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Review: Does Measurement of Regional Cerebral Blood Flow Reflect Synaptic Activity?—Implications for PET and fMRI

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INTRODUCTION

Measurement of regional cerebral blood flow (rCBF) has become an increasingly powerful method of identifying brain areas associated with specific functions in humans *in vivo*. Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) are different methods of monitoring changes in rCBF or flow-related phenomena.

In the normal (nondiseased) brain, neuronal activity can be monitored with PET using a modification of the 2-deoxyglucose method developed by Sokoloff *et al.* (1977), i.e., 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG; for review see Herscovitch, 1994). Perfusion data can be obtained by use of radioactive tracers like $C^{15}O_2$, $H_2{}^{15}O$, or ^{15}O-butanol (for reviews see Frackowiak and Friston, 1994; Posner and Raichle, 1994; Woods *et al.*, 1994). Sequential measurements of regional cerebral blood flow with PET permit the attribution of specific functions to brain areas. The analysis of functional activations often depends on a comparison or subtraction of a control condition from an experimental condition. The performance of a specific cognitive or behavioral task may thus help to analyze functional specializations in the brain (Watson *et al.*, 1993; Frackowiak and Friston, 1994). Correlations of blood flow with task performance may also be performed (Frackowiak and Friston, 1994).

Using fMRI, changes in rCBF may be detected by a wide range of different tools, e.g., by the use of paramagnetic tracers like gadolinium diethylenetriaminepentaacetic acid (Gd-DTPA) or deoxygenation contrast (for review see Turner and Jezzard, 1994). This latter technique is based on the measurement of a deoxyhemoglobin signal that correlates with rCBF (Turner, 1994; Edelman *et al.*, 1994; Cohen and Bookheimer, 1994). Similar to PET, the analysis of activations with fMRI usually depends on a comparison or subtraction of a control from an experimental state or correlation with the temporal characteristics of the stimulus (e.g., on–off).

However, the application of these techniques is based on several assumptions: (i) regional cerebral blood flow correlates with local energy consumption and (ii) local energy consumption of the brain correlates with synaptic activity. In the present paper, we will therefore review the literature on these two major assumptions. Furthermore, we will discuss two major controversies: (i) does energy consumption reflect excitation or inhibition or both and (ii) to what extent does energy consumption reflect glial cell activity?

DOES REGIONAL CEREBRAL BLOOD FLOW CORRELATE WITH ENERGY CONSUMPTION?

Indirect Evidence for Coupling of Blood Flow and Metabolism

Under normal conditions, the brain uses glucose as its only source of energy (Wree and Schleicher, 1988; Clarke and Sokoloff, 1994; Hasselbalch *et al.*, 1994; Redies *et al.*, 1989; Duncan and Stumpf, 1991; Phelps *et al.*, 1981; Schwartz *et al.*, 1979; Fox *et al.*, 1988). After prolonged starvation, the brain may also use ketone bodies for its energetic needs (Hasselbalch *et al.*, 1994; Redies *et al.*, 1989; Clarke and Sokoloff, 1994).

As there are only minor glycogen stores in the human brain, a permanent supply of glucose via the blood is necessary (Clarke and Sokoloff, 1994). The average extraction fraction of glucose from the blood is approximately 8% (Hawkins *et al.*, 1983). Any interruption of this permanent energy supply causes an immediate failure of brain function as can be seen from the rapid loss of consciousness after interruption of blood supply to the brain (Wree and Schleicher, 1988; Clarke and Sokoloff, 1994). Although these facts provide indirect evidence for the importance of a permanent blood supply to the brain, they do not necessarily mean that energy consumption and blood flow are coupled on a *regional* level.

