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GLUCOSE AND RELATED BRAIN METABOLISM IN DEMENTIA OF ALZHEIMER TYPE AND ITS MORPHOLOGICAL SIGNIFICANCE

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ABSTRACT

A unifying hypothesis of the pathobiochemical events leading to cell damage and cell death in DAT brain is advanced. This hypothesis is based upon the early and the most prominent disturbances in the glycolytic glucose breakdown and pyruvate oxidation, associated with an excessive protein catabolism as were found in early-onset DAT. The abnormality in intracellular glucose homeostasis is hypothesized to be caused by a deficiency at the insulin/insulin receptor level of the neuron giving rise to a cascade of cell damaging events. These include the formation of neurotoxic amino acids, disturbance of intracellular Ca^{2+} homeostasis and the degradation of intracellular components as well as membranes and cell surface receptors. The pathobiochemical changes are related to the morphological hallmarks as are neuronal loss, and the formation of neurofibrillary tangles and neuritic plaques in DAT. It is assumed that neurons equipped with high densities of both insulin receptors and glutamatergic N-methyl-D-aspartate receptors, as is the case in hippocampal and cortical pyramidal cells, are particularly vulnerable and are prone to the formation of abnormal structures, such as neurofibrillary tangles and neuritic plaques, and to cell death.

INTRODUCTION

In a previous article (1), the biochemical properties of the glycolytic and oxidative cerebral glucose metabolism and its relation to amino acid metabolism and cellular homeostasis in the brain were discussed with respect to normal cerebral aging. This process may be associated with an incipient perturbation of cerebral circulation and metabolism causing an imbalance of cell homeostasis beyond the age of 70 years of life. From this critical threshold onward, the normal cerebral aging process may be jeopardized with development of dementia in old age. Alzheimer type dementia symptoms in middle age and late life may be distinguished in dementia of Alzheimer type (DAT) with early onset and with late onset (2-5). The clinical course of early-onset DAT is more rapid and foudroyant than that of late-onset DAT pointing to more severe and/or different pathobiochemical abnormalities in DAT brains with early onset as compared to the late subtype of DAT.

No changes of cerebral blood flow (CBF) were detectable at the onset of DAT (6-9). Likewise, the cerebral metabolic rate (CMR) of oxygen was normal or only slightly diminished (7, 10, 11).

