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A Comparison of Local Rates of Glucose Utilization in Spinal Cord and Brain in Conscious and Nitrous Oxide- or Pentobarbital-treated Rats

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Local rates of glucose utilization in the spinal cord and brain were measured with the 2-[^{14}C]deoxyglucose method in conscious and in paralyzed and mechanically ventilated pentobarbital- or 70% nitrous oxide-treated rats. In conscious animal lumbar spinal cord glucose utilization is only 40–50% that of the cerebral cortex and shows little laminar heterogeneity. Pentobarbital reduces and nitrous oxide increases the cerebral glucose utilization of most structures. The effect of paralysis and nitrous oxide analgesia on lumbar spinal cord glucose utilization is quantitatively similar to that produced in brain; 15–25% increases occur in most spinal cord laminae and cerebral structures. In contrast, the 10–20% reduction in spinal cord gray matter metabolism in the paralyzed and pentobarbital-treated animals is considerably less than the 20–50% depression measured in most brain structures. From these data the authors conclude that, relative to that of most cerebral structures, spinal cord metabolism is less sensitive to depression by barbiturates and suggest that differences in the cell populations of these tissues may account partially for this observation. (Key words: Anesthetics, gases: nitrous oxide. Anesthetics, intravenous: pentobarbital. Brain: glucose utilization; metabolism; regional. Metabolism: central nervous system. Spinal cord: glucose utilization; metabolism, regional.

THE LITERATURE is replete with studies of the cerebral metabolic effects of anesthetic and analgesic agents, but none has included the spinal cord in the structures examined. Those who study experimental conditions that require anesthesia and in which knowledge of the spinal metabolic effects of the drug are important for interpreting the results often have assumed that spinal cord metabolism responds much the same as that of the brain to anesthesia.[1–3] Although the assumption that brain and spinal cord are affected equally by anesthesia is likely to be qualitatively correct (*i.e.*, a drug that depresses cerebral metabolism is unlikely to stimulate that of the cord), the approach is complicated by the fact that anesthetic agents often produce regionally variable, and occasionally even opposite, metabolic effects in brain.[4–6] Furthermore, in view of the substantial differences in spinal cord and cortical gray matter cell populations[7,8] and metabolic rates in the conscious state,[9,10] it would not be surprising to find quantitative differences in their metabolic response to anesthesia. Therefore, in order to determine whether the brain and spinal cord respond similarly to anesthetic agents, we measured simultaneously the regional spinal and cerebral metabolic effects of pentobarbital (PB) anesthesia and nitrous oxide (N_2O) analgesia in paralyzed and mechanically ventilated rats. The results show that the metabolic rate of lumbar spinal cord in conscious rats is about 50% that of the cerebral cortex and displays minimal laminar heterogeneity. Pentobarbital reduces and nitrous oxide increases both spinal and cerebral glucose utilization, but whereas the effect of N_2O is small and quantitatively similar in brain and spinal cord, the depression of spinal metabolism by PB is far less than that which the drug produces in more metabolically active brain structures.

Methods

Local glucose utilization in both spinal cord and brain was measured with the 2-[^{14}C]deoxyglucose (2-[^{14}C]DG) technique[11] in adult, male Sprague–Dawley rats. Femoral arterial and venous catheters were inserted during approximately 15 min of 1% halothane:70% N_2O anesthesia. Control rats were restrained by a loosely-fitting pelvic plaster cast and were allowed to awaken after anesthesia was discontinued. Rats in the drug-treated groups had a tracheostomy performed and were paralyzed with gallamine (4 mg iv and supplemented) and ventilated mechanically. Five rats were ventilated with room air and received PB, 40 mg/kg, intraperitoneally soon after the halothane and nitrous oxide were discontinued; this was supplemented with PB, 10 mg/kg iv, 5

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min prior to the start of the experiments. Another five animals received 70% N_2O:30% O_2 delivered through a blender calibrated with an O_2 analyzer (Bird Corp., Palm Springs, California). Arterial blood gases and *p*H, mean arterial blood pressure (MABP), and rectal temperature were measured; temperature was maintained with a heat lamp, and the ventilator was adjusted to keep arterial blood gas tensions in the normal range.

