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Oxidative Energy Metabolism in Alzheimer Brain

Studies in Early-Onset and Late-Onset Cases*

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ABSTRACT

Reduction of the cerebral metabolic rate of glucose is one of the most predominant abnormalities generally found in the Alzheimer brain, whereas the cerebral metabolic rate of oxygen is only slightly diminished or not at all the beginning of this dementive disorder. This metabolic abnormality may induce severe functional disturbances, obviously preceding morphobiological changes. From the cerebral metabolic rates of oxidized glucose and oxygen, the cerebral ATP formation rate was calculated in incipient early-onset, incipient late-onset and stable advanced dementia of Alzheimer type. A reduction of ATP formation was found from at least 7% in incipient early-onset, to around 20% in incipient late-onset DAT, and from 35% to more than 50% in stable advanced dementia. This approximation was adjusted to findings demonstrating diminished activities of enzymes active in glucose metabolism and formation of oxidation equivalents for ATP production from substrates other than glucose. A reduction for energy formation to the same range was found, as was also recently reported, in vivo in Alzheimer patients. From this rather theoretical point of view, a permanent loss of energy by at least 7–20% in incipient and progressively advancing dementia of the Alzheimer type may

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be assumed, with an increasing tendency in stable advanced dementia to around 50% energy loss. This energy deficit may have drastic impacts on brain function.

Index Entries: Dementia of Alzheimer type; brain; glucose metabolism; energy formation; energy deficit.

INTRODUCTION

The etiopathogenesis of dementia of Alzheimer type (DAT) is still largely unclear. In this respect, attention is presently focused on the classic morphological markers for this disorder. However, the mechanism(s) leading to cell death in distinct neuronal populations in the hippocampus and in the cortical layers II, III, and V (Coleman and Flood, 1987; Hyman et al., 1984, 1986; Mann et al., 1985) are poorly understood, as is the pathobiochemistry of the formation of neurofibrillary tangles and neuritic plaques, although the molecular biological basis of the amyloid generation of the latter has been described in great detail, thus contributing to our understanding of some aspects of DAT (Cohen et al., 1988; Higgins et al., 1988; Kang et al., 1987; Lewis et al., 1988). However, these markers may be assumed to label the advanced rather than the incipient state of this neurodegenerative disorder; in other words, abnormalities in brain metabolism may precede and probably cause neurodegeneration along with the formation of neurofibrillary tangles and neuritic plaques, and not vice versa: In DAT, early and drastic changes occur in brain glucose and related metabolism, giving rise to an energy deficit and subsequent neuronal damage in the brain (Hoyer, 1988).

In the mature, healthy, nonstarved mammalian brain, glucose is the only substrate for oxidation (Cohen et al., 1967; Hoyer, 1970a) and thus for the formation of energy in the form of ATP (Erecinska and Silver, 1989; Siesjö, 1978) to maintain synaptic transmission (Lipton and Whittingham, 1982) and calcium homeostasis (Siesjö, 1981), for example. ATP formation is coupled with a series of different metabolic steps (Lehninger, 1971), starting with six different dehydrogenating processes by which a total of 10 $NADH_2$ and 2 $FADH_2$ is formed and transferred into the respiratory chain (Fig. 1.). Here, the transformation of protons into electrons is coupled with ATP formation from ADP and Pi at three different metabolic steps. The oxidation of 10 mol $NADH_2$ provides a total of 30 mol ATP, and that of 2 mol $FADH_2$ another 4 mol ATP. A further 2 mol ATP derives from the succinyl-CoA-synthase reaction. Another 2 mol ATP is formed by way of other processes than oxidation in glycolysis (Erecinska and Silver, 1989). As a whole, 1 mol glucose yields 38 mol ATP.