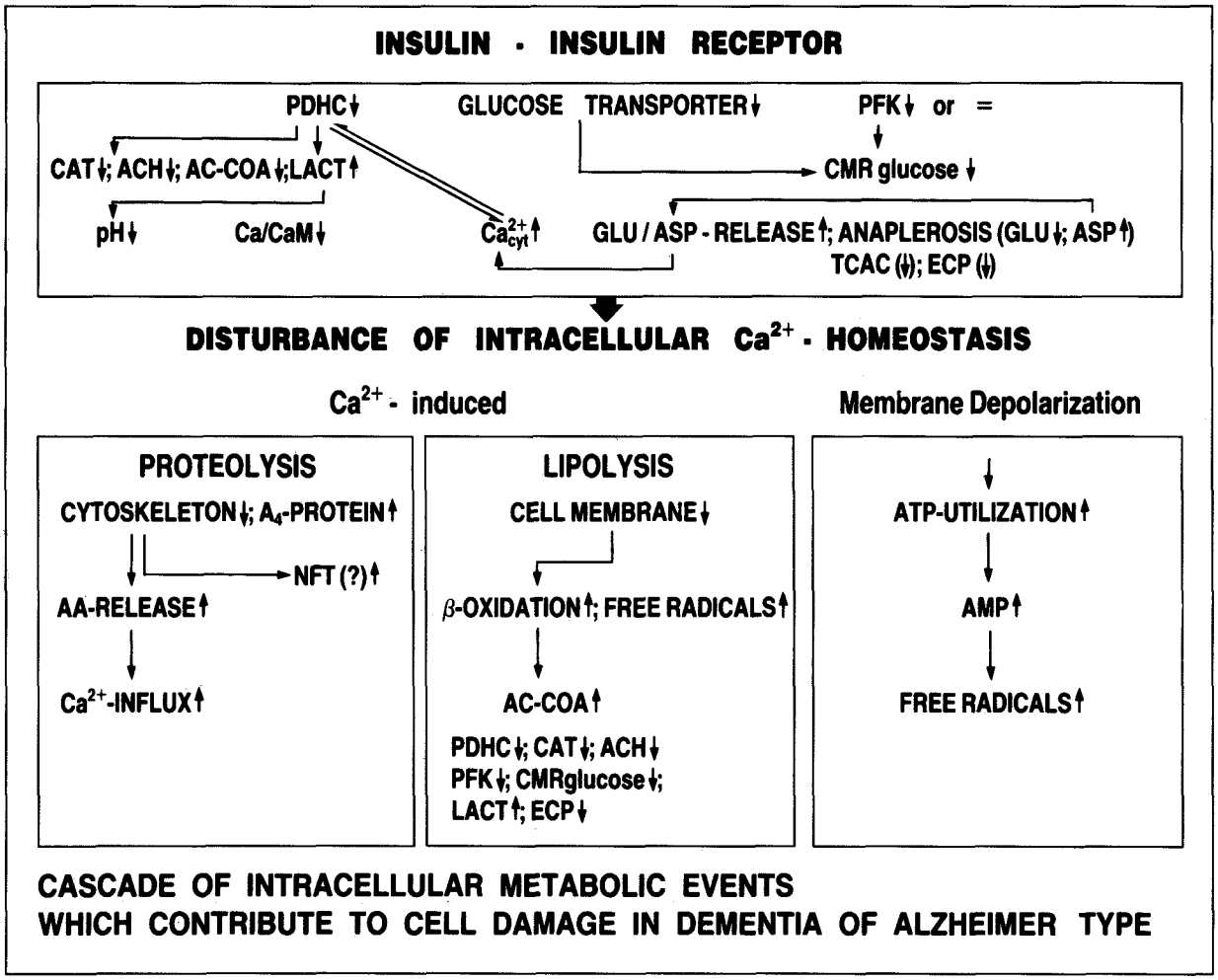
Glucose metabolism is centered in the brain and plays a pivotal role in providing the neuron with sufficient energy. In several studies performed in DAT, massive abnormalities in CMR glucose have been demonstrated in DAT patients with short histories of the disease (for review, see 12). Therefore, this article is focused on brain glucose and related metabolism at the cellular and molecular level in early-onset DAT with respect to morphological abnormalities.

DISCUSSION

Glucose and Related Metabolism in DAT

In early-inset DAT, an early and predominant disturbance was found in a 44% reduction in CMR glucose whereas CBF and CMR oxygen were unaltered (13). The diminished CMR glucose cannot be attributed to an insufficient glucose supply to the brain because of normoglycemia. A diminution of CMR glucose of similar extent in Alzheimer patients with dominant inheritance had been reported (14). CMR oxygen is not compromised in early-onset DAT and may be expected to be unchanged as can also be deduced from either the normal or elevated respiration rate and oxygen uptake rate of mitochondria of freshly sampled homogenates of frontal neocortex of DAT (15, 16). Furthermore, the normal CO_2 production, and the nearly normal ATP formation as measured in the same tissue samples, may indicate an undisturbed substrate oxidation in the tricarboxylic acid cycle, the working enzymes of which are largely mitochondrial (17). Interestingly, the mitochondrial area in tangle-bearing pyramidal neurons of temporal cortex from DAT patients was found to be preserved, indicating a normally maintained oxidative metabolism (18). Therefore, the reduction of cerebral glucose utilization in DAT resulting in neuronal starvation may have other causes than a perturbation in substrate oxidation.

Several findings clearly demonstrated reduced activities of enzymes acting in glycolytic glucose breakdown. The flux-controlling enzyme phosphofructokinase has been found to be decreased to 10% of control values (19, 20). Pyruvate formation



CASCADE OF INTRACELLULAR METABOLIC EVENTS WHICH CONTRIBUTE TO CELL DAMAGE IN DEMENTIA OF ALZHEIMER TYPE

AA:	amino acids	**ATP:**	adenosine triphosphate	**GLU:**	glutamate	**PFK:**	phosphofructokinase
ACH:	acetylcholine	**CAT:**	choline acetyltransferase	**LACT:**	lactate	**TCAC:**	tricarboxylic acid cycle
AC-COA:	acetyl CoA	**CMR:**	cerebral metabolic rate	**NFT:**	neurofibrillary tangles	↑:	increase/production
ASP:	aspartate	**ECP:**	energy charge potential	**PDHC:**	pyruvate dehydrogenase complex	↓:	decrease/degradation

