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Coexisting Cholinergic and Parahippocampal Degeneration: A Key to Memory Loss in Dementia and a Challenge for Transgenic Models?

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Abstract
One century after Alzheimer's initial report, a variety of animal models of Alzheimer's disease (AD) are being used to mimic one or more pathological signs viewed as critical for the evolution of cognitive decline in dementia. Among the most common are, (a) traditional lesion models aimed at reproducing the degeneration of one of two key brain regions affected in AD, namely the cholinergic basal forebrain (CBF) and the transentorhinal region, and (b) transgenic mouse models aimed at reproducing AD histopathological hallmarks, namely amyloid plaques and neurofibrillary tangles. These models have provided valuable insights into the development and consequences of the pathology, but they have not consistently reproduced the severity of memory deficits exhibited in AD. The reasons for this lack of correspondence with the severity of expected deficits may include the limited replication of multiple neuropathology in potentially key brain regions. A recent lesion model in the rat found that severe memory impairment was obtained only when the two traditional lesions were combined together (i.e. conjoint CBF and entorhinal cortex lesions), indicative of a dramatic impact on cognitive function when there is coexisting, rather than isolated, damage in these two brain regions. It is proposed that combining AD transgenic mouse models with additional experimental damage to both the CBF and entorhinal regions might provide a unique opportunity to further understand the evolution of the disease and improve treatments of severe cognitive dysfunction in neurodegenerative dementias.

From Alzheimer to Transgenic Mice

On November the 3rd 1906, at a local psychiatry meeting in Germany (the 37th Meeting of Southwest German Psychiatrists, Tübingen), Aloïs Alzheimer (1864–1915) presented one of the most important observations in brain science and published these findings the following year [1]. As is well known, he had found two neuropathological abnormalities in the cortex of a 56-year-old dementia patient, Auguste Deter. The first neuropathological feature was the presence of intracellular neuro-

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fibrillary tangles (NFTs), now known to result from hyperphosphorylation of the cytoskeletal protein tau [2], which is involved in microtubule assembly and stabilization. The second hallmark was the presence of what are now called senile plaques, which are extracellular deposits of β-amyloid peptide (Aβ) that result from the abnormal cleavage of the amyloid protein precursor (APP) [see, for example 2, 3]. The two hallmarks described by Alzheimer allow postmortem confirmation of a prior Alzheimer's dementia, but the clinical course of the condition itself is characterized by a protracted decline in functional independence through progressive worsening of a broad range of higher cognitive functions, of which severe deficits in long-term episodic memory and spatial disorientation are of the most prominent neurobehavioral signs [4]. Some recent evidence suggests that neuritic plaques are more influential than tangles in the earlier stages of Alzheimer's disease (AD) [e.g. 5, but see 6]. The modern era of interest in the pathological events that lead to this dementia began in the mid-1970s with a focus on the degenerative changes in cholinergic basal forebrain (CBF) projections [7, 8]. The most significant of these findings was that a decline in neocortical cholinergic markers in the temporal lobes correlated strongly with the degree of overall cognitive impairment [9] and the association between cholinergic dysfunction and dementia continues to receive support [e.g. 10–15, but see 16]. Parallel clinical and experimental work led to the influential cholinergic hypothesis of Bartus et al. [17] of geriatric memory dysfunction based on the idea of a causal link between CBF degeneration and the early memory deficits that provide the essential cognitive signature of dementia of the Alzheimer type [18]. The cholinergic hypothesis provided the rationale for developing cholinomimetic therapy, which remains the frontline drug treatment for dementia, although its efficacy has been less promising than initially expected [3, 19–22]. However, the pioneering work by Perry et al. [9] has been based on information derived from AD patients with severe dementia. Actually, neither patients at risk for AD (MCI) nor mild AD patients appear to have marked depletion of cholinergic indicators in the neocortex [e.g. 2, 23 vs. 24–26]. Some MCI patients even show upregulation of cholinergic function, which may reflect early adaptive mechanisms in response to ongoing neurodegenerative processes [26].