With respect to oxidative energy metabolism, the allosteric multienzyme complexes pyruvate dehydrogenase (PDHC), isocitrate dehydrogenase (ICDHC) and oxyglutarate dehydrogenase (OGDHC) attain

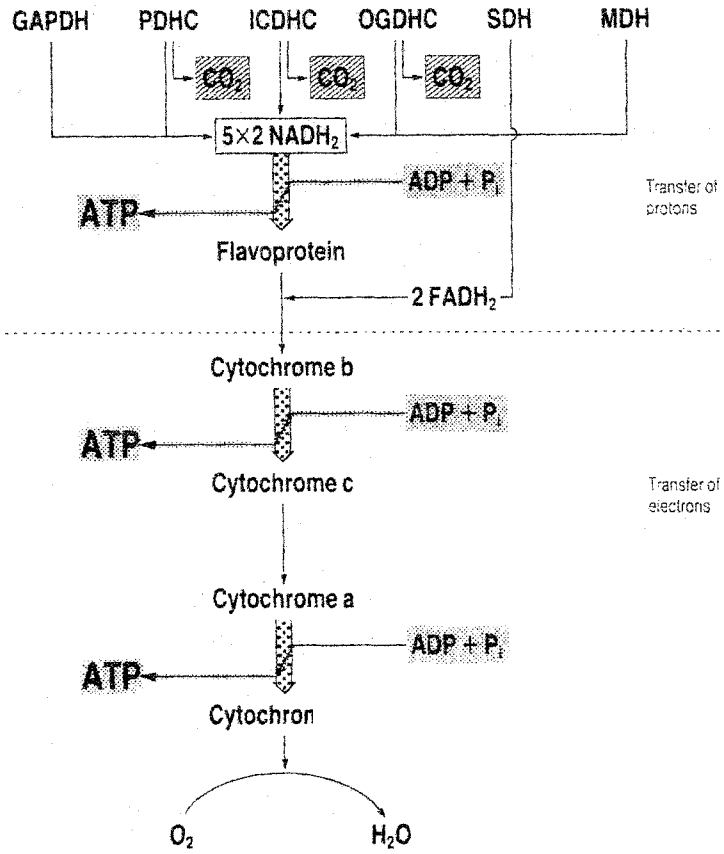

Fig. 1. Schematic survey on substrate oxidation, CO_2 production, and ATP formation in the glycolytic chain, the tricarboxylic acid cycle, and the respiratory chain. GAPDH, glyceroaldehyde phosphate dehydrogenase; PDHC, pyruvate dehydrogenase complex; ICDHC, isocitrate dehydrogenase complex; OGDHC, oxyglutarate dehydrogenase complex; SDH, succinate dehydrogenase; MDH, malate dehydrogenase; $NADH_2$, nicotineamid adenine nucleotide (reduced); ATP, adenosine triphosphate; ADP, adenosine diphosphate; Pi, inorganic phosphate.

particular significance. Carbon dioxide from oxidation is formed exclusively at these metabolic steps. They can be activated and regulated by Ca^{2+} (Wan et al., 1989), and there is evidence that PDHC contributes to cellular Ca^{2+} homeostasis (Browning et al., 1981; Hansford and Castro, 1985). Acetylcholine synthesis is functionally tightly coupled with the activation state of PDHC (Blass and Gibson, 1979; Perry et al., 1980). Finally, these three multienzyme complexes yield 50% of oxidation equivalents, and contribute up to 47% of the total ATP formation in the brain.

In the present study, the cerebral ATP production rate was calculated from the cerebral metabolic rates (CMRs) of oxygen, glucose, and lactate, which had been studied earlier in healthy young adult volunteers (Hoyer,

1970a), in healthy middle-aged controls, and in patients with early-onset and late-onset DAT (Hoyer et al., 1988, 1991). What is considered are the metabolic abnormalities in glycolytic and oxidative glucose breakdown and in oxidative phosphorylation that might cause the energy deficit in the Alzheimer brain and the compensation mechanisms that exist.