Correlation of Regional Cerebral Blood Flow and Local Glucose Metabolism

The question of whether regional CBF correlates with regional glucose metabolism has been examined

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in a large number of studies. Most of these used the deoxyglucose technique developed by Sokoloff and co-workers (1977). 2-Deoxy-glucose enters the brain using the same carrier system as glucose (Kennedy *et al.,* 1976; Clarke and Sokoloff, 1994; Wree and Schleicher, 1988; Lancet *et al.,* 1982; Hawkins *et al.,* 1985). Its metabolism, however, is restricted to the initial phosphorylation without any further catabolism within the glycolytic pathway (Wree and Schleicher, 1988; Clarke and Sokoloff, 1994; Lancet *et al.,* 1982; Hawkins *et al.,* 1985; Nelson *et al.,* 1984). It therefore accumulates in metabolically active structures and can thus be used to monitor glucose consumption.

Regional cerebral blood flow can be monitored using radiolabeled iodoantipyrine either separately (Lear *et al.,* 1981; Mies *et al.,* 1981) or in combination with 2-deoxyglucose as a double tracer technique (Lear *et al.,* 1981; Sokoloff, 1981; Ginsberg *et al.,* 1986, 1987; Furlow *et al.,* 1983) to monitor changes in blood flow and changes in glucose consumption under the same conditions.

Using these autoradiographic techniques, Sokoloff and co-workers demonstrated a close relationship between rCBF and glucose consumption in the rat brain as shown by a correlation coefficient of $r \geqq 0.95$ ($P < 0.001$; Sokoloff, 1981; Kuschinsky *et al.,* 1981, 1983; Clarke and Sokoloff, 1994). Similar results have been reported by other groups using double-label autoradiography in animals (Mies *et al.,* 1981; Lear *et al.,* 1981; Kelly and McCulloch, 1983; Ginsberg *et al.,* 1986, 1987; Wree and Schleicher, 1988; Hawkins *et al.,* 1983, 1985; Iadecola *et al.,* 1983).

Double-tracer techniques have also been applied in humans to monitor cerebral blood flow and glucose metabolism on a regional level. Again, these studies revealed a close coupling of rCBF and metabolism: Baron *et al.* (1982) examined rCBF and local glucose metabolism by consecutive measurements in the same subjects. They used inhalation of $C^{15}O_2$ to monitor rCBF and iv injection of 2-[^{18}F]fluoro-2-deoxy-D-glucose to examine glucose metabolism under resting conditions. Glucose utilization and blood flow were coupled as shown by a correlation coefficient of 0.92 ($P < 0.001$). Similar results have been reported by others for coupling of global (Freygang and Sokoloff, 1958; Sokoloff and Kety, 1960) and local blood flow and metabolism (Raichle *et al.,* 1976; Finklestein *et al.,* 1980; Blomqvist *et al.,* 1990; Clarke and Sokoloff, 1994).

In the above-mentioned studies, increases of neuronal activity lead to an increase in rCBF. However, the reverse has also been demonstrated. Kelly and McCulloch (1983) analyzed the effects of intravenous administration of muscimol on rCBF and local cerebral glucose utilization (lCGU). The GABA agonist is known to decrease neuronal activity mainly via its actions on central nervous $GABA_A$ receptors. Muscimol decreased blood flow and lCGU to the same extent in all 38 brain areas investigated. Thus, the relationship between the two parameters that was found in normal control rats was maintained after administration of muscimol.

Correlation of Regional Cerebral Blood Flow and Local Oxygen Consumption

In a normal adult man, the global cerebral blood flow is approximately 57 ml/min/100 g tissue. Global cerebral glucose utilization is ~5.5 mg/min/100 g, which is equivalent to a rate of glucose consumption of 31 μmol/min/100 g. Global cerebral oxygen consumption is ~3.5 ml/min/100 g, corresponding to a rate of 156 μmol/min/100 g (Clarke and Sokoloff, 1994).