Experiments were initiated a minimum of 1.5 h after discontinuation of halothane by the bolus injection of 125 μCi/kg of 2-[^{14}C]DG (spec. act., 51–55 mCi/mmol) and were continued for 45 min, during which period timed arterial blood samples were taken for measurement of plasma glucose and 2-[^{14}C]DG concentrations. Animals were killed by an overdose of PB, and the lumbar spinal cord and brain were removed and autoradiographed along with calibrated [^{14}C]methylmethacrylate standards as described previously.[11] The autoradiographs of lumbar cord generated by this procedure were analyzed with the aid of a computerized image-processing system[12]; brain autoradiographs were analyzed with a manual densitometer (Densichron PPD, Sargent-Welch Scientific, Skokie, Illinois). In the absence of distinct nuclear boundaries in cord, measurements were made in six gray and three white matter regions approximating the organization of laminae and tracts within the cord.[13] Because of their small size, the metabolic activity of some functionally distinct laminae had to be measured together. Local tissue ^{14}C concentrations were determined by comparison of the optical densities of the regions of interest with those of the calibrated standards. Rates of glucose utilization were calculated from the local tissue ^{14}C concentrations, the time courses of the plasma 2-[^{14}C]DG and glucose concentrations, and the rate and lumped constants of the normal rat brain according to the operational equation of the method.[11]

Statistical comparisons were made with the Dunnett's *t* test for multiple comparisons.[14]

Results

Except for MABP and Pa_{O_2}, there were no differences between groups in the physiologic variables (table 1). MAPB was lower in the PB group but remained within the autoregulatory range and, therefore, probably had no effect on glucose utilization. Similarly, we know of no evidence that the slightly higher Pa_{O_2} of the N_2O group, which was anticipated because this group received 30% O_2, affects the metabolic rate of neural tissue. In conscious rats the glucose utilization of lumbar spinal cord is lower than that of most brain regions and is only 50% that of the sensorimotor cortex (tables 2 and 3). The metabolic rate of spinal white matter is less than that of gray, and although some regional heterogeneity exists in the glucose utilization of lumbar gray matter, the variation is not as striking as that found in brain. Spinal laminae I–III and X have, respectively, the lowest and highest rates of glucose utilization in the spinal cord of conscious animals (table 2).

TABLE 1. Physiologic Variables

	Control (5)	PB (5)	N_2O (5)
Mean arterial blood pressure (mm Hg)	121 ± 3	87 ± 10*	131 ± 6
Rectal temperature (°C)	37.4 ± 0.2	37.1 ± 0.1	36.9 ± 0.1
Arterial *p*H	7.41 ± 0.02	7.46 ± 0.02	7.45 ± 0.02
P_{O_2} (mmHg)	92 ± 4	86 ± 6	134 ± 2†
P_{CO_2} (mmHg)	39 ± 3	39 ± 2	45 ± 2

Data represent mean ± SEM for five animals.
* $P < 0.05$; † $P < 0.01$ as determined by Dunnett's *t* statistics.

In the pentobarbital-treated animals there was a 12–20% decrease in the glucose utilization of most cord regions, but the reduction was statistically significant only in laminae IV–VI and the lateral funiculus (table 2). On the other hand, the cerebral glucose utilization of these same animals was statistically significantly reduced 20–50% in most structures (table 3). During N_2O analgesia the rate of glucose utilization increased in all spinal regions, and the changes were statistically significant in all laminae except I–III (table 2). The largest per cent increase (33–36%) in spinal glucose utilization during N_2O analgesia occurred in laminae VIII and IX of the ventral horn; dorsal horn laminae (I–III, IV–VI) showed lesser increases (14–20%). The cerebral metabolic effects of N_2O analgesia varied from a 5% reduction in the auditory cortex to a 28% increase in the medial geniculate body. Although 15–25% increases occurred in most brain regions during N_2O analgesia, the changes reached statistical significance in only five structures (table 3).

TABLE 2. Local Spinal Cord Glucose Utilization ($\mu mol \cdot 100\ g^{-1} \cdot min^{-1}$)

	Control (5)	PB (5)	N_2O (5)
Spinal gray matter			
Lamina (e) I–III	36 ± 2	31 ± 2	41 ± 2
IV–VI	44 ± 1	35 ± 3*	53 ± 2*
VII	46 ± 2	39 ± 3	58 ± 3*
VIII	45 ± 1	39 ± 2	61 ± 3*
IX	43 ± 1	38 ± 2	57 ± 3*
X	50 ± 2	43 ± 3	64 ± 3†
Spinal white matter			
Posterior funiculus	18 ± 1	17 ± 1	20 ± 1
Lateral funiculus	30 ± 1	24 ± 1*	36 ± 2*
Anterior funiculus	26 ± 0.3	25 ± 1	35 ± 3*

Data represent mean ± SEM for five animals.
* $P < 0.05$; † $P < 0.01$ as determined by Dunnett's *t* statistics.