MATERIALS AND METHODS

Subjects

The groups of subjects studied were as follows:

1. Physically and mentally healthy young adult volunteers (HYAV): $n=15$; age 24 ± 2 yr; mostly medical students (Hoyer, 1970a; Hoyer et al., 1988).
2. Healthy middle-aged controls (HMAC): $n=11$; age 44 ± 11 yr; subjects with a complete check-up (Hoyer et al., 1988).
3. Early-onset dementia of Alzheimer type (EODAT): $n=20$; age 46 ± 9 yr; incipient cases with histories of about 4 mo; four patients with suspected "familial" DAT (Hoyer et al., 1988).
4. Late-onset dementia of Alzheimer type (LODAT), subdivided into incipient (inc.) and stable advanced (adv.) LODAT: inc. LODAT: $n=11$; age 66 ± 5 yr, history going back less than 2 yr (Hoyer et al., 1991); adv. LODAT: $n=7$; age 75 ± 5 yr (I), during the second study 75.5 ± 5 yr (II); history of 8–12 yr (Hoyer et al., 1991).

All DAT patients suffered from severe rather than moderate dementia symptoms, which had been verified by a battery of psychometric tests. Patients with EODAT and inc. LODAT underwent EEG, CT of the brain, and intensive physical examinations. The latter revealed no risk factors, no endocrine abnormalities, no vitamin deficits, and so forth. In particular, normoglycemia and normoketonemia were present in incipient EODAT and LODAT (medical records endorsed: physically healthy except for brain function). In advanced LODAT normoglycemia existed. During the measurement of cerebral blood flow and the respective cerebral metabolic rates, all subjects studied were in a steady state of individual arterial normotension, of arterial normoglycemia, normocapnia, and normoxemia and in normothermia. For futher detailed diagnostic criteria, ascertainment of diagnosis, inclusion criteria, exclusion criteria, and consent procedure, *see* Hoyer et al. (1988, 1991).

Since we did not have a group of healthy elderly controls above the age of 60 yr in our sample of normal subjects, the data reported for normal elderly men (NEM; $n=26$; age 71 ± 1 yr) from Dastur et al. (1963) and Dastur (1985) were also used in calculation of the ATP production rate.

Methods

The CMRs of oxygen, CO_2, glucose, and lactate and also cerebral blood flow were studied in the subjects detailed earlier by means of a modified Kety-Schmidt technique (Kety and Schmidt, 1948). The cerebral arteriovenous differences for amino acids and ammonia were obtained by the same procedure. Their concentrations were determined by the method of Moore and Stein (1954a,b). For further methodological details *see* Hoyer et al. (1988).

Statistical significances were tested by means of Student's two-tailed *t*-test. Statistical significance was assumed at $p < 0.05$.

Calculation Procedure

The measured CMR of glucose was reduced by the measured CMR of lactate to give the calculated rate of oxidized glucose (CMR of $glucose_{ox}$). Multiplication by 6 of this calculated CMR of $glucose_{ox}$ results in the calculated CMR of oxygen necessary for the oxidation of this amount of glucose. Multiplication by 6 of the calculated CMR of oxygen yields the rate of ATP produced in the course of oxidative phosphorylation of $glucose_{ox}$. The proportion of glucose oxidation is calculated from the ratio $(glucose_{ox}) \times 6/oxygen$ (measured). This ratio is termed the glucose oxidation ratio. A positive balance between the measured and the calculated CMR of oxygen indicates how much oxygen is used for the oxidation of substrates other than glucose. As may be calculated from the generation of oxidation equivalents (*see* earlier discussion and Fig. 1), 1 mol oxygen oxidizes 2 mol hydrogen to form 6 mol ATP whatever the substrate(s) (glucose, amino acids, free fatty acids [FFA], etc.) from which the hydrogen derives. If amino acids are used instead of glucose, their transformation either into pyruvate or into oxyglutarate is necessary. FFA are oxidized via beta-oxidation, which has been demonstrated to occur in the brain (Allweis et al., 1966; Little et al., 1969; Singh et al., 1989; Spitzer, 1973).