More recently, the retrohippocampal region in the medial temporal lobe has been proposed as the brain area that shows some of the earliest signs of neurodegeneration. Given this region's complex interconnections with the hippocampal formation, it is presumed that it must play an essential role in the emergence of prominent episodic memory deficits [27]. In particular, early atrophy and hypometabolism of the transentorhinal region has been highlighted by postmortem and recent in vivo brain imaging studies of dementia patients [e.g. 28–30]. Moreover, changes in the entorhinal cortex, specifically, have been found to be good predictors for the conversion from MCI to AD [14, 31–34]. In addition to the atrophy of medial temporal lobe structures, afferent and efferent pathways and functionally connected regions contribute to the memory impairments found in patients at the earliest stages of AD [30, 35]. For example, a recent study by Nestor et al. [36] is particularly revealing in showing that medial temporal lobe degeneration, in isolation, does not explain the marked episodic memory impairment characteristic of AD. While these authors focused on the importance of limbic-diencephalic neurocircuitry beyond the medial temporal lobe, their findings point to the more general importance of considering multiple, conjoint degenerative processes in explaining severe episodic memory loss. We suggest that the recent approach focusing almost exclusively on the CBF or the entorhinal cortex region with respect to memory decline in AD ignores the potential influence of changes to multiple neural systems. Specifically, it may be the concurrent degeneration in both the CBF and the entorhinal cortex, and the loss of their functional interactions that provides a major reason for the severity of memory decline in dementia. While it is clear that AD represents a complex disorder, and the role of neuropathological changes are central to an understanding of AD, the prominence of cognitive deficits must remain a central focus of attention because it is the cognitive and behavioral deficits that pose the daily handicap for the patient and their relatives.

In the following brief review, we summarize evidence on some of the more common rodent models of AD, including those using transgenic manipulations to induce amyloid and/or tangle histopathology in mice, and those using classic lesion methodologies to mimic either CBF or entorhinal cortex degeneration. The main contributions and limitations of each approach to understand AD pathology and cognitive changes are reviewed. It is clear that the extent of cognitive impairment expressed in most single lesion or transgenic models appears to be relatively limited, even with extensive lesions or heavy amyloid or tangle histopathology. We then briefly describe the dramatic memory deficits obtained in a recent rat AD model, which examined the effects of combined CBF and

entorhinal cortex lesions to reproduce the effects of conjoint degenerative changes in these regions. The success of the latter strategy prompts us to propose the advantage of combining the strengths of this multiple lesion model with those of transgenic mouse models to optimize new models of AD.

Benefits and Limits of Transgenic Mouse Models Bearing Plaques and/or NFTs

The aim of transgenic manipulations in mice is to model the fundamental neuropathology underlying AD and develop molecular treatment strategies aimed at reversing this neuropathology [for more detailed reviews, see for example 37–39]. Recent advances in the molecular neurobiology and genetics of AD have engendered several mouse lines bearing plaques and/or NFTs, which resulted in valuable progress in understanding some key steps in the development of AD-like pathophysiology and its consequences for brain function. For example, single and multiple transgenic models have proven to be powerful tools to study both the individual role of several AD-related proteins (e.g. ApoE, BACE-1, presenilin-1) in the abnormal metabolism of APP, Aβ and tau, as well as the synergistic relationships between Aβ and tau pathologies [e.g. 24, 40–44]. However, a further motivation in creating these lines was to evaluate the impact of either amyloid plaques, NFTs or both on memory function as a means to clarify their involvement in the cognitive symptomatology of AD. Table 1 summarizes the neuropathology and cognitive deficits reported for some of the more representative AD transgenic mouse models. The first transgenic models, which were mainly plaque-bearing mice overexpressing human APP (h-APP) mutated genes, have now been characterized in terms of cognitive ability at different developmental stages [e.g. 37, 38, 45] (table 1).

