiment for plasma glucose and 2-[14C]DG determinations. Animals were killed by an overdose of pentobarbital, and the lumbar spinal cord was removed, frozen in isopentane (−50°C), and processed for autoradiography as described previously.\textsuperscript{12} Serial sections 20 μm thick were later cut at −20°C in a cryostat and autoradiographed along with a set of previously calibrated 14C methyl-methacrylate standards (Amersham, Arlington Heights, Illinois). Optical density measurements of the autoradiographic sections were made with a computerized image-processing system\textsuperscript{13} in five gray and three white matter regions approximating the organization of laminae and tracts in the spinal cord.\textsuperscript{14,15} A weighted average measurement for gray and white matter was also obtained. Local tissue 14C concentration was determined from the optical density measurements and the calibrated 14C standards. Local spinal glucose utilization was calculated from the tissue 14C concentrations, plasma glucose, and 2-[14C]DG concentrations, and the rate and lumped constants of the normal rat brain according to the operational equation of the method.\textsuperscript{12} Since oxygen is utilized in the central nervous system (CNS) almost entirely for the oxidation of glucose and the stoichiometry of this relationship is known, the rate of glucose utilization reflects directly CNS oxidative energy metabolism.\textsuperscript{16}

Local spinal blood flow was measured with the autoradiographic iodo-[14C]antipyrine (IAP) technique.\textsuperscript{17} IAP (Amersham, Arlington Heights, Illinois), 50–60 μCi in 1.5 ml physiologic saline, was infused intravenously at an increasing rate over 45 s. Timed arterial blood samples were collected and weighed, and the volume determined by assuming a specific gravity of 1.05 g/ml blood.\textsuperscript{17} Animals were killed by decapitation, and the lumbar spinal cord was removed within 2–3 min and
processed for autoradiography as discussed for 2-[14C]DG experiments. IAP autoradiographs of cord were also analyzed with the aid of an image-processing system in the same regions of the spinal cord described for the 2-[14C]DG experiments. Local spinal blood flow was calculated from the tissue and arterial blood concentrations of the tracer, a tissue–blood partition coefficient of 0.80, and the appropriate correction for lag and washout in the catheter as described by Sakurada et al.17

STATISTICS

All data were analyzed with an unpaired \( t \) test and \( P < 0.05 \) was considered significant. In addition, a linear correlation was performed between the per cent changes in MABP and SCBF (using weighted average values) produced by intrathecal bupivacaine.

Results

Intrathecal bupivacaine produced a clear and reversible increase in the latency of the tail-flick response, which lasted 25–30 min (fig. 1). During this time animals were alert and moved their forepaws both spontaneously and in response to pinch. Despite such evidence of lumbosacral anesthesia, the motor blockade was not always complete. An exaggerated, seemingly hyperreflexic tail withdrawal response was elicited in a few animals by pinching the tail, but no relationship between the presence of this response and higher rates of blood flow or glucose utilization was evident. For the purposes of statistical analysis, the physiologic data from the two control and two experimental groups were pooled (table 1). Subarachnoid bupivacaine had no effect on most of the physiologic variables (table 1) but, presumably because of sympathetic blockade, produced a 14% decrease in MABP (\( P < 0.01 \)).

Subarachnoid bupivacaine reduced both spinal blood flow and glucose utilization (table 2). The overall (i.e., weighted average) rate of blood flow to spinal gray and white matter decreased 34% (\( P < 0.01 \)) and 24% (\( P < 0.01 \)), respectively, and there was no correlation (\( r = 0.08 \) ) between this effect and the reduction in MABP. Blood flow to individual laminae and white matter tracts decreased 27–34%, and all such changes were significant (\( P < 0.01 \)). In contrast to its regionally uniform SCBF effects, spinal anesthesia produced a variable and less marked decrease in glucose utilization (table 2). Thus, overall spinal glucose utilization decreased only 10% (\( P > 0.1 \)), but the metabolic rate of lateral and anterior spinal white matter decreased 15% (\( P < 0.05 \)) and 21% (\( P < 0.05 \)), respectively. While laminae VII (−15%, \( P = 0.06 \)), VII (−15%, \( P = 0.09 \)), and IV–V1 (−13%, \( P > 0.1 \)) showed a trend toward metabolic depression, the metabolism of laminae I–III and dorsal white matter was affected little or not at all by spinal anesthesia. In fact, the per cent decrease in SCBF produced by subarachnoid bupivacaine exceeded that in glucose utilization in all individual spinal gray and white matter areas (fig. 2).

