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4. Counted by B.P.
5. Symbols for the herbariums are those according to *Index Herbariorum* (International Association of Plant Taxonomists Utrecht, ed. 6, 1974): B, Berlin Botanical Gardens, Berlin Dahlem; BH, Bailey Hortorium, Cornell University; BM, British Museum of Natural History, London; CHAPA, College of Agriculture, Chapingo, Mexico; F, Chicago Natural History Museum; GH, Gray Herbarium, Harvard University; ENCB, Polytechnic Institute of Mexico City; ILL, University of Illinois, Urbana; K, Kew Gardens, London; L, Leiden, Holland; LIL, Instituto Lillo, Tucuman, Argentina; MEXU, National Herbarium of Mexico; MICH, University of Michigan; MO, Missouri Botanical Gardens, St. Louis; NA, National Arboretum, Washington, D.C.; P, Natural History Museum, Paris; TAES, Texas A & M, College Station; TEX, University of Texas, Austin; UC, University of California, Berkeley; US, U.S. National Herbarium, Smithsonian Institution, Washington, D.C.; WIS, University of Wisconsin, Madison; XAL, Institute of Biotic Resources, Xalapa, Mexico.
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Cerebral Glucose Utilization: Local Changes During and After Recovery from Spreading Cortical Depression

Abstract. *Cerebral glucose utilization is markedly increased in most areas of the cerebral cortex and reduced in many subcortical structures during spreading cortical depression. During recovery, cortical glucose utilization is still elevated, but the increased metabolic activity is distributed in columns running perpendicularly through the cortex.*

Spreading cortical depression, a phenomenon first described by Leão in 1944 (*1*), remains a puzzling and still poorly understood response of the cerebral cortex to a variety of noxious stimuli. It can be elicited by mechanical, electrical, thermal, and chemical stimuli (*2*) and is characterized by a spread of transient intense neuronal activity followed by depression in all directions from the site of initiation at a rate of 2 to 5 mm/min (*2*). This rate of spread is similar to that seen in the Jacksonian march of convulsions or the development of the scotomata of migraine in man (*2, 3*). The electrophysiological changes consist of depolarization and decreased electrical activity of neuronal units, depression of amplitude of the electroencephalogram, increased electrical impedance, and a negative shift in the d-c potential of the affected cortex (*2*). There is also evidence of chemical changes in the depressed cortex, for instance, a release of K^+ and an increase in extracellular K^+ (*4*), decreased cortical pO_2 (*2*), decreased concentrations of glycogen, glucose, and phosphocreatine (*5*), and increased concentrations of inorganic phosphate and lactic acid (*5*). Some of these chemical changes are suggestive of increased energy metabolism, but measurements of cerebral cortical energy metabolism in spreading cortical depression have not been reported. We have, therefore, employed the [^{14}C]deoxyglucose method (*6*) to determine the regional rates of glucose utilization within the brain during and after the evocation of spreading cortical depression.

The experiments were performed on normal male Sprague-Dawley rats weighing between 370 and 410 g. The procedure for measuring local cerebral glucose utilization has been described (*6*). Briefly, polyethylene catheters were inserted into a femoral artery and vein under light halothane-nitrous oxide anesthesia, and the animal was then restrained by application of a loose-fitting abdominal-pelvic plaster cast. Holes, approximately 2 to 3 mm in diameter, were drilled through the skull over the occipitoparietal cortex on both sides of the head to expose the dura, which was then kept covered with mineral oil. At least 2 hours were then allowed for complete recovery of the animal from the effects of anesthesia.