Unfortunately, some mouse lines, such as PDAPP mice, display age-independent memory deficits in some tasks and age-dependent deficits in other tasks, the latter deficits emerging well before amyloid plaques are detected. The age-independent deficits are presumably related to early neurodevelopmental abnormalities, consistent with a role of APP in brain ontogeny [e.g. 41, 136]. By contrast, many other h-APP transgenic lines, such as APP23 mice and Tg 2576 mice, show age-dependent amyloid deposits and memory deficits, which is more desirable for an animal model of AD. Of particular interest in modeling the progressive changes in AD, these models also often display some behavioral deficits before the onset of plaque formation. Such findings pointed to the deleterious effects of the soluble forms of Aβ (e.g. Aβ oligomers) on synaptic and cognitive function, which suggests that soluble Aβ may play a role in early AD cognitive impairments [25, 40, 42, 93, 127, 137, 138]. The major problem with the h-APP transgenic models is, however, that even the oldest mice with a severe amyloid burden may show greater than expected improvements in spatial learning tasks, such as the water maze or the Barnes maze [e.g. 54, 119]. Deficits in spatial working memory and spatial reference memory tasks are important because they provide useful animal analogues of AD-related impairments in episodic memory and spatial disorientation [139]. However, even the same transgenic mouse model may produce mixed findings, sometimes even when the same task is used (memory is impaired in some of the tasks and not in others or, using the same task, memory is impaired in some studies and not in others; table 1). For instance, PSAPP have been reported to exhibit impaired acquisition in a water-maze task but normal retention, or normal acquisition but then impaired retention, or alterations of both (table 1), and the same remark applies to NFT transgenic models, such as JNPL3 mice, in the same task [109].

Thus, current transgenic mouse models of AD are extremely valuable, but have certain limitations because they reproduce only partially the progression, severity and range of deficits in spatial memory tasks used to model those found in AD. As it is known that degeneration of the CBF and the entorhinal regions are both involved in the AD cognitive decline, it is pertinent to examine whether similar cholinergic and transentorhinal neurodegenerative events are found in transgenic mouse models.

As shown in table 1, however, most research on transgenic mice has focused on pathological signs in the hippocampus and the whole neocortical mantle, rather than in the transentorhinal region even though the latter shows the earliest evidence for neurodegeneration in AD [e.g. 29]. A few studies have shown some histopathological and functional alterations in the entorhinal region of transgenic mouse lines, such as Tg 2576 or PSAPP mice [42, 52, 140, 141] (table 1). However, no quantitative evidence for cell loss or hypometabolism in the entorhinal cortex has been reported in transgenic mouse models yet [142, 143]. In contrast to the paucity of data concerning the entorhinal cortex, the cholinergic system of several h-APP transgenic mice has been examined more frequently, although not systematically, most probably be-

cause of the popularity of the cholinergic hypothesis of AD dementia. Most h-APP transgenic mice do show some alterations of cholinergic markers, although these are mainly restricted to the hippocampus and the cortex, which are the target structures of the basal forebrain projections [50, 51, 85, 138, 142, 144] (table 1). The disruption of their cholinergic inputs is usually explained in terms of the deleterious effect of local (target) amyloid load, which perturbates cholinergic presynaptic terminals and fibers [87, 140, 142, 144]. Within the basal forebrain, reduced size of cholinergic cells or weakened cholinergic enzyme activities have been observed in two but not all transgenic mouse models [51, 142]. Moreover, the few studies that have tried to quantify the cholinergic neurons in the basal forebrain did not report a significant loss of cell bodies [e.g. 73]. Clearly, such weak cholinergic neuropathology fails to replicate that seen in dementia, which in turn might be one reason for the incomplete correspondence between the expected cognitive phenotype in old h-APP transgenic mice when modeling deficits found in AD patients. This lack of cholinergic neuron loss may be related to compensatory effects of the APP transgene, too short life span of the mouse for development of a complete neuropathologic scheme or resistance of the mouse basal forebrain to Aβ neurotoxicity. With regard to NFT models, it is interesting that some show a general atrophy of the forebrain, which suggests a significant cell loss in this area, but it is not yet known whether this atrophy includes any substantial cholinergic cell loss per se [106]. Of more direct relevance, multiple transgenic mice expressing both amyloid plaques and NFTs do show evidence of neuronal loss in the entorhinal cortex (table 1). Evidently, further neuroanatomical and behavioral data are needed to establish their complete neuropathological scheme and try to relate it to the extent of their cognitive impairment.