may then diminish. This decrease and the reduced activity of the pyruvate dehydrogenase complex (PDHC) in DAT (21, 22) may further decrease the formation of acetyl CoA for oxidation and acetylcholine production (23, 24). Reduced PDHC activity may induce increased lactate formation, as was found in early-onset DAT (13). Interestingly, a significant increase in lactate production in fibroblasts of patients suffering from morphologically confirmed Alzheimer's disease has been reported (25). Since the abnormalities in glucose metabolism were intense even at the beginning of early-onset DAT, the primary metabolic disturbance may be suggested in the glycolytic breakdown of glucose and its first step of oxidation at the PDHC level (13, 26). In early-onset DAT, the diminished CMR glucose was accompanied by a severe loss of amino acids and ammonia from the brain indicating catabolic proteolysis (13). In ante mortem frontal and temporal cortices of DAT patients, an increased concentration of aspartate was found, whereas glutamate was reduced in temporal cortex but was unchanged on frontal cortex (27). These findings coincided with data from early-onset DAT patients in whom aspartate and glycine were released from the brain in significantly high concentrations whereas glutamate did not show significant changes (28). From these results, it may be deduced that the deficiency in neuronal glucose may be partly substituted by endogenous glutamate which is used in the aspartate aminotransferase reaction. Aspartate may accumulate in and be released from the brain in high concentration. When the neuron is starved of glucose under the different condition of arterial hypoglycemia causing slow waves-polyspikes in EEG, or depression of CNS functions in behavior, respectively, CMR glucose fell to 54% of control, whereas CMR oxygen and the concentration of energy-rich phosphates in brain cortex remained unchanged (29). The brain cortical concentrations of glutamine and alanine decreased, and that of

aspartate rose, whereas that of glutamate did not vary under the above conditions. In hippocampus, glutamate and glutamine diminished, and aspartate increased (30). The concentration changes in the tissue were reflected in the amounts of amino acids released from the brain: the extracellular concentration of aspartate rose most, followed by rather moderate increases of glutamate, taurine and γ-aminobutyric acid, whereas glutamine fell (31). It may thus be concluded that, irrespective of the cause, the disturbed intracellular glucose homeostasis is followed by proteolytic changes with glutamate and aspartate being most severely involved.

Brain Morphology in DAT Related to Metabolism

Morphological studies displayed the general finding that the severity of neuropathological changes in DAT (cell loss, neurofibrillary tangles, neuritic plaques) was always maximal in the hippocampus, the entorhinal cortex, and in the association cortex. An obvious cell layer-specific damage in cerebral cortex and hippocampus with respect to the distribution of neurofibrillary tangles and neuritic plaques could be demonstrated. Neurofibrillary tangles were mainly observed in cortical layers III and V, in the latter twice as many with the majority being located in pyramidal cells. Neuritic plaques occurred in all layers throughout the cerebral cortex but predominantly affected layers II and III (32). In entorhinal cortex, layers II, III and IV revealed severe cell loss, and in layers II and III, the origin of the perforant pathway, neurofibrillary tangles accumulated. Neuritic plaques were abundantly found in the middle portion of the stratum moleculare of the dentate gyrus, which is the termination zone of the perforant pathway, and which contains granule cells (33, 34). In the hippocampus, a marked cell loss and large numbers of neurofibrillary tangles were seen in the subiculum and the CA_1 subfield affecting pyramidal cells, whereas in adjacent hippocampal areas such as CA_3 subfield neurofibrillary tangles appeared rarely, and pyramidal cells were preserved. Neuritic plaques occurred mainly in the dorsal half of the stratum pyramidale of the subiculum and in the stratum radiatum of the adjacent CA_1 subfield. Reduced plaque numbers were present in the remaining Ca_1 and CA_3 subfields, located in the pyramidal cell layer (33, 34). Otherwise, the distribution of neuritic plaques failed to correspond to cholinergic, noradrenergic, and serotonergic afferents to the stratum moleculare of the dentate gyrus and the CA_1 subfield of the hippocampus (35).