In one group of animals spreading cortical depression was induced in one cerebral hemisphere by the application of a filter paper disk soaked in 3*M* or 5*M* KCl to the exposed dura on that side. Another disk soaked in 0.15*M*, 3*M*, or 5*M* NaCl was applied to the exposed dura on the opposite or control side. Both disks were replaced with freshly soaked disks at 15- to 20-minute intervals until the end of the experimental procedure. The animals so treated remained conscious, but spreading cortical depression appeared within 3 to 5 minutes after application of the KCl disks and was manifested by a marked hemiparesis and hemianesthesia on the side of the body contralateral to the side of KCl application. Measurement of local cerebral glucose utilization was initiated 15 to 20 minutes after the first application of the KCl and NaCl disks by the administration of a pulse of 50 μCi of 2-deoxy-D-[1 − ^{14}C]glucose (specific activity, 50 to 55 μCi/μmole) via the femoral venous catheter. Arterial blood samples were rapidly drawn immediately after the pulse and at timed intervals for 45 minutes. The blood samples were immediately centrifuged to separate the red cells, and the plasma samples were stored on ice until subsequently analyzed for glucose and [^{14}C]deoxyglucose concentrations as described (*6*). At the end of the 45-minute period, the animal was decapitated, and the brain was removed as rapidly as possible, frozen in Freon XII chilled to −60° to −70°C with liquid nitrogen, sectioned, and subjected to quantitative autoradiography as described (*6*). Local cerebral glucose utilization was calculated from the time courses of the plasma [^{14}C]deoxyglucose and glucose concentrations and the tissue ^{14}C concentrations by the operational equation of the [^{14}C]deoxyglucose method (*6*).

In another group of animals spreading cortical depression was induced by the application of KCl directly on the surface of the parietal cortex. In these experiments the animal was reanesthetized with intravenous pentobarbital approximately 2 hours after recovery from the halothane-nitrous oxide anesthesia, the exposed dura was opened, and artificial cerebrospinal fluid containing 20 to 80 m*M* KCl was applied to one side of the parietal cortex and artificial CSF without added KCl was applied to the other side. The d-c potential of the cortical surface was monitored continuously by means of Marshall glass pore electrodes (outer diameter, 2 mm) (*2*). The recording electrode was applied to the surface of the cortex approximately 3 mm from the site of KCl application, and the reference electrode was placed in the subcutaneous tissues of the back of the neck. The outputs of the electrodes were amplified in a differential amplifier and displayed on the face of a Tektronix type RM565 oscilloscope or recorded by means of a Beckman model R611 polygraph. Local cerebral glucose utilization was measured under two sets of conditions in these experiments: (i) during sustained spreading cortical depression manifested by repeated waves of negative shifts of d-c potential caused by repeated applications of KCl, and (ii) immediately after return of the d-c potential to the normal value after a single wave of depression

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provoked by a single application of KCl. The procedure for the measurement of local cerebral glucose utilization was the same as that described above.

In all experiments, mean arterial blood pressure and arterial pCO_2, pO_2, and pH were monitored repeatedly throughout the experiment. Experiments were completed only if these physiological variables remained within normal limits.

In the conscious animals in which spreading cortical depression was induced by KCl application to the intact dura, glucose utilization increased markedly in most regions of the homolateral cerebral cortex as compared to the corresponding areas of the contralateral cortex exposed to NaCl (Table 1). These effects were so prominent that they could be readily visualized directly by increased optical density in the autoradiographs (Fig. 1A). The most prominent and consistent effects were in the frontal cortex and frontal pole. The effects in the parieto-occipital cortical area were more variable, possibly because of variations in the exact location of the holes in the skull (Table 1). In the affected cortical regions the glucose utilization increased in all layers of the cortex, but most dramatically in layers I and VI, and resulted in the loss of distinction of the cytoarchitectural cortical layers generally visible in the autoradiographs of the normal side (Fig. 1A). Layer IV is normally prominently represented in the autoradiographs of normal cortex; it could not be seen in the presence of spreading cortical depression (Fig. 1A), partly because of increased glucose utilization in the other layers and also because in some regions of the cortex (such as the auditory cortex) its metabolic rate was even slightly reduced.

In contrast to the increased metabolism in the cerebral cortex, glucose utilization was strikingly depressed in a number of subcortical structures of the experimental hemisphere (Table 1 and Fig. 1A). This depression of energy metabolism was particularly prominent in the caudate-putamen and thalamus; this may reflect the functional decortication associated with spreading cortical depression (*7*) and the consequent reduced cortical input through well-established corticocaudate and corticothalamic pathways to these regions. Structures of the midbrain and brainstem were affected very slightly if at all by spreading cortical depression (Table 1).