In the resting brain, oxygen is almost entirely used for the oxidation of carbohydrates with only a small excess of glucose being metabolized to lactate (Clarke and Sokoloff, 1994). Thus, glucose and oxygen consumption are coupled via their chemical stochiometry

$$C_6H_{12}O_6 + 6O_2 \rightarrow 6H_2O + 6CO_2.$$

In accordance with these findings, Baron *et al.* (1982) reported a close correlation of oxygen and glucose consumption, which were consecutively examined in the same subjects at rest ($r \geqq 0.91$, $P < 0.001$). Furthermore, in the same subjects, the rate of oxygen and glucose consumption was closely coupled to regional cerebral blood flow ($r = 0.913$, $P < 0.001$). Similarly, Raichle *et al.* (1976) reported a close correlation of rCBF and oxygen consumption at rest. Furthermore, these authors also reported a correlation between rCBF and oxygen consumption during hand and forearm movements ($r = 0.91$, $P < 0.001$).

Temporal Coupling of Regional Cerebral Blood Flow to Neuronal Activity

Despite the vast amount of data demonstrating the close relationship between rCBF and lCGU (e.g., Clarke and Sokoloff, 1994; Raichle *et al.,* 1976; Wree and Schleicher, 1988), little is known about the regulation of cerebral blood flow at a regional level. Some authors claim that rCBF is mainly regulated by local carbon dioxide tension (pCO_2) and to a lesser degree by pO_2 and pH (Sokoloff and Kety, 1960; Clarke and Sokoloff, 1994). However, others stress the more important role of extracellular K^+ ions or of neurogenic factors (Fox and Raichle, 1986; Paulson and Newman, 1987; Gjedde, 1993).

Whatever the ultimate mechanism of regulation may be, the adjustment of rCBF to changes in neuronal activity seems to occur within a few seconds of the change in neuronal activity (Leniger-Follert and Hossmann, 1979; Sandman *et al.,* 1984; Fox *et al.,* 1988; Turner, 1994; Turner and Jezzard, 1994; Cohen and Bokkheimer, 1994). Leniger-Follert and Hossmann (1979) an-

alyzed changes of rCBF using local hydrogen clearance measured by electrochemical detection of changes in hydrogen partial pressure. They assessed changes of rCBF related to direct electrical stimulation of the cortex and effects of peripheral stimulation on blood flow in the sensorimotor cortex of the cat. After direct electrical stimulation of the cortex, blood flow increased within 1 s and persisted until the end of stimulation. Activation of the sensorimotor cortex by stimulation of the contralateral forepaw caused changes of rCBF which correlated with the site and amplitude of the primary evoked potentials. Similar results have been reported by Fox *et al.* (1988). Sandman *et al.* (1984) reported an averaged evoked vascular response measured with bioimpedance techniques. Changes in blood flow occurred 150 to 250 ms after onset of acoustic stimulation. These changes were thought to be neurogenically mediated vascular responses in preparation for an altered metabolic demand.

Recent fMRI experiments revealed that an increase in local neuronal activity causes a transient *hyper*emia within 5 to 10 s after onset of neuronal activity (Turner, 1994; Cohen and Bookheimer, 1994; Turner and Jezzard, 1994; Binder *et al.,* 1994). The initial hyperemia outweighs the effects of increased oxygen consumption (Turner, 1994). Therefore, the concentration of deoxyhemoglobin *de*creases with increasing neuronal activity (Turner, 1994; Turner and Jezzard, 1994; Cohen and Bookheimer, 1994; Binder *et al.,* 1994).

Does Physiological Stimulation Cause Uncoupling of Blood Flow and Oxidative Metabolism?

There is a general agreement about the coupling of oxygen and glucose consumption *at rest* (e.g., Clarke and Sokoloff, 1994; Raichle *et al.,* 1976; Yarowski and Ingvar, 1980; Hasselbalch *et al.,* 1994; DiRocco *et al.,* 1989; Kageyama and Wong-Riley, 1986; Baron *et al.,* 1982; Fox *et al.,* 1986, 1988).

Considerable controversy exists about the question whether oxygen consumption increases with physiological stimulation. Ackermann and Lear (1989) examined oxidative and nonoxidative glucose consumption in rats during visual stimulation with 16-Hz flashes. Glucose metabolism was oxidative in all brain areas except the optic tectum. Raichle *et al.* (1976) found a very good correlation between rCBF and oxygen consumption during hand and forearm movements ($r = 0.91$, $P < 0.001$). Similar results have also been reported by others (e.g., Clarke and Sokoloff, 1994; Leniger-Follert and Hossmann, 1979; Yarowski and Ingvar, 1980; Di Rocco *et al.,* 1989; Kageyama and Wong-Riley, 1986; Baron *et al.,* 1982).