RESULTS

The CMRs of oxygen, CO_2, and oxidized glucose ($Gluc_{ox}$) in HYAV, HMAC, incipient EODAT and LODAT, and advanced LODAT are listed in Table 1. CMR $Gluc_{ox}$ is the calculated difference from the CMRs of glucose and lactate (*see* earlier discussion). As has been reported earlier, a 44% reduction in the CMR of glucose and a fourfold increase in the CMR of lactate could be demonstrated, whereas no significant changes in cerebral blood flow or the CMR of oxygen were found in incipient EODAT as compared with HMAC (Hoyer et al., 1988). In incipient LODAT, significant reductions in cerebral blood flow, and in the CMRs of oxygen and glucose became apparent, the latter being the most prominent. CMR of

Table 1
Cerebral Metabolic Rates (CMRs, Measured and Calculated in μmol/g×min) of Oxygen (O_2), CO_2, and Oxidizable Glucose ($Gluc_{ox}$) and ATP Formation Rate in HYAV, HMAC, and NEM (Dastur et al., 1963), EODAT, Incipient LODAT and Advanced LODAT

	O_2	CO_2	$Gluc_{ox}$	ATP	% of HAMC	Glucose oxidation ratio
HYAV						
measured	1.58±0.18	1.68±0.21	0.26±0.04			
calculated	1.56±0.18	1.56±0.20		9.36±0.88		0.99±0.02
balance	+0.02±0.00	+0.12±0.01				
HMAC						
measured	1.54±0.11	1.67±0.19	0.26±0.01			1.01±0.02
calculated	1.56±0.11	1.56±0.18		9.36±0.81		
balance	−0.02±0.00	+0.11±0.01				
NEM						
measured	1.49±0.04		0.26±0.01 (inclusive lactate)			0.97
calculated	1.44		0.24 (exclusive lactate)	8.64	92	
balance	+0.05					
inc. EODAT						
measured	1.45±0.10	1.50±0.13	0.12±0.01*		46*	0.50±0.02*
calculated	0.72±0.06*	0.72±0.08*		4.32±0.34*		
balance	+0.73±0.06*	+0.78±0.09*				

(continued)

Table 1 (Continued)

	O_2	CO_2	$Gluc_{ox}$	ATP	% of HAMC	Glucose oxidation ratio
inc. LODAT						
measured	1.27±0.22*	1.24±0.25*	0.14±0.03*		54*	0.66±0.03*
calculated	0.84±0.11*	0.84±0.13*		5.04±0.46*		
balance	+0.43±0.06*	+0.60±0.09*				
adv. LODAT I						
measured	1.03±0.20*	1.13±0.26*	0.11±0.04*		42*	0.64±0.06*
calculated	0.66±0.13*	0.66±0.12*		3.96±0.43*		
balance	+0.37±0.06*	+0.47±0.09*				
adv. LODAT II						
measured	0.73±0.12*	0.78±0.14*	0.09±0.02*			0.74±0.07*
calculated	0.54±0.08*	0.54±0.08*		3.24±0.36	35*	
balance	+0.19±0.03*	+0.24±0.03*				

The calculation procedure of ATP formation from the above CMRs is given in detail in Material and Methods. The CMRs were taken from Dastur et al., (1963) and Hoyer et al., (1988, 1991). Since Dastur et al. did not measure CMR of lactate, a normal rate of this compound was assumed to calculate CMR of oxidizable glucose, and this value was used for further calculation. The glucose oxidation ratio represents the proportion of oxidized glucose and was calculated from $(Gluc_{ox}) \times 6/O_2$ measured.

*$p \leq 0.05$ from HMAC.