In the anesthetized animals in which spreading depression, manifested by the shift in cortical d-c potential, was induced and sustained by repeated applications of KCl directly to the surface of the cerebral cortex, the changes in local cerebral glucose utilization were essentially the same as those seen in the animals studied with the intact dura (Fig. 1B). When, however, glucose utilization was measured in these animals during the recovery period—that is, in the period immediately after the return of the d-c potential to normal following a single wave of spreading cortical depression produced by a single application of KCl—increased cerebral cortical glucose utilization was still apparent, but it appeared to be distributed in a pattern of darkened columns arrayed perpendicularly to the cortex and alternating with columns of almost normal or even depressed glucose utilization (Fig. 1B). These columns were particularly prom-

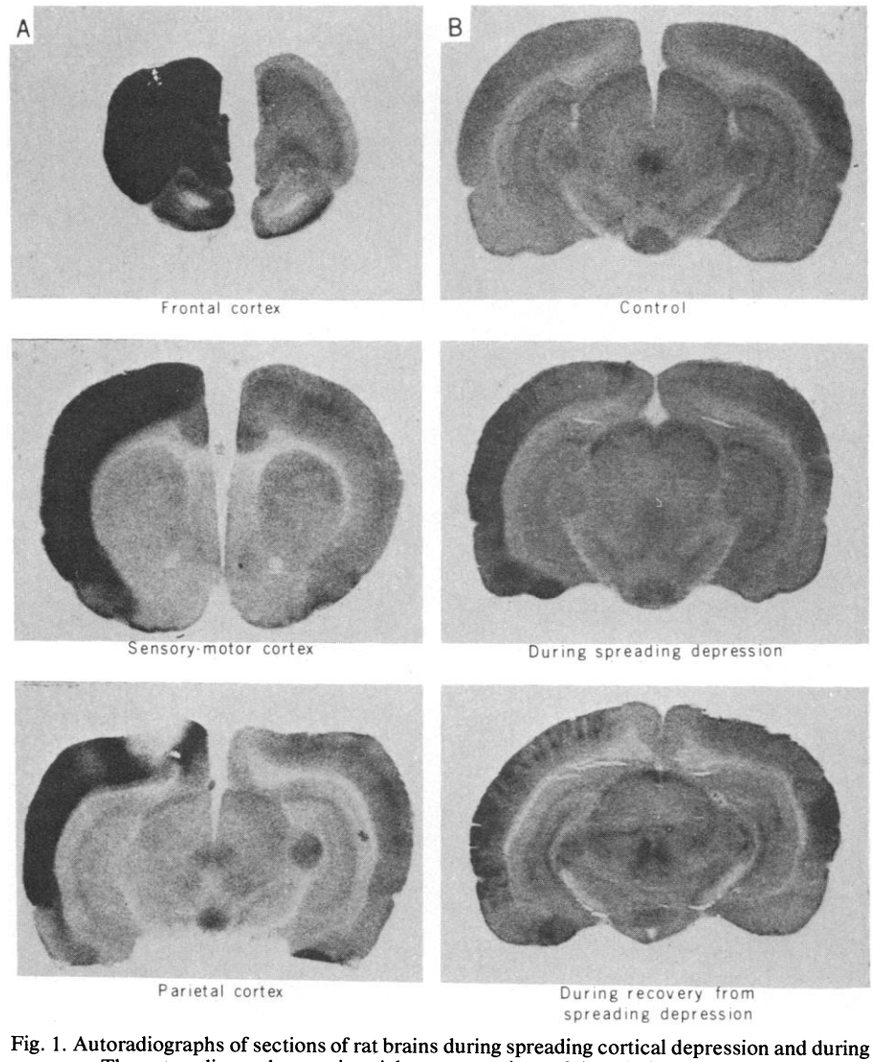

Fig. 1. Autoradiographs of sections of rat brains during spreading cortical depression and during recovery. The autoradiographs are pictorial representations of the relative rates of glucose utilization in various parts of the brain; the greater the density, the greater the rate of glucose utilization. The left sides of the brain are represented by the left hemispheres in the autoradiographs. In all the experiments illustrated, the control hemisphere was treated the same as the experimental side except that equivalent concentrations of NaCl rather than KCl were used. The NaCl did not lead to any detectable differences from hemispheres over which the skull was left intact and no NaCl was applied. (A) Autoradiographs of sections of brain at different levels of cerebral cortex from a conscious rat during spreading cortical depression induced on the left side by application of 5*M* KCl to the intact dura overlying the left parietal cortex. The spreading depression was sustained by repeated applications of the KCl at 15- to 20-minute intervals throughout the experimental period. (B) Autoradiographs from sections of brain at the level of the parietal cortex from three animals under barbiturate anesthesia. The top section is from a normal anesthetized animal; the middle section is from an animal during unilateral spreading cortical depression induced and sustained by repeated applications of 80 m*M* KCl in artificial cerebrospinal fluid directly on the surface of the left parieto-occipital cortex. At the bottom is a comparable section from an animal studied immediately after the return of cortical d-c potential to normal after a single wave of spreading depression induced by a single application of 80 m*M* KCl to the parieto-occipital cortex of the left side.