However, Fox *et al.* (1986, 1988) reported that during visual stimulation, glucose uptake and blood flow increased by 51 and 50%, respectively. The oxygen consumption increased by only 5%. The authors argued that the oxidative glucose metabolism at rest is already working at (or near) its maximum capacity. Any further increase in neuronal activity must therefore lead to nonoxidative glucose metabolism, i.e., to glycolysis and lactate production under conditions of normal oxygenation.

Gjedde (1993) further analyzed the question of increased oxygen consumption due to physiological stimulation. He summarized the controversial results by different groups. Some authors reported that photic stimulation was accompanied by an increase in glucose uptake and blood flow without an increase in oxygen consumption. On the other hand, reversing checkerboard stimulation resulted in a 25% increase in blood flow paralleled by a 28% increase in oxygen consumption. Gjedde concluded that uncoupling of oxygen and glucose consumption may occur and that increases in oxygen consumption depend significantly on the neuronal pathway and the stimulus.

Therefore, the issue of whether physiological stimulation increases oxidative metabolism remains unresolved at the moment. However, three further aspects may be important:

(*i*) *Energetic demands.* While aerobic glucose metabolism yields about 30 mol of ATP/mol glucose, anaerobic glycolysis only yields 2 (Clarke and Sokoloff, 1994; Sokoloff, 1991). Thus, production of ATP from anaerobic glycolysis would be an enormous waste of energy resources (Sokoloff, 1991).

(*ii*) *Distribution of mitochondria.* Oxidative metabolism occurs in mitochondria, and cytochrome oxidase (C.O.) is one of the enzymes in the respiratory chain catalyzing the anabolism of ATP in the inner membrane of the mitochondrial cristae. The distribution of mitochondria and cytochrome oxidase reactivity therefore reveals foci of intense oxidative metabolism. Presynaptic axon terminals as well as postsynaptic regions are especially rich in C.O. (Gjedde, 1993; DiRocco *et al.,* 1989; Kageyama and Wong-Riley, 1986), thus indicating that neuronal activity does involve *oxidative* glucose metabolism. In other words, why should synapses be equipped with the organelles for oxidative metabolism (mitochondria) and not make use of them?

(*iii*) *Observations in humans.* Simultaneous measurements of rCBF, glucose, and oxygen consumption revealed a close correlation among these three parameters (Baron *et al.,* 1982). Physiological stimulation (e.g., hand and forearm movements) increased rCBF and oxygen consumption (Raichle *et al.,* 1976).

Although the effect of physiological stimulation on oxygen consumption is still a matter of debate, there is a general agreement that local cerebral glucose consumption and rCBF are coupled at rest *and* during physiological stimulation. Measurement of regional cerebral blood flow with PET or fMRI therefore reflects

energy (glucose) metabolism at rest as well as during physiological stimulation.

DOES ENERGY CONSUMPTION REFLECT NEURONAL ACTIVITY?

Biochemical Considerations

Under normal conditions, the brain uses glucose as its only source of energy (Wree and Schleicher, 1988; Clarke and Sokoloff, 1994; Hasselbalch *et al.,* 1994; Redies *et al.,* 1989; Duncan and Stumpf, 1991; Phelps *et al.,* 1981; Schwartz *et al.,* 1979; Fox *et al.,* 1988). Any increase in neuronal activity leads to an increase of regional cerebral blood flow. But what happens to glucose once it arrives in the brain? Is it needed for structural or functional metabolism?