Discussion

Whether because of the proven safety of subarachnoid block,18 its largely extraspinal cord site of action,1 or the lack of suitable methods, studies of the spinal cord circulatory effects of spinal anesthesia have been infrequent. Smith et al.7 and De Rosayro et al.8 used microspheres to measure SCBF and reported that intrathecally administered lidocaine, tetracaine, and meptivacaine, with and without epinephrine, have no effect on the SCBF of anesthetized cats or dogs. Using similar methods, Kozody et al.9 studied tetracaine spinal anesthesia in anesthetized dogs and, despite a 28% decrease in MABP,

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Pooled data from the two control and two experimental groups expressed as mean ± SEM for number of animals in parentheses. * \( P < 0.01 \).
found a 150–188% increase in blood flow to the lumbo-sacral spinal cord. Unfortunately, interpretation of these preliminary studies is complicated by measurement of only an unweighted average of the normally very different gray and white matter flows, the use of super-

imposed barbiturate anesthesia, and problems inherent in using microspheres to measure SCBF. Perhaps for these reasons, the variability in the SCBF data, indicated by standard deviations averaging 60% of the mean, is large and obviates conclusions about the effects of spinal anesthesia on SCBF. In the only previous full report on the spinal cord circulatory effects of spinal anesthesia, Dohi et al. hypothesized that intrathecally administered lidocaine would reduce SCBF but they were unable to confirm such an effect. They measured lumbar SCBF by hydrogen clearance in 0.5% halothane anesthetized dogs with L3–5 laminectomies. Although the variance in their data is minimal, the fact that both halothane and laminectomy may affect SCBF could explain why no spinal circulatory effect of subarachnoid lidocaine was demonstrated. Indeed, so unexpected was this negative result that Dohi et al. considered it the “striking observation” of their report.

An important and unique feature of the present study is that the spinal cord circulatory and metabolic effects of an intrathecally administered local anesthetic were examined in conscious animals. Because this required insertion of a subarachnoid catheter, the SCBF effects of which have not been reported, one must consider the possibility that the catheter itself might bias the results. Inasmuch as others have demonstrated that animals with subarachnoid catheters remain neurologically normal for months, any direct effect of the catheter on spinal physiology would appear to be minimal. Directly supporting this view is the fact that the rates of local spinal glucose utilization in the present control animals are nearly identical to those obtained previously in this laboratory in similarly treated rats without spinal catheters.
Perhaps because the confounding influence of general anesthesia was eliminated and a sensitive measure of SCBF used, the present study demonstrates that subarachnoid bupivacaine decreases local SCBF 27–34%. Of the many factors that regulate SCBF under physiologic circumstances, subarachnoid bupivacaine altered spinal metabolic rate and systemic blood pressure. Even though no cause and effect relationship has been demonstrated, the fact that metabolic rate is a major determinant of blood flow in the CNS makes it reasonable to assume that reduced metabolic demand might explain a fall in SCBF. However, since spinal cord glucose utilization decreased only 3–21% (table 2), reduced metabolic demand can, at most, account only partially for the blood flow effects of subarachnoid bupivacaine. An alternative hypothesis is that the decrease in SCBF simply reflects systemic hypotension. Of course, this hypothesis assumes that, possibly by a direct vascular effect or sympathetic blockade, autoregulation of SCBF is impaired by spinal anesthesia. While evidence suggests that local anesthetics are vasodilators and that the sympathetic nervous system may play a role in controlling SCBF, it remains unknown whether autoregulation of SCBF is affected by spinal anesthesia. Even if autoregulation were completely abolished, however, it seems unlikely that the 14% decrease in MABP produced by subarachnoid bupivacaine could explain fully a 27–34% decrease in SCBF. In any event, the fact that there was no correlation between the decreases in MABP and SCBF indicates that, at least over the narrow range of blood pressures encountered, MABP was not a major determinant of the SCBF effects of bupivacaine. Finally, a combined effect of metabolic depression and a hypotension-induced reduction in SCBF is also improbable, since the former affects blood flow through increased vascular resistance, while the latter implies that vascular resistance is low and fixed. Thus, while subarachnoid bupivacaine decreases spinal cord blood flow, neither the associated regional spinal metabolic depression nor systemic hypotension provides an entirely satisfactory explanation for the effect.

The present results are not completely consistent with the prediction that intrathecal administered local anesthetics reduce spinal metabolic rate. The glucose utilization of lumbar spinal cord decreased 3–21% after subarachnoid bupivacaine, but not all changes were statistically significant (table 2). The decrease in glucose utilization could result indirectly from reduced sensory input to the spinal cord or, because intrathecally administered local anesthetics diffuse into it, a direct spinal cord effect. Given the profound sensory and motor blockade that characterizes spinal anesthesia, however, it may be surprising that spinal cord glucose utilization is not decreased further. The spinal cord metabolic effect of subarachnoid bupivacaine is similar, nevertheless, to that reported for other states of pharmacologic or pathologic depression of the spinal cord. For example, during both barbiturate anesthesia and the acute phase of spinal shock, local spinal glucose utilization decreases only 10–20% and it is reduced approximately 30% by halothane. It appears, therefore, that the spinal metabolic effects of subarachnoid bupivacaine do not differ greatly from those of general anesthesia.

Regardless of whether it acts on the spinal cord itself or on extraspinal cord structures (e.g., spinal roots) to produce anesthesia, intrathecal bupivacaine produces an altered spinal cord circulatory and metabolic state. It remains to be determined, however, whether a greater decrease in SCBF than metabolism is peculiar to spinal anesthesia with bupivacaine and what effect, if any, intrathecally administered local anesthetics have on autoregulation of SCBF. The availability of a reproducible experimental model of spinal anesthesia in conscious animals should prove useful in addressing these questions.

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