In conclusion, transgenic mouse models of AD have enabled considerable progress in understanding the genesis and consequences of the amyloid and/or NFT burden, but they have thus far provided little specific evidence on the influence of regional pathology. Many of the approaches in transgenic mice have tried to focus on possible relationships between the two neuropathological hallmarks of AD and the cognitive phenotype, but only a few of them have tried to establish a more direct connection between the neurodegenerative consequences of the transgene and the cognitive phenotype. Thus transgenic mice studies could focus more specifically on regional neurodegenerative changes and behavior, particularly the CBF and the transentorhinal region.

Lesions of the CBF or Lesion of the Entorhinal Cortex as Models of AD? Combining Both Lesions Provides a Better Model

By contrast with transgenic models, models based on a traditional lesion approach can provide a more direct test of the critical importance of one or more degenerating regions as a basis for severe memory loss in dementia. Initially, the proposed relationship between cholinergic dysfunction and AD or age-related memory alteration was supported by experimental studies using animal models based on either systemically administered anticholinergic drugs or nonspecific lesions of the basal forebrain region. The fundamental basis of the cholinergic hypothesis faltered, however, when evidence emerged from a series of experimental studies that used more selective, even if extensive, immunotoxic cholinergic lesions of the basal forebrain in rats [e.g. 15, 16]. Contrary to expectations, these selective cholinergic lesions more consistently induced impairments in attention rather than memory, or they produced deficits on some learning tasks that provided ambiguous models of episodic memory. These newer observations were useful in terms of characterizing cognitive decline related to dementia, because dementia entails deficits well beyond any isolated memory impairment, but they conflict with the notion of the key importance of the CBF in episodic memory deficits. Deficits in attention were evident in animal lesion studies that damaged the nucleus basalis magnocellularis, the source of cholinergic afferents of the cortical mantle [e.g. 43, 145, 146]. Conversely, cholinergic lesions in the septohippocampal system did not reliably alter attention [e.g. 147], but, beside a few exceptions showing clear-cut memory deficits, they also generally failed to consistently induce dramatic effects on memory function [e.g. 16; but see 147]. It is noteworthy that these findings were apparent even with massive (>90%) depletion of cholinergic markers such as choline acetyltransferase or acetylcholinesterase in the cortical mantle and/or the hippocampus [e.g. 15, 16]. Clearly, the manner in which cholinergic damage can account for memory impairment is an unresolved issue.

Similar conclusions can be drawn from lesions made in the transentorhinal region. Indeed, it is interesting that while fiber-sparing damage to the perirhinal and even the entorhinal cortex may result in some memory impairment, these deficits are seldom as dramatic as might be expected on the basis of the neural connectivity of this region with the hippocampus or the severity of memory impairment found in dementia patients [139].

Table 1. Summary of the main physiopathological alterations in the cortex, cholinergic basal forebrain and hippocampus, and cognitive status reported in the most frequent transgenic models of AD (references in square parentheses)