Glucose enters the brain via a carrier system (Kennedy *et al.,* 1976; Clarke and Sokoloff, 1994; Wree and Schleicher, 1988; Lancet *et al.,* 1982; Hawkins *et al.,* 1985). Within the neuron, it may be metabolized via different pathways (Clarke and Sokoloff, 1994; Hothersall *et al.,* 1982; Nelson *et al.,* 1984; Gaitonde *et al.,* 1983; Wree and Schleicher, 1988; Hasselbalch *et al.,* 1994; Dienel *et al.,* 1992):

(*i*) *Synthesis of glycogen.* This accounts for approximately 2% of the resting glucose consumed by the brain. This pathway is almost completely restricted to glial cells.

(*ii*) *Synthesis of nucleotides and lipids.* The hexose-monophosphate shunt provides NADPH (nicotinamide-adenine-dinucleotide phosphate in reduced form) and all pentoses needed for the synthesis of DNA and RNA. It accounts for a maximum of 5–10% of the overall glucose utilization in the brain.

(*iii*) *Synthesis of proteins.* Only a minor portion of cerebral glucose is needed for protein synthesis (approximately 0.5%).

(*iv*) *Metabolism via the glycolytic pathway.* Most of the cerebral glucose is metabolized to pyruvate (85 to 90%). Pyruvate enters the mitochondrion (Clarke and Sokoloff, 1994; Smith *et al.,* 1978) and is further catabolized to carbon dioxide and water via the citric acid cycle. However, approximately 10% of pyruvate entering the mitochondrion is temporarily needed for the GABA-shunt (GABA, γ-aminobutyric acid). While there seems to be some "leak" of glucose (via glutamic acid decarboxylase into synthesis of GABA), most of the carbon atoms used for the synthesis of this transmitter are recycled into the citric acid cycle at a later stage.

Thus, at rest approximately 10–15% of cerebral glucose is needed for structural metabolism while the remaining 85–90% is needed to produce ATP (adenosine triphosphate). Most of the cerebral glucose is therefore used for oxidative metabolism to provide energy for functional metabolism in the brain. However, these numbers refer to metabolism *at rest.* When PET and fMRI are used to measure changes of rCBF, the energetic needs of structural metabolism are eliminated (e.g. activation studies). Therefore, these techniques reflect glucose metabolism which provides energy for functional neuronal activity.

Physiological Considerations

As explained above, glucose utilization can be monitored using the 2-deoxyglucose technique. Yarowski *et al.* (1983, 1985) examined the effects of electrical stimulation on glucose consumption. The rat superior cervical ganglion served as a model of the central nervous system. There was an almost linear increase in glucose utilization with increasing frequency of stimulation (correlation coefficient $r = 0.91$; Yarowski *et al.,* 1983, 1985). Similar effects have been observed with electrical stimulation of the sciatic nerve or visual stimulation (Kadekaro *et al.,* 1985, 1987; Clarke and Sokoloff, 1994; Kennedy *et al.,* 1975, 1976). Increases in glucose consumption with increasing neuronal activity have also been reported elsewhere (Yarowski and Ingvar, 1980; Phelps *et al.,* 1981).

The reverse of these effects has also been examined, i.e., decreases of functional activity lead to a reduced rate of glucose utilization. Sokoloff (1977) reported that the auditory pathway of the rat can be examined using the 2-deoxyglucose technique. Bilateral auditory deprivation by occlusion of the external auditory canals caused a depression of metabolic activity in this pathway. Reduction of neuronal activity by injection of muscimol, a GABA receptor agonist, caused a reduction in glucose utilization (Kelly and McCulloch, 1983). Similar decreases in glucose utilization due to reduced neuronal activity have been reported by others (Wree and Schleicher, 1988; Clarke and Sokoloff, 1994; Yarowski and Ingvar, 1980).

However, as most of these studies have been carried out in rodents, it is important to know whether the interpretation can be applied to experiments in humans. Blin *et al.* (1991) compared regional cerebral glucose consumption in rats and humans. They found a significant positive correlation of metabolic values ($r = 0.72$, $P < 0.001$) and coefficients of variation ($r = 0.59$, $P < 0.01$) between rats and humans under resting conditions. Thus, there is a considerable degree of similarity of glucose metabolism in the rodent and the human brain. Results obtained in rats may therefore help us to understand experiments performed in human subjects.