Investigations of the distribution of precursor amyloid-β-protein mRNA in normal cerebral cortex displayed a high density in most regions in layers II, III, and in the superficial portion of layer V. In DAT, high numbers of neurofibrillary tangles coincided with a reduced expression of precursor amyloid-β-protein mRNA. On the other hand, many neurons which expressed this high mRNA in healthy brain never developed neurofibrillary tangles in DAT. With respect to neuritic plaques, no association between their density and neurons containing precursor amyloid-β-protein mRNA could be observed (36). In hippocampus, amyloid-β-protein mRNA was found to be widely expressed by neurons although its level varied between cells of different location. Most of the pyramidal neurons of the CA_1 and CA_3 subfields showed a very high abundance of mRNA. In the dentate gyrus, both the granule and hilar neurons contained high densities of this mRNA. Less amyloid-β-protein mRNA density was found in neurons of the subiculum and the entorhinal cortex. However, in DAT, surviving neurons of the subiculum exhibited nearly the same mRNA density as was found in pyramidal neurons of the hippocampal subfield CA_3, which may be indicative of an increased expression of amyloid-β-protein mRNA in subiculum in DAT brain (37). Amyloid-β-protein mRNA expression was also found in neurons of the nucleus basalis of Meynert, in DAT brains more abundantly than in normal ones (38).

One of the precursors of amyloid-β-protein was described to resemble a cell surface receptor (39). Another one showed protease inhibitory activity (40-42).

Glutamatergic N-methyl-D-aspartate (NMDA) receptors are most densely distributed in the hippocampal subfield CA_1 in the stratum oriens containing basal dendrites of the pyramidal cells, and in the stratum radiatum containing apical pyramidal dendrites. Furthermore, they are abundantly found in the cerebral cortical layers I, II, III, and Va containing large pyramidal neurons except layer I. NMDA receptors work in concert with quisqualate receptors, but are obviously complementary to the kainate receptor system (43). In the dentate gyrus, the target zone of the perforant pathway possesses uptake sites for glutamate and aspartate (44), and the granule cells of the dentate gyrus are glutamatergic (45).

Although the role of insulin in the brain has not been clarified as yet, evidence exists that the brain synthesizes its own insulin in the hypothalamus, and that this insulin may have a similar effect as in non-neuronal tissue (46, 47). Insulin may then control the intraneuronal carbohydrate homeostasis, may activate the cellular glucose transporter, may activate protein synthesis and lipogenesis beside other anabolic effects (48, 49). Insulin receptors have been demonstrated in different brain structures being particularly high in entorhinal cortex, ventral subiculum, amygdaloid nucleus, hippocampal CA_1 subfield and in lateral septum (50), and being present at brain synaptosomes (51).

With respect to the morphological hallmarks in DAT, namely neuronal loss, the formation of neurofibrillary tangles and neuritic plaques, a co-localization and abundance of glutamatergic NMDA receptors and insulin receptors along with

Table 1: Co-localization of amyloid-β-protein mRNA, neurofibrillary tangles, neuritic plaques, glutamatergic receptors and insulin receptor in hippocampal subfields and cell layers and in adjacent areas

	A-β-PmRNA normal/DAT	*NMDA*	*GLU-REC QA*	*KA*	*INS-REC*	*NFT*	*NP*
Hippocampus							
CA_1	++++(PC)	++++	++++	+	++++	++++(PC)	++(PC)
stratum rad.		++++	++++	+	++++		+++(PC)
stratum oriens		++++	++++	+	++++		
stratum pyr.		++	++++	+			
CA_2					++		
CA_3	++++(PC)	++			++	+	++(PC)
mossy fibers terminal field (stratum luc.)		+		+++	++		
Schaffer collateral terminal field		+++		+			
Subiculum stratum pyr.	++/++++				++++	++++(PC)	+++ +++
Dentate gyrus stratum molec.	++++(GC)	++ ++	+	+++ +++	+++ +++	+	+++ +++(GC)
Lateral septum			+++		+++		

A-β-PmRNA : amyloidβ-protein mRNA
GLU-REC : glutamatergic receptor
KA : kainate
NMDA : N-methyl-D-aspartate
QA : quisqualate
INS-REC : insulin receptor
GC : granule cell
PC : pyramidal cell
NFT : neurofibrillary tangle
NP : neuritic plaque
++++ : very high density
+++ : high density
++ : moderate density
+ : low density