Transgenic mouse model (name)	Gene expressed	Amyloid deposits	NFTs	Neuropathology (cortex, hippocampus) or physiopathological alterations
APP23	APP Swe Mut cDNA	Yes (Ctx, Hp) Onset between the age of 12 and 18 months [46]	No (but hP-Tau is present) [e.g. 46]	Cell loss in CA1 (no loss in Ctx) [46] Fiber distortion in Hp plaque vicinity + aberrant sprouting in Hp [47] Reduction of synaptic transmission in the Hp, but LTP is normal; no effects in the frontal Ctx [48] No change in the number of synaptophysin-positive terminals in the Ctx, even at 24 months [49]
PDAPP	APP minigene, v717F mutation	Yes (Ctx and Hp) Onset between the age of 6 and 12 months [e.g. 60–63]	No (but hP-Tau is present) [62]	Hypometabolism in several subcortical and cortical regions [64] Reduced Hp volume, shortened corpus callosum, shrunken fornical commissure [65–67] Dentate gyrus shrinkage and reduced corpus callosum [68, 69] Amyloid deposits in Hp, especially in the projection areas of the EC [63] Reduced spine density in Hp [70] Reduced size of neurons in the locus coeruleus [71] Reduced hippocampal neurogenesis [72]
Tg2576	APP Swe cDNA	Yes (Ctx, Hp) Onset between the age of 14 and 18 months [e.g. 80, but see 81]	No (but hP-Tau is present) [e.g. 82]	Decreased synapse density in dentate gyrus outer molecular layer [83] No cell loss in CA1 [61] Increased cholinergic synapse density in the frontal [84] and parietal cortices [85] Loss of dendritic spines in CA1 [70] Normal ChAT activity in the frontolateral sensorimotor cortex [86] Decreased spine density; no marked volumetric change in the Hp [87]
JNPL3, pR5, also ALZ7 or ALZ17 in Spires and Hyman[39]	4R tau (4R tau P301 L)	No	Yes (Ctx, Hp, amygdala, locus coeruleus and substantia nigra) Onset between the age of 18 and 20 months, but reports show earlier appearance [101–104] Injections of A 42 accelerates NFTs formation [105]	Reactive astrocytes in Ctx and amygdala; apoptosis in the somatosensory Ctx, not in the Hp [105] Brain atrophy, especially in the temporal lobe and Hp (almost complete loss of pyramidal neurons in CA1 and CA2) [103, 106]
PSAPP	Tg2576 + PS1 M146L	Yes (Ctx and Hp, mainly C1A) Onset between the age of 8 and 12 weeks [111–113]	hP-Tau is present [112]	Decreased cholinergic synapses density in frontal Ctx [84] and Hp [85] Minor loss of neurons in Ctx and Hp, mainly CA1 [112] Reduced ChAT activity in occipital Ctx, but not the Hp [114] Neuron-free holes in the Ctx [113] Reduced mRNA of several synaptic plasticity-related genes in amyloid-containing regions [115] Marked reduction of number of CA1 neurons [116] Normal LTP in Hp, but accelerated decay [117]; abnormal LTP [118]
TAPP	Tg2576x + JNPL3	Yes (Ctx, Hp) Onset at 6–7 months, numerous deposits at 8.5–15 months [43] Amyloid burden increased in Ctx and Hp, more in females [125]	Yes (olfactory, entorhinal Ctx, amygdala, subiculum Hp-tau) Onset at 3 months (in spinal cord and pons in females at 9–11 months) [43]	Granulovacuolar degeneration in the subiculum [43] Age-dependent reduction of the number of neurons in the Hp (CA1) [125]
3xTg-AD	APP (Swe mut) + PS1 + tau	Yes (Ctx, then Hp) Onset at about 3 months [e.g. 126, 127]	Yes (Hp then Ctx) Later onset, with tau apparent at 6 months, undergoing hP much later[e.g. 126]	LTP deficits in Hp before tangle and plaque formation [e.g. 128]

This table provides a nonexhaustive glance at the literature concerning the most frequent and/or some recent transgenic models of AD, with particular focus on neuropathological features in the cortex, the hippocampus, and more specifically in the cholinergic basal forebrain and the entorhinal cortex (when available). This table also briefly summarizes the various learning and memory deficits that could be identified (or not) so far, and in various tests, in each of these models.

AChE = Acetylcholinesterase; Acq = acquisition; Barnes = Barnes maze; ChAT = choline acetyltransferase; Cons = consolidation; CTA = conditioned taste aversion; Ctx = cortex; Ctxt fear Cond = contextual fear conditioning; EC = entorhinal cortex; Hp = hippocampus; hP-Tau = hyperphosphorylated Tau; H-W Mz = Hebb and Williams maze; LTP = long-term potentiation; MW Mz = Morris water maze; NBM = nucleus basalis magnocellularis; n.d. = not determined; NFTs = neurofibrillary tangles; Obj Rec = object recognition task; Pass Av = passive avoidance; PS1 = preseniline 1; RAD Mz = radial maze; Ret = retrieval; Ref Mem = reference memory; Swe Mut = Swedish mutation; Y-Mz = Y-maze alternation; T-Mz = T-maze alternation; vAChT = vesicular acetylcholine transporter; WM = working memory.