Furthermore, experiments in monkeys (Kennedy *et al.,* 1976) show similar effects of neuronal activity on glucose utilization. Moreover, Phelps *et al.* (1981) demonstrated effects of increased and decreased neuronal activity in humans: using the 2-deoxyglucose method (FDG), increases in cerebral glucose utilization were found in the visual pathway after stimulation with white light. Visual deprivation (either in subjects with

eyes closed or in a patient with neonatal blindness) decreased glucose utilization in the same areas.

DOES ENERGY CONSUMPTION REFLECT SYNAPTIC ACTIVITY?

Energy Consumption in the Perikaryon, Axon, and Synapse

As shown in the previous paragraph, glucose utilization reflects neuronal activity. However, it is not clear from the above-mentioned studies whether the energy is mainly needed in the perikaryon, the axon, or the synapse.

High-resolution autoradiography helps to further analyze this question. Cerebral metabolism examined at a cellular level in rats (Duncan *et al.,* 1987, 1991) revealed the contribution of neuronal cell bodies, neuropil, and glial cells to the process of 2-DG uptake. The frequency distribution of silver grain densities was examined in layers 2 and 3 of the somatosensory cortex (area of high 2-DG uptake) and in the lateral hypothalamus (area of low 2-DG uptake). In both areas, most of the 2-DG uptake occurred in the neuropil, i.e., not in cell bodies but areas rich in synapses, dendrites, and axons. Although a cellular resolution could be achieved with this technique, it does not clarify the problem completely.

As pointed out above, cerebral glucose is used for oxidative metabolism. These catabolic reactions are carried out in mitochondria which contain the enzyme complexes for the citric acid cycle as well as the respiratory chain. The cellular distribution of cytochrome oxidase (as one enzyme of the respiratory chain) therefore reveals sites of metabolic activity. The highest density of cytochrome oxidase is found in soma–dendrite regions opposite presynaptic axon terminals (Kageyama and Wong-Riley, 1986; DiRocco, 1989). Thus there is much more glucose utilization in axon terminals and dendrites (synapses) than in neuronal perikarya.

Several other studies support the view that glucose consumption mainly reflects synaptic activity: when rats are maintained on a sodium-rich diet (2% NaCl in drinking water for 5 days), the hypothalamo-neurohypophyseal system is physiologically stimulated (Schwartz *et al.,* 1979). During this experiment, glucose utilization was found to increase in the posterior pituitary, i.e., in axon terminals in the target area of hypothalamic osmoregulative cells. However, there was no increase in glucose utilization in the paraventricular and supraoptic nuclei which contain the cell bodies of the same neurons (Schwartz *et al.,* 1979).

When the transected sciatic nerve was stimulated electrically, glucose utilization increased in the dorsal horn of the spinal cord (Kadekaro *et al.,* 1985). The increase of glucose utilization in the dorsal horn was frequency dependent, i.e., there was a linear relationship between frequency of stimulation and glucose utilization. However, no such correlation was found for dorsal root ganglion cells. Thus, increased functional activity lead to enhanced metabolic activity in axon terminals and not the corresponding cell bodies. Identical results have also been reported by others (Wree and Schleicher, 1988; Clarke and Sokoloff, 1994; Nudo and Masterson, 1986; DiRocco *et al.,* 1989).

Does Glucose Utilization Reflect Pre- or Postsynaptic Activity?

From the above-described experiments, the important contribution of axon terminals to glucose consumption in functionally activated cells seems obvious. However, the next question is whether the increase in glucose utilization reflects pre- or postsynaptic activity.

Several groups have examined this question (Schwartz *et al.,* 1979; Kadekaro *et al.,* 1985, 1987; Nudo and Masterson, 1986; Wree and Schleicher, 1988; DiRocco *et al.,* 1989). The study by Schwartz *et al.* (1979) has already been presented: osmotic stimulation caused an increase in glucose utilization in axon terminals of the posterior pituitary (which does not contain postsynaptic neurons) but not in the corresponding neuronal cell bodies.