TABLE 3. Local Cerebral Glucose Utilization ($\mu mol \cdot 100\ g^{-1} \cdot min^{-1}$)

	Control (5)	PB (5)	N_2O (5)
Sensorimotor cortex	88 ± 2	51 ± 4*	95 ± 4
Caudate nucleus	86 ± 2	54 ± 5*	109 ± 4*
Globus pallidus	49 ± 3	36 ± 2†	56 ± 4
Hypothalamus	43 ± 3	38 ± 4	50 ± 2
Thalamus: lateral nucleus	80 ± 6	51 ± 6*†	98 ± 3†
Auditory cortex	121 ± 4	62 ± 4*	115 ± 5
Medial geniculate	93 ± 4	52 ± 4*	120 ± 8*
Hippocampus	62 ± 3	53 ± 3	77 ± 2*
Dentate gyrus	49 ± 3	43 ± 3	53 ± 3
Substantia nigra	53 ± 4	40 ± 3†	60 ± 3
Visual cortex	81 ± 4	57 ± 7†	100 ± 4†
Inferior colliculus	148 ± 4	115 ± 9†	152 ± 9‡

Data represent mean ± SEM for five animals.
* $P < 0.01$; † $P < 0.05$ as determined by Dunnett's t statistics.
‡ Four animals.

Discussion

Certain characteristics of spinal cord glucose utilization in conscious rats are similar to those reported recently for the monkey.[10] In both species the rate of spinal gray matter glucose utilization is only 40–50% that of the sensorimotor cortex (tables 2 and 3)[9,10] and is among the lowest of central nervous system gray matter structures. Furthermore, there is relatively little metabolic heterogeneity in the laminae of the spinal cord[10]; in the rat only laminae I–III and X have rates of glucose utilization that differ moderately from the remaining spinal gray matter areas (table 2). Pentobarbital anesthesia resulted in a 20–50% reduction in local cerebral glucose utilization, an effect consistent with that reported previously in both spontaneously breathing, thiopental-anesthetized rats[11] and in paralyzed, mechanically ventilated, phenobarbital-treated rats.[15] In contrast, we find reductions of considerably lesser magnitude (10–20%) in spinal cord glucose utilization during PB anesthesia. The reported effects of nitrous oxide analgesia on cerebral glucose utilization have been less consistent; in spontaneously ventilating animals, slight reductions were found,§ whereas no change,[16] or small, region-specific increases[15,17] have been reported in paralyzed and ventilated rats. The present results, also obtained in paralyzed, mechanically ventilated animals, are consistent with the latter findings in that statistically significant increases in Glucose utilization during 70% N_2O analgesia are evident in a few cerebral structures. Nitrous oxide analgesia, however, produced quantitatively similar changes in spinal and cerebral glucose utilization. It has been suggested[15] that nitrous oxide stimulates directly cerebral glucose utilization and that this effect is attenuated by muscle paralysis. Perhaps the somewhat greater metabolic stimulation during 70% N_2O analgesia in the present study reflects lesser paralysis than that obtained in previous studies. In fact, it is not entirely accurate to attribute the effects reported in the present study to PB or N_2O alone, since control animals breathed spontaneously but both experimental groups were paralyzed and ventilated mechanically. As a practical matter, however, N_2O seldom is used experimentally without muscle paralysis, and barbiturates are known to have similar regional metabolic effects in unparalyzed[11] and paralyzed[15] animals.

Quantification of glucose utilization with the deoxyglucose method requires knowledge of the rate constants and the lumped constant, which have not been measured in spinal cord. Fortunately, a 45-min experimental period permits wide latitude in the values of the rate constants with very little error in the estimate of glucose utilization.[18] The lumped constant of the rat brain thus far has been found to vary only during pathologic conditions, such as extreme hypoglycemia[19] or status epilepticus,[20] and because the cord has a blood–tissue barrier and biochemical properties similar to those of the brain, there is little reason to suspect that the lumped constant of spinal cord would differ appreciably from that of brain. Indirectly supporting this opinion are the results of Hayashi *et al.*,[21] who measured spinal oxygen consumption with an oxygen microelectrode. Assuming a stoichiometric ratio of at least 5.5 $\mu mol\ O_2$ consumed in the oxidation of 1 μmol of glucose,[22] Hayashi *et al.*[21] found that the thoracic spinal gray matter of PB- and ketamine-anesthetized rats consumes sufficient oxygen to oxidize 27 μmol of glucose $\cdot 100\ g^{-1} \cdot min^{-1}$. Considering differences in anesthesia and that lumbar cord probably has a slightly higher rate of glucose utilization than thoracic cord,[10] their results compare favorably with the 38 μmol of glucose $\cdot 100\ g^{-1} \cdot min^{-1}$ utilized in the ventral horn of our PB-anesthetized animals. In addition, the fact that spinal blood flow is generally about 45–50% less than that of the cerebral cortex[23] suggests comparable differences in the metabolic rates of these regions; in conscious rats, the glucose utilization of lamina VIII is 51% less than that of the sensorimotor cortex (tables 2 and 3). Therefore, it is unlikely that use of the rate and lumped constants of brain introduces more than minor errors in the estimation of absolute rates of spinal glucose utilization.