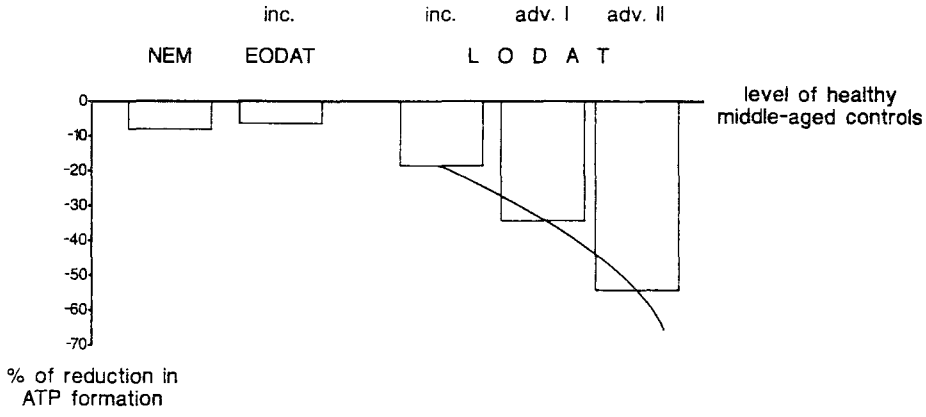

Fig. 2. Reduction in ATP formation in normal elderly men (NEM) and in patients suffering from dementia of Alzheimer type (DAT). EODAT inc., incipient early-onset DAT; LODAT inc., incipient late-onset DAT; LODAT adv. I, advanced late-onset DAT, first study; LODAT adv. II, advanced late-onset DAT, second study 6 months after I. The data are given as the means (% of healthy middle-aged controls, HMAC, Table 2) for DAT; for NEM, see Table 1.

lactate did not change. In advanced LODAT, the biological brain parameters studied all settled down at between 55% and 65% of the corresponding control values (Hoyer et al., 1991). With respect to amino acids and ammonia, an excess release from the brain was demonstratable in incipient EODAT (Hoyer and Nitsch, 1989; Hoyer et al., 1990). All the data from the studies referred to formed the basis for the calculation of ATP formation in the different groups of subjects, as well as the basis for further discussion.

The rates of ATP formation calculated from glucose breakdown exclusively of the different groups of healthy and demented subjects studied are tabulated in Table 1. In both HYAV and HMAC, ATP formation was 9.36 μmol/g$\times$min, which is in agreement with physiological data recently reported (Erecinska and Silver, 1989). In normal elderly men (NEM) (71-yr-old on average), a slight reduction of 8% was found compared with HMAC (*see* Fig. 2).

In all groups of demented patients studied, ATP formation from glucose only dropped drastically, to around 50% in incipient early-onset and late-onset dementia states and to around 40% and 35% in stable advanced ones compared with HMAC. Furthermore, the rate of oxygen not utilized for glucose oxidation decreased markedly, from 0.73 μmol/g$\times$min in EODAT to 0.19 μmol/g$\times$min in stable advanced LODAT, i.e., to around 25% of the value recorded for EODAT. All these data were found to be statistically different from those in HMAC. The glucose oxidation ratio, which was close to 1.00 in HYAV and HMAC, dropped significantly in all groups of dementia patients studied.

Table 2
Rates of ATP Formation from Substituted Endogenous Substrates as Calculated from the CMRs (measured in μmol/g×min) of Oxygen Not Utilized for Glucose Oxidation (Balance)

	O_2	ATP	Total ATP	% of HMAC
inc. EODAT balance	+0.73±0.06	4.38±0.38	8.70±0.81	93
inc. LODAT balance	+0.43±0.06	2.58±0.23	7.62±0.73*	81
adv. LODAT I balance	+0.37±0.06	2.22±0.19	6.18±0.59*	66
adv. LODAT II balance	+0.19±0.03	1.14±0.11	4.38±0.41*	47

Total ATP is considered to be the sum of ATP formation from glucose oxidation (Table 1) and from oxidation of glucose substitutes.
*$p \leq 0.05$ from HMAC.