Kadekaro *et al.* (1985, 1987) used orthodromic and antidromic stimulation of the proximal stump of the transected sciatic nerve. Orthodromic stimulation activated pre- and postsynaptic elements causing an increase of glucose utilization. However, antidromic stimulation of the ventral root activated only postsynaptic structures. Interestingly, antidromic stimulation did not change glucose utilization. Thus, neither antidromic conduction nor excitation of postsynaptic cells lead to a significant increase of glucose utilization.

Nudo and Masterson (1986) performed an elegant experiment on antidromic stimulation of the medial superior olive (MSO) in the cat. After removal of the two cochlear nuclei, stimulation of the inferior colliculus resulted in pure antidromic stimulation of the ipsilateral MSO. Electrical stimulation caused an increase in glucose utilization in each of the orthodromically activated ascending and descending collicular projection targets. However, no elevation of 2-DG labeling occurred in the antidromically stimulated MSO.

To our knowledge, there is only one study which shows activation of postsynaptic cell bodies due to antidromic stimulation (Yarowski *et al.,* 1985). Stimulation of the external carotid nerve in rats caused a frequency-dependent increase in glucose utilization in the caudal portion of the ganglion which contains the cell bodies of origin of the external carotid nerve. However, due to the complex anatomy of the ganglion it is not clear in what postsynaptic element the increased glucose utilization occurred (Kadekaro *et al.,* 1985). In sev-

eral other experiments by the same group (Kadekaro *et al.,* 1985, 1987), the authors claimed that presynaptic elements of the axon terminals (synapses) are the sites of enhanced metabolic activity. These results were confirmed by experiments from other groups (Schwartz *et al.,* 1979; Nudo and Masterson, 1986; Wree and Schleicher, 1988).

What Are the Energy Consuming Processes in Synapses?

The physiology of synaptic transmission is far to complex to be reviewed here. We would thus like to refer the reader to the literature (e.g., Erulkar, 1994). However, the above-mentioned studies showed that glucose utilization is coupled mainly to presynaptic neuronal activity.

Mata *et al.* (1980) performed an elegant experiment to further identify the energy consuming processes in axon terminals. They used an *in vitro* preparation of the rat posterior pituitary (which is rich in axon terminals) as a model for synaptic nerve endings of the brain. Electrical stimulation of the pituitary induced an increase of glucose utilization by 29%. When ouabain was added to inhibit the Na^+/K^+-ATPase and the sodium pump, electrical stimulation did not change glucose utilization. When veratradine was added to the incubation medium, an influx of sodium ions caused a depolarization of the axon terminals and an increase in glucose utilization by 37%. The effect of veratradine could be antagonized by addition of tetrodotoxin. This neurotoxin blocked the activation of sodium channels and prevented the veratradine-induced increase in glucose uptake. The authors concluded that the ouabain-sensitive sodium pump is the critical event coupling energy consumption to neuronal (electrical) activity.

Similar results were reported by Astrup *et al.* (1981). Synaptic transmission and related metabolism in the canine brain were reduced by pentobarbital. In the EEG-arrested brain, inhibition of Na^+ and K^+ fluxes lead to a further 40% decrease in metabolism as measured by oxygen and glucose consumption. The observed decrease in metabolism might even underestimate the relevance of ion transport mechanisms for two reasons: (i) the examination was performed in a state of reduced neuronal activity (pentobarbital), (ii) the pharmacological manipulations were induced by systemic injection of the drugs (lidocaine and ouabain) which might not cross the blood–brain barrier sufficiently. Nonetheless, both studies demonstrate the relevance of ion transport processes for synaptic transmission.

DOES ENERGY CONSUMPTION REFLECT EXCITATION OR INHIBITION?

Once a neuron has been excitated above threshold level, the action potential is conducted to the axon terminal. Calcium ions then trigger a complex process of exocytosis which releases a neurotransmitter into the synaptic cleft (for review see Erulkar, 1994). The neurotransmitter binds to postsynaptic receptor sites and triggers an ionotropic or metabotropic reaction (for review see McGonigle and Molinoff, 1994). As shown previously, mainly presynaptic processes contribute to glucose consumption. Therefore, excitation as well as inhibition should increase neuronal glucose utilization.