That spinal cord metabolism is decreased during PB anesthesia to a lesser extent than that of cerebral structures with greater spontaneous metabolic rates is fun-

§ Sakurada O, Shinohara M, Kennedy C, Sokoloff L: Personal Communication.

damentally consistent with work demonstrating that neither general[24] nor spinal anesthesia[25] alter spinal blood flow. For example, in contrast to their profound effect on cerebral blood flow,[26] barbiturates have been found not to reduce spinal blood flow.[24] Moreover, previous work[27] showing large increases in spinal but not cerebral glucose utilization during somatosensory stimulation of PB-anesthetized animals indicates that stimulation-evoked spinal metabolism is also relatively resistant to depression by barbiturates. In fact, maximal pharmacologic depression of spinal metabolism may be less than the 50% achievable in brain.[28] While no data bear directly on this question, available evidence regarding both anesthetic effects[24,25,27] and spinal shock,[10] where, despite complete functional depression of the cord, only a 10–22% decrease in spinal glucose utilization occurs, suggests that, in general, spinal metabolism is perturbed less readily and extensively than cerebral metabolism.

Regional variability in the brain metabolic response to anesthesia is, of course, well documented.[4–6] The reasons for the difference are a matter of conjecture, however. With regard to the present study, the ratio of neurons to glia in rat cervical spinal cord is approximately 1:4,[7] while in cortex this ratio, at 4:1, is reversed.[8] The lower density of neurons in spinal cord partially may account for the lower spontaneous metabolic rate of this tissue because neurons are more metabolically active than most glial cells.[29] Furthermore, inasmuch as barbiturates reduce metabolism by reducing electrical or synaptic activity,[28,30] a tissue such as spinal cord with a low neuron:glia ratio may have fewer synapses that are susceptible to depression by barbiturates. Indeed, there appears to be a loose relationship between spontaneous local metabolic rate and magnitude of barbiturate-induced metabolic depression. The spinal cord response to PB anesthesia approximates more closely that of cerebral structures with comparably low spontaneous metabolic rates (*e.g.*, globus pallidus, hypothalamus) than those that are more metabolically active (*e.g.*, cortical regions, caudate, thalamus).

Among the implications of the present study, the most important is probably that extrapolation to spinal cord of results on the cerebral metabolic effects of anesthetics, particularly if the results are weighted toward cortical structures, may not be quantitatively valid. A practical corollary of this study is that any putative advantage that reduced metabolic demand conveys in the face of trauma or reduced perfusion may be minimal in spinal cord if PB or other similarly acting central nervous system depressants are chosen to achieve this end.