Table 2 shows the ATP formation rates in dementia patients when substitution of missing glucose may occur by means of substrates other than glucose. As becomes obvious, the rate of total ATP formation is found to be considerably higher than that of ATP formation from glucose only in incipient dementia states (Table 1). Total ATP formation in incipient EODAT just failed to reach statistical significance compared with HMAC. In all states of LODAT, total ATP formation was markedly diminished compared with HMAC. In stable advanced dementia states, the differences between ATP formation rates calculated from the oxidation of glucose only (Table 1) and from the oxidation of substrates other than glucose became considerably smaller than in incipient LODAT.

DISCUSSION

This study is the first attempt to calculate ATP formation in the brain on the basis of the cerebral utilization rates of oxygen and glucose in healthy and demented subjects, and to relate abnormal energy metabolism to distinct disturbances in glucose breakdown in DAT brain.

There is ample evidence that the CMR of glucose diminishes by between 20% and 40% from mild to more severe DAT (Chase et al. 1983; Cutler et al. 1985; Foster et al. 1983, 1984; Haxby et al. 1985; McNamara et al. 1987). In a recent study performed in mild, moderate, and severe states of obviously late-onset DAT, the reduction in global CMR of glucose ranged from 19% (mild) to 41% (severe) (Kumar et al. 1991), in-

dicating that severity of dementia may parallel the diminution in the CMR of glucose. In recent studies in both incipient EODAT and LODAT patients who suffered from severe rather than moderate dementia, a decrease of the same degree (44%/45%) in the CMRs of glucose was found (Hoyer et al. 1988, 1991). Otherwise, the reduction in the CMR of glucose was obviously not accompanied by a similarly severe diminution in the CMR of oxygen: There was no abnormality in incipient EODAT, and a decrease by 18% in incipient LODAT. To our knowledge, there is only one study that deals with cerebral oxygen consumption in obviously incipient late-onset DAT: The CMR of oxygen, as determined by positron emission tomography, was diminished by 24% in patients with moderate to severe dementia (Frackowiak et al. 1981). From these results, it may be deduced that at least in incipient severe dementia states, a disproportion exists between the decreases in the CMRs of glucose and oxygen, as was demonstrated earlier (Gottstein et al., 1964; Hoyer, 1970b; Hoyer and Becker, 1966) and has been confirmed by recent investigations (Hoyer et al. 1988, 1991). This abnormal metabolic pattern may bring the cerebral glucose metabolism into focus as the point of primary metabolic damage in DAT and raises the questions as to which substrate(s) other than glucose is (are) utilized from the remaining oxygen for energy formation.

In postmortem studies in DAT brain in which the onset of dementia had been obviously late, the activity of phosphofructokinase was found to be decreased to 10% of control values by Bowen et al. (1979) and Iwangoff et al. (1980) and to 60% in a more recent study (Marcus et al., 1988). The hexokinase activity in microvessels taken from fresh autopsy material was diminished by 34% compared with normal controls (Marcus et al. 1989).

In oxidative metabolism, PDHC activity was diminished in different cortical areas by 20–40%, whereas there was no change in the activities of citrate synthase, succinate dehydrogenase or fumarese (Perry et al., 1980; Sorbi et al., 1983; Yates et al., 1990). OGDHC activity was the most markedly reduced: by around 90% in the frontal and occipital cortices and by 100% in the midtemporal cortex (Gibson et al., 1988). In obviously early-onset DAT, the activity of the glycolytic enzyme hexokinase was decreased by nearly 40%, i.e., to the same range as in obviously late-onset DAT, whereas that of lactate dehydrogenase was increased by 13% in the nucleus basalis of Meynert. The concentration of the energy-utilizing enzyme (Na^+, K^+)-ATPase dropped to 54% in this brain region, whereas Ca^{2+}-ATPase did not vary (Liguri et al., 1990). Otherwise, in neocortical tissue samples removed at diagnostic craniotomy from patients with apparently early-onset DAT, no clear changes were found in the activity of phosphofructokinase: In two out of four samples, values greater than 2 SD below the control mean were reported, corresponding to a 20% reduction (Sims et al., 1987a). In spite of this inconsistent result in a small number of samples, overall the aforementioned findings suggest that in the DAT brain, there is a functional insufficiency of en-

zymes, particularly severe in those involved in glycolytic glucose breakdown and in pyruvate oxidation. Clearly, the suspected 40% reduction in the activities of glycolytic enzymes and PDHC would diminish the glucose utilization rate by the same amount, as detailed earlier.