inent in the parietal cortex. The basis of this columnar arrangement of increased glucose utilization in the cerebral cortex during recovery from spreading cortical depression is unknown, but it may be related to the functional and morphological columnar organization of the cortex in units of afferent-efferent connectivity (*8*) or, possibly to the observation of a columnar distribution of adenosine triphosphate in the cerebral cortex (*9*).

Table 1. Effects of unilateral spreading cortical depression on local cerebral glucose utilization in conscious rats. Potassium chloride (5*M*) was applied to intact dura over the occipito-parietal cortex of the experimental hemisphere. The control side was treated similarly with physiological saline, 3*M* or 5*M* NaCl. The data represent the means ± standard error of mean obtained in seven animals. Probability values are for paired comparisons between control and experimental hemispheres.

Area	Glucose utilization (μmole per 100 g per minute)	
	Control hemisphere	Experimental hemisphere
Gray matter		
Visual cortex: layer IV	87 ± 4	76 ± 11
Visual cortex: layer VI	72 ± 1	98 ± 14
Auditory cortex: layer IV	115 ± 4	86 ± 5*
Auditory cortex: layer VI	89 ± 3	117 ± 11
Parietal cortex: layer IV	83 ± 4	108 ± 7*
Parietal cortex: layer VI	73 ± 3	102 ± 9*
Sensory-motor cortex: layer IV	92 ± 6	87 ± 5
Sensory-motor cortex: layer VI	72 ± 5	101 ± 5*
Olfactory cortex	82 ± 3	86 ± 5
Frontal cortex: layer IV	78 ± 2	121 ± 12*
Frontal cortex: layer VI	64 ± 2	136 ± 12†
Frontal pole	76 ± 4	160 ± 12†
Thalamus: lateral nucleus	81 ± 3	45 ± 2†
Thalamus: ventral nucleus	76 ± 4	47 ± 2†
Medial geniculate	93 ± 4	54 ± 3†
Lateral geniculate	77 ± 4	44 ± 1†
Hypothalamus	47 ± 2	44 ± 2*
Hippocampus: Ammon's horn	67 ± 3	54 ± 3†
Hippocampus: dentate gyrus	58 ± 3	53 ± 3*
Amygdala	40 ± 2	33 ± 2*
Septal nucleus	39 ± 2	36 ± 2*
Nucleus accumbens	61 ± 3	60 ± 4
Caudate-putamen	80 ± 3	54 ± 4†
Globus pallidus	45 ± 2	35 ± 1†
Substantia nigra	47 ± 2	41 ± 2*
Superior olive	109 ± 9	107 ± 7
Lateral lemniscus	91 ± 2	80 ± 7
Inferior colliculus	166 ± 11	146 ± 17
Superior colliculus	78 ± 3	64 ± 3*
Pontine gray	52 ± 2	49 ± 2
Vestibular nucleus	94 ± 4	95 ± 4
Cochlear nucleus	106 ± 7	110 ± 5
Cerebellar hemisphere	41 ± 1	43 ± 2
Cerebellar nucleus	80 ± 4	81 ± 3
White matter		
Internal capsule	26 ± 2	23 ± 2‡
Cerebellar white	29 ± 1	29 ± 2

*$P < .01$. †$P < .001$. ‡$P < .05$.

The present studies quantify the changes in energy metabolism throughout the brain during and after recovery from spreading cortical depression. Glucose utilization is increased in most areas of the cerebral cortex during repeated waves of spreading cortical depression, but columnar patterns suggestive of metabolic or functional cortical organization appear after a single wave of spreading cortical depression has passed. Glucose utilization is depressed in subcortical structures functionally connected to the cortex of the experimental side. The local and global changes reported here may be similar to those in focal epilepsy (*2*) and migraine (*3*) in humans, conditions that have some features in common with spreading cortical depression (*2*, *3*).

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