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References

1. Marcus ML, Heistad DD, Ehrhardt JC, Abboud FM: Regulation of total and regional spinal cord blood flow. Circ Res 41:128–134, 1977
2. Oldfield EH, Plunkett RJ, Nylander WA Jr, Meacham WF: Barbiturate protection in acute experimental spinal cord ischemia. J Neurosurg 56:511–516, 1982
3. Senter HJ, Venes JL, Kauer JS: Alteration of post-traumatic ischemia in experimental spinal cord trauma by a central nervous system depressant. J Neurosurg 50:207–216, 1979
4. Crosby G, Crane AM, Sokoloff L: Local changes in cerebral glucose utilization during ketamine anesthesia. ANESTHESIOLOGY 56:437–443, 1982
5. Shapiro HM, Greenberg, JH, Reivich M, Ashmead G, Sokoloff L: Local cerebral glucose uptake in awake and halothane-anesthetized primates. ANESTHESIOLOGY 48:97–103, 1978
6. Myers RR, Shapiro HM: Local cerebral metabolism during enflurane anesthesia: Identification of epileptogenic foci. Electroencephalogr Clin Neurophysiol 47:153–159, 1979
7. Mayhew TM, Momok CK: Stereological description of the anterior horn cervical cord of the adult rat: A quantitative study using the optical microscope. J Comp Neurol 156:107–122, 1974
8. Bass NH, Hess HH, Pope A, Thalheimer C: Quantitative cytoarchitectonic distribution of neurons, glia, and DNA in rat cerebral cortex. J Comp Neurol 143:481–490, 1971
9. Kennedy C, Sakurada O, Shinohara M, Jehle J, Sokoloff L: Local cerebral glucose utilization in the normal conscious macaque monkey. Ann Neurol 4:293–301, 1978
10. Schwartzman RJ, Eidelberg E, Alexander GM, Yu J: Regional metabolic changes in spinal cord related to spinal shock and later hyperreflexia in monkeys. Ann Neurol 14:33–37, 1983
11. Sokoloff L, Reivich M, Kennedy C, DesRosiers MH, Patlak CS, Pettigrew KD, Sakurada O, Shinohara M: The [^{14}C]-deoxyglucose method for the measurement of local cerebral glucose utilization: Theory, procedure, and normal values in the conscious and anesthetized rat. J Neurochem 28:897–916, 1977
12. Goochee C, Rasband W, Sokoloff L: Computerized densitometry and color coding of [^{14}C]deoxyglucose autoradiographs. Ann Neurol 7:359–370, 1980
13. Rexed B: The cytoarchitectonic organization of the spinal cord in the cat. J Comp Neurol 96:415–466, 1952
14. Dunnett CW: New tables for multiple comparisons with a control. Biometrics 20:482–491, 1964
15. Ingvar M, Abdul-Rahman A, Siesjö B: Local cerebral glucose consumption in the artificially ventilated rat: Influence of nitrous oxide analgesia and of phenobarbital anesthesia. Acta Physiol Scand 109:177–185, 1980
16. Tommesino C, Shapiro HM: Effect of nitrous oxide analgesia on local cerebral glucose utilization during immobilization stress. J Cereb Blood Flow Metab 3(Suppl 1):S572–573, 1983
17. Ingvar M, Siesjö BK: Effect of nitrous oxide on local cerebral glucose utilization in rats. J Cereb Blood Flow Metab 2:481–486, 1982
18. Sokoloff L: The radioactive deoxyglucose method. Theory, procedure, and applications for the measurement of local glucose utilization in the central nervous system, Advances

in Neuroschemistry, Vol. 4. Edited by Agranoff BW, Aprison MH. New York, Plenum Press, 1982, pp 1–82
19. Suda S, Shinohara M, Miyaoka M, Kennedy C, Sokoloff L: Local cerebral glucose utilization in hypoglycemia. J Cereb Blood Flow Metab 1:S62, 1981
20. Diemer NH, Gjedde A: Autoradiographic determination of brain glucose content and visualization of the regional lumped constant. J Cereb Blood Flow Metab 3:S79–80, 1983
21. Hayashi N, Green BA, Gonzales-Carvajal M, Mora J, Veraa RP: Local blood flow, oxygen tension, and oxygen consumption in the rat spinal cord. J Neurosurg 58:516–525, 1983
22. Siesjö BK: Brain Energy Metabolism. New York, John Wiley and Sons, 1978, pp 101–130
23. Sakurado O, Kennedy C, Jehle J, Brown JD, Carbin GL, Sokoloff L: Measurement of local cerebral blood flow with iodo[^{14}C]antiyprine. Am J Physiol 234:H59–66, 1978
24. Griffiths IR: Spinal cord blood flow in dogs. I. The "normal" flow. J Neurol Neurosurg Psychiatry 36:34–41, 1973
25. Smith SL, Albin MS, Watson WA, Pantoja G, Bunegin L: Spinal cord and cerebral blood flow responses to intrathecal local anesthetics with and without epinephrine. ANESTHESIOLOGY 59:A312, 1983
26. Pierce EC, Lambertsen CJ, Deutsch S, Chase PE, Linde HW, Dripps RD, Price HL: Cerebral circulation and metabolism during thiopental anesthesia and hyperventilation in man. J Clin Invest 41:1664–1671, 1962
27. Crosby G, Crane AM, Jehle J, Sokoloff L: The local metabolic effect of somatosensory stimulation in the central nervous system of rats given pentobarbital or nitrous oxide. ANESTHESIOLOGY 58:38–43, 1983
28. Michenfelder JD: The interdependency of cerebral functional and metabolic effects following massive doses of thiopental in the dog. ANESTHESIOLOGY 41:231–236, 1974
29. Siesjö BK: Brain Energy Metabolism. New York, John Wiley and Sons, 1978, pp 140–147
30. Richards CD: In search of mechanisms of anesthesia. Trends in Neuroscience 3:9–13, 1980