Apart from these theoretical considerations, there are several studies which show that both processes, excitation as well as inhibition, increase synaptic glucose uptake. The most elegant of these experiments was performed by Nudo and Masterson (1986). The authors studied the 2-DG uptake in the lateral superior olive (LSO) in the brain stem auditory system of cats. Electrophysiological recordings showed that afferents from the ipsilateral ear are excitatory while the afferents from the contralateral ear are inhibitory. Furthermore, the LSO is strictly tonotopic, i.e., stimulation with a pure tone activates a certain band of tissue. A shift in the frequency of the stimulating tone shifts the location of the stimulated band. Stimulation with pure tones resulted in discrete zones of heavy 2-DG labeling in the excited ipsilateral LSO according to the frequency of the stimulating tone. However, the stimulation also caused similar zones of 2-DG labeling in the inhibitory, contralateral LSO. The study demonstrated that (i) inhibition and excitation lead to increased glucose uptake and (ii) glucose was mainly used in *pre*synaptic structures, since postsynaptic elements of the contralateral LSO were inhibited.

Similar results have been reported from studies of cytochrome oxidase distribution (Kageyama and Wong-Riley, 1986; DiRocco *et al.,* 1989) and inhibition of neuronal activity after injection of the GABA agonist muscimol (Kelly and McCulloch, 1983).

TO WHAT EXTENT DOES ENERGY CONSUMPTION REFLECT GLIAL CELL ACTIVITY?

An amazingly small number of publications analyzed the energetic demands of glial cell activity. Using high-resolution autoradiography, Duncan *et al.* (1987, 1991) determined the distribution of 2-deoxyglucose uptake at the cellular level. Most of the uptake was found in regions of neuropil, followed by a smaller amount of uptake by neuronal cell bodies. Only a "small" number of intensely labeled small cells were found. Due to their anatomical location, these cells were identified as satellite glial cells. Unfortunately, no exact numbers of neuronal cell bodies per volume were given. However, from their figures it can be concluded that approximately 100 neuronal cell bodies per 100,000 μm^2 (in somatosensory cortex) were labeled. The number of glial cells (intensely labeled small cells) was less than 1 per 100,000 μm^2 in somatosensory cortex.

Kageyama and Wong-Riley (1986) examined the distribution of cytochrome oxidase-reactive mitochondria in the cat striate cortex. According to their amount of metabolic activity, these authors distinguished dark, moderate and lightly reactive mitochondria. Darkly labeled mitochondria in glial cells accounted for 1% of all mitochondria in layer Ia. In total, glial cells contained 12.5% of all (dark, moderate and lightly) labeled mitochondria (layer Ia). Similar numbers were found in the other layers of striate cortex. However, as glia cells have been mixed with "other" cells, the exact numbers are not obvious. In total, glial cell activity may account for up to 15% of oxidative cerebral glucose utilization.

SUMMARY AND CONCLUSIONS

The energy metabolism of the adult human brain almost completely depends on glucose. The functional coupling of regional cerebral blood flow and local cerebral glucose metabolism has been established in a wide range of experiments using autoradiographic techniques in rats, cats, and monkeys as well as double-tracer techniques in humans. Glucose utilization in turn reflects neuronal activity and more specifically synaptic, mainly presynaptic, activity. The majority of glucose is needed for the maintenance of membrane potentials and restoration of ion gradients.

PET as well as fMRI may be used to study changes in blood flow or flow-related phenomena in human subjects *in vivo*. Both techniques monitor changes of synaptic activity in a population of cells. These changes may be due to excitation or inhibition. More than 85% of cerebral glucose is used by neurons (mainly presynaptic axon terminals), while the remainder may at least partly account for metabolic processes in glial cells. Monitoring of regional cerebral blood flow with PET or fMRI thus mainly reflects neuronal and more specifically (pre-) synaptic activity.

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