Since the activities of citrate synthase, succinate dehydrogenase and fumarase were found not to be changed in DAT brain (*see* earlier discussion), it may be tentatively assumed that the function of the tricarboxylic acid cycle (TCAC) is not disturbed in the incipient and progressively advancing states of this disorder. This may also be deduced from the normal CO_2 production, as shown in Table 1, and from the normal to slightly increased CO_2 formation from tissue samples removed at diagnostic craniotomy (Sims et al., 1983). In stable advanced DAT, however, CO_2 production from glucose and other substrates may drop (Swerdlow et al., 1989; Table 1), because of the reduced enzymatic activity of the TCAC (Gibson et al., 1988). The maintenance of oxidative metabolism in DAT brain was also assumed from the preservation of the mitochondrial area in tangle-bearing pyramidal neurons (Sumpter et al, 1986). Mitochondrial function, measured as oxygen uptake in vitro, did not reveal any differences between control and Alzheimer samples removed at diagnostic craniotomy either under resting or under uncoupling conditions (Sims et al., 1987b).

From the CMRs of oxygen, CO_2, and glucose in incipient EODAT and LODAT, as well as from the enzymatic abnormalities in DAT brain previously discussed, it may be deduced that the primary site of metabolic abnormalities may be in glycolytic glucose breakdown and in pyruvate oxidation by PDHC. Consequently, ATP formation from glycolysis via GADPH, including GPT, and via PDHC may be expected to decrease by 40%, i.e., total ATP formation may fall to approximately 84% compared with normal. This value is considerably higher than the two values given in Table 1 for inc. EODAT and inc. LODAT. However, these latter data started from the principle that (1) glucose metabolism (and thus energy formation) may be perturbed throughout all catabolic steps and (2) lacking glucose may not be substituted by other substrates. Another tentative conclusion may be drawn from the data just discussed. There is no support for the idea that the reduction in the ATP formation rate was induced by an uncoupling of oxidative phosphorylation as was postulated by Blass et al. (1990), and speculated for conditions of submaximal activity of mitochondrial respiration in vitro (Sims et al., 1987b). If an uncoupling of oxidative phosphorlyation is set in motion, a loss of energy formation to a greater extent must be expected than was found in vivo in DAT brain (*see* earlier discussion), and on the basis of our present data. Furthermore, uncoupling of oxidative phosphorylation may be associated with an increase rather than a decrease such as was found in DAT brain, of enzymes active in the formation of oxidation equivalents (Fig. 1).

The disporportionate reductions in the CMRs of glucose and oxygen in incipient EODAT and LODAT raise the question of which substrate(s) other than glucose is (are) oxidized to form ATP and to attentuate the

severe energy deficit (Table 1). The healthy and apparently nondemented brain was shown to be capable of oxidizing ketone bodies instead of glucose. However, hypoglycemia and ketonemia were demonstrated to be required for ketone body utilization by the brain (Dietze et al., 1975; Owen et al., 1967; Ruderman et al., 1974). As in normoglycemic rats, in which the percentage of calculated oxygen consumption resulting from ketone bodies was less than 1% (Ruderman et al, 1974), the present study in normoglycemic HYAV and HMAC (also normoketonemic) did not yield any support for the utilization of substrates other than glucose by the brain: In both groups, the glucose oxidation ratio was very close to 1.00 (Table 1). Otherwise after fasting (12–16 h), in normal subjects (clinical diagnosis: vertigo; slight cerebral arteriosclerosis), a small amount of acetoacetate was taken up and utilized by the brain besides glucose (Gottstein et al., 1971). In contrast, nonesterified fatty acids were not utilized by the brain in these subjects, and with a longer duration of fasting, brain utilization of free fatty acids was most inconsistent (Owen et al., 1967),

Clearly both the reduced glucose oxidation rate and the total ATP formation rate (Table 2) in incipient EODAT and LODAT indicate the oxidation of other substrates besides glucose under these dementing conditions in the presence of normoglycemia and normoketonemia.