amyloid-β-protein mRNA may be of functional significance. In hippocampal CA_1 subfield, both insulin receptor and NMDA receptor density are very high, and amyloid-β-protein mRNA is very abundantly available: cell loss is extensive, neurofibrillary tangles are found to be enriched in pyramidal cells, and neuritic plaques in the pyramidal cell layer. In contrast to the CA_1 subfield, cell loss and the formation of neurofibrillary tangles and neuritic plaques are rather rare or less pronounced in the also well-studied CA_3 subfield. In this area, the densities of both insulin receptor and NMDA receptor were demonstrated to be lower than in CA_1 subfield whereas amyloid-β-protein mRNA in pyramidal cells was found to be as dense as in the CA_1 subfield (Table 1; for brain cortex see Table 2). It may thus be assumed that glutamatergic pyramidal cells possessing NMDA receptors and insulin receptors are particularly vulnerable and are thus prone to cell damage and cell death along with the formation of neurofibrillary tangles. Interestingly, the localization of neurofibrillary tangles in glutamatergic neurons in the hippocampus has been demonstrated in DAT (52). Clearly, the formation of neuritic plaques is associated with amyloid-β-protein mRNA containing cells. However, high levels of amyloid-β-protein expression and the enrichment of neuritic plaques may not be coupled to the density of NMDA receptors as is the case in dentate gyrus (Table 1). Thus, other pathobiochemical abnormalities promoting neuritic plaque formation may have to be taken into account.

Pathobiochemistry of Cell Necrotizing Events In DAT: A Unifying Hypothesis.

Based upon the abnormalities in overall cellular glucose metabolism in DAT brain detailed above, and with respect to the rather particular effect of a disturbed intracellular carbohydrate homeostasis upon glutamatergic pyramidal cells, the following cascade of cell necrotizing events is advanced (Figure 1).

In DAT brain, availability of insulin, or its binding at the α-subunit of the neuronal insulin receptor, or the activation of the β-subunit of the insulin receptor, or the availability of the latter may have become defective. As a result of each of these abnormalities, or its combination, the insulin signal

may be insufficiently transmitted into the neuron. This may result in a diminished PDHC activity combined with a fall in both CAT activity and acetylcholine formation, as well as in an increased lactate production. The activity of the glucose transporter may decrease. As a consequence, CMR glucose may diminish. Recent findings demonstrated a 40% to 50% reduction of the glucose transport protein in DAT brain (53) which is in agreement with the 40% to 50% diminution of CMR glucose in DAT as mentioned above (13). The activity of phosphofructokinase may be either reduced or unchanged (54) depending on the degree and duration of the disorder.

Three processes may then start to run in parallel. First, lactacidosis may give rise to a drop in cellular pH which may decrease the Ca^{2+} affinity to calmodulin (55). The cytosolic Ca^{2+} concentration may increase. Second, Ca^{2+}-dependent release of glutamate and aspartate may start from glutamatergic neuronal pools (56, 57). Furthermore, since the sequestration of cytosolic Ca^{2+} into mitochondria was found to be highly dependent on the activation state of PDHC (58), the reduced PDHC activity may hamper mitochondrial calcium accumulation, attributing to an elevated cytosolic Ca^{2+} concentration. Third, pyruvate-derived acetyl CoA may be less available to condensate with oxaloacetate to form citrate in the tricarboxylic acid cycle. The (relative) increase in oxaloacetate may shift the aspartate aminotransferase reaction. Glutamate is used to form α-ketoglutarate and aspartate. Whereas α-ketoglutarate may be used for further oxidation in the tricarboxylic acid cycle, aspartate may accumulate. By means of this anaplerotic compensation mechanism, the amount of oxidizable C-skeletons in the tricarboxylic acid cycle may be only slightly reduced, and energy metabolism may be maintained close to normal.

At this stage, aspartate may be released from the neuron in high concentration into the extracellular space and may bind to glutamatergic NMDA receptors which control Ca^{2+} channels. As a result, the intracellular, i.e., cytosolic, Ca^{2+} concentration may increase. As a consequence, a steady depolarization of the affected neuron may occur, during which the energy balance in the cell may become negative (utilization > production). The neuronal Ca^{2+} homeostasis cannot be maintained any longer. Ca^{2+}-dependent proteases and phospholipases may be activated.

Proteolysis may initiate the degradation of components of the cytoskeleton including the precursors of the A_4 protein. Ubiquitin, which has been identified as a component of neurofibrillary tangles, may participate in protein breakdown (59, 60). Ca^{2+}-dependent protein kinases may be activated, too, and may phosphorylate cellular proteins (for review, see 61) obviously involved in the formation of neurofibrillary tangles (62). Catabolic proteolysis may be the source of the increased production of amino acids among which neurotoxic ones such as glutamate and aspartate may be found in high concentrations. As a consequence, aspartate NMDA receptor binding may maintain Ca^{2+} influx into neurons on the one hand, and may enhance Ca^{2+} influx into as yet non-affected neurons on the other.