Although the CMR of glucose was found to be reduced by 25%, no enhanced cerebral uptake of acetoacetate and/or beta-hydroxybutyrate was observed in presenile dementia compared with healthy subjects (Lying-Tunell et al., 1981). Furthermore, since activity of acetoacetyl-CoA thiolase was demonstrated to be reduced in Alzheimer brain (Perry et al., 1980), it is rather unlikely that exogenous fatty acids (and amino acids, too; *see below*) serve as substitute substrates for lacking glucose in brain in incipient EODAT and LODAT. Also, the pentose pathway may not be assumed to have a substitute role in Alzheimer's disease, insofar as the activity of transketolase was reduced by more than 45% (Gibson et al., 1988).

When the substitution of lacking brain glucose by means of other exogenous substrates is obviously of no significance, it may be of interest to find whether or not endogenous brain substrates can serve as substitute fuels. In principle, FFA may be considered as substrates. FFA exist in a pool in brain tissue (Westerberg et al., 1987), or may be formed from phospholipid catabolism during neurodegeneration (Farooqui et al, 1988) ready for oxidation in the TCAC as acetyl CoA from beta-oxidation (Singh et al., 1989; Spitzer, 1973). It will, however, have to be proven whether or not endogenous FFA are used instead of glucose in incipient EODAT and LODAT.

Recent findings have provided evidence that endogenous amino acids (AA) may substitute lacking glucose in the brain affected by incipient Alzheimer disease. AA were not taken up by the brain from arterial blood in incipient EODAT, but were released from the brain in excess in particular aspartate and glycine. Otherwise, the release of glutamate was not

significantly enhanced (Hoyer and Nitsch, 1989). A common finding in antemortem temporal cortex in DAT (Procter et al., 1988) and in postmortem DAT brain unequivocally revealed a fall in glutamate concentration differing in degree in cortical and subcortical brain regions (Arai et al., 1985; Ellison et al., 1986; Sasaki et al., 1986). These data suggest that glutamate is used in incipient DAT via the aspartate aminotransferase reaction. With respect to the metabolic abnormalities in glucose breakdown, previously discussed, the transfer of glutamate to oxyglutarate in this reaction becomes likely and the oxidation of acetyl-CoA from FFA via beta-oxidation is probable. Otherwise, AA utilization via the alanine aminotransferase reaction may be rather restricted, because of the reduced availability of pyruvate. Thus, the limiting factor for additional ATP formation from FFA and/or AA for example, is both the availability of these compounds and that of oxygen.

The approximation of ATP formation based on reduced enzyme activities in DAT, as detailed earlier, would result in a reduction of around 20% in incipient and progressively advancing LODAT. This reduction was found to be in the same range when ATP formation was calculated from the CMRs of oxygen and $glucose_{ox}$ in incipient LODAT as shown in Table 2. The ATP formation rate calculated in this way by means of indirect procedures agrees well with the ATP formation rate in neocortical DAT tissue samples removed at diagnostic craniotomy (Sims et al., 1983), and from in vivo ^{31}P NMR profiles (Brown et al., 1989): reduction of available energy in DAT by 20–25%. However, in incipient EODAT, the calculated ATP formation rate was 93% of HMAC and thus in the same range of normal elderly men aged over 70 yr. Nevertheless, a permanent reduction of energy by at least this amount may be assumed. This seemingly relative small decrease in incipient and progressively advancing EODAT (less marked) and LODAT (more marked) may be supposed to permanently damage cell function as becomes obvious in stable advanced DAT in which the loss of energy is much greater when missing glucose cannot well be substituted by endogenous FFA, AA, or both.

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