Lipolysis may cause an increase in the concentration of free fatty acids with arachidonic acid being particularly enhanced in the CA, hippocampal subfield (63). Free fatty acids may, at least in part, be metabolized by β-oxidation to acetyl CoA. As a consequence, PDHC-activity may be inhibited further by its product. Both CAT activity and acetylcholine formation may decrease further whereas elevated lactate formation may be maintained, the latter depressing mitochondrial ATP production (64, 65). Fatty acids were found to reduce the activity of phosphofructokinase causing a diminished glucose flux through glycolysis and thus a further reduction of CMR glucose. As a result, energy production may decrease more and more. Excitotoxin-induced neuronal degeneration may be mediated by superoxide radicals generated by xanthine oxidase (66). Free radicals may also derive from increased catabolism of free fatty acids and AMP (61, 67). Finally, oxygen radicals may stimulate intracellular proteolysis (68).

The cascade of cell-necrotizing events in DAT postulated above may damage neurons initially only to a limited extent offering the chance to repair. However, in a later period with Ca^{2+} homeostasis maintaining disturbed, it may develop into a self-propagating process which may accelerate neuronal degeneration exponentially. This neuron-damaging cascade may be assumed for early-onset DAT as well as for late-onset DAT.

However, for the latter, abnormalities other than a disturbance at the insulin/insulin receptor level may have to be considered as factors causing slowly progressive damage of highly vulnerable neurons such as glutamatergic pyramidal cells, and cell death. To give a few examples: The activity of free radicals may increase with advancing age and may induce membrane damage via lipid peroxidation, and proteolysis, too (see above). Subsequently, intracellular Ca^{2+} homeostasis may become abnormal, and the cell-damaging cascade may start at this level (Figure 1). Similar events may be expected after chronic exposition to organic solvents damaging cell membranes. Environmental factors may be assumed to impair intracellular Ca^{2+} homeostasis, or may reduce energy production by influencing oxidation processes. In general, factors which may be able to cause neuronal dysfunction may be considered as such which are able to initiate the cell-necrotizing cascade below the insulin/insulin receptor level. This may occur in particular when no or an insufficient possibility of cell repair is given as may happen in old age (69) and after nerve growth fac-

Table 2: Co-localization of amyloid-β-protein mRNA, neurofibrillary tangles, neuritic plaques, glutamatergic receptors and insulin receptor in cerebral cortical areas and cell layers

	A-β-PmRNA	*GLU-REC*					
	normal/DAT	*NMDA*	*QA*	*KA*	*INS-REC*	*NFT*	*NP*
Cortex							
frontal		+ + +	+ + +	+ +	+ +		
sensory							
parietal					+ +		
temporal							
Occipital		+ + +	+ + +	+ +	+ +		
Layer I		+ + +	+ + +	+ +			
Layer II	+ + +	+ + +	+ + +	+ +		+ +	+ + +
Layer III	+ + +/+	+ + +	+ + +	+ +	+ +	+ + +(PC)	+ + +
Layer V	+ + +/+	+ + +	+ +	+ + +		+ + + +(PC)	+ +
Layer VI		+	+	+ + +			
Entorhinal Cortex	+ +				+ + + +		
Layer II						+ + + +	
Layer III						+ + +	
Layer IV						+ +	

A-β-PmRNA : amyloidβ-protein mRNA
GLU-REC : glutamatergic receptor
KA : kainate
NMDA : N-methyl-D-aspartate
QA : quisqualate
INS-REC : insulin receptor
GC : granule cell
PC : pyramidal cell
NFT : neurofibrillary tangle
NP : neuritic plaque
+ + + + : very high density
+ + + : high density
+ + : moderate density
+ : low density

tor synthesis is ceased subsequent to a damage of pyramidal cells in the hippocampus and the dentate gyrus (70). It may thus be assumed that late-onset DAT may be caused by factors of different origin.

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ABBREVIATIONS

ATP is adenosine triphosphate; CAT is choline acetyltransferase; CBF is cerebral blood flow; CMR is cerebral metabolic rate; DAT is dementia of Alzheimer type; NMDA is N-methyl-D-aspartate; PDHC is pyruvate dehydrogenase complex.

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