Cholinergic basal forebrain	EC	Memory deficits
AChE-positive fiber distortion in Ctx plaque vicinity [46] Reduction of ChAT activity in the frontal Ctx, but no change in the number of neurons in the NBM complex [50] AChE and ChAT activity reduced in the basal forebrain [51]	Qualitative loss of neurons in the EC [52, 53] Reduction of ChAT-positive boutons in the EC [50]	Pass Av: Ret impaired at 25 months [54] MW Mz: deficit in Acq before amyloid deposits [55]; attenuated by cholinesterase inhibitors [56] Plus-shaped water maze: impaired Acq, Cons still possible, WM impaired but not obliterated [57] RAD Mz: no deficit of WM [58] 'Complex' Mz: impaired, but improved performance [58] Barnes Mz: slower Acq, preserved Cons and Ret [59]
Hypometabolism in the septum [64] Decreased cholinergic terminals in the Ctx and Hp, but no loss of cholinergic neurons in the medial septum and diagonal band of Broca; reduction of ChAT activity in the cingulate Ctx [73] Reduced acetylcholine release (microdialysis) in hippocampus and attenuated responsiveness of the release towards scopolamine; augmented high affinity uptake of choline [74]	Aβ deposits in molecular and laminar layers II, III of the EC (also in the Hp) [75] No metabolic change in the EC [64]	Obj Recog: age-dependent deficit [64]; impairments also found in other studies [e.g., 76]; no deficit in another study [77]. RAD Mz: robust, age-dependent deficits in hetero- and homozygotes [64] MW Mz: age-independent and age-dependent deficits [77]; marked deficit from an early age onwards [60, see also 78] Barnes Mz: age-dependent deficit [79] Eyeblink conditioning: impaired [69] Holeboard task: impaired [76]
Normal size of neurons in the medial septum and the NBM [85] Normal ChAT and AChE activity, vAChT and choline uptake in Ctx, cerebellum, Hp and striatum [88] Normal AChE and ChAT activity, reduced choline uptake, reduced M1, M2 and nACh receptor binding in some regions [89, 90] Degeneration of ChAT-positive fibers in the Ctx [91] Normal ChAT activity in frontal Ctx [86] Reduced ChAT activity in pedonculopontine nucleus, but not in laterodorsal tegmentum and medial septum [92]	Decreased synapse density in layers II and III [83] Normal size or density of cholinergic boutons in EC [85] Perforant path stimulation-induced LTP is altered in dentate gyrus [87]	MW Mz: age-dependent deficit, although ACq is not totally prevented; CONS and RET seem impaired [80, 81, 93, 94] or no deficit [95] Barnes Mz: no deficit [96] RAD Mz: no deficit of WM [97]; impaired WM in aquatic version of the task [94] Y-Mz: alternation is at random [81, 94, 98,] Obj Recog: impaired, especially after relocation [99] Fear conditioning: contextual processing impaired [100]; severely impaired in an age-dependent manner [87]
No data found in the literature	Tauopathy in the lateral EC [102,104] Tau inclusions in oligodendrocytes of the EC [107] Neurons with degenerated cytoplasm and condensed nuclei in the EC [103]	CTA: impaired memory (with considerable heterogeneity) [103]; accelerated extinction in another study [104] MW Mz: normal Acq and Ret of Ref Mem [94, 103], but WM impaired [103]; Ref Mem performance negatively correlated with the number of tau-positive neurons in the Hp [94]; impaired [106, 108,]; normal Ref Mem and impaired WM [109] Y-Mz: alternation rates are normal [94] RAD Mz: deficit, but performance improves over trials; deficit more pronounced with tangles vs. pretangles [103]; normal in aquatic version [94] Obj Recog: normal performance at a short post-Acq delay (1 h), but not at a longer one (3.5 h) [110]
Normal neuron size in medial septum and NBM [85] Normal ChAT activity in medial septum, a trend to reduction in NBM complex [114]	Normal size or density of cholinergic boutons in the EC [85]	Barnes Mz: no deficit [119] MW Mz: no deficit of Ref Mem during Acq, but some indication of altered Ret [120]; impaired Acq but normal Ret [119]; impaired Acq and Ret [121,122,123]; RAD Mz: impaired performance [120]; impaired WM in aquatic version of the task [118, 119, 122, 124] Y-Mz: normal alternation [119, 122] Obj Recog: impaired performance [120] H-W Mz: marked deficit [116]
No data found in the literature	Amyloid deposits, NFTs and granulovacuolar degeneration [43] Age-dependent reduction of the number of neurons in the EC [125]	MW Mz: age-dependent impairment in visible platform task, impaired Acq in Ref Mem and age-dependent Ret deficit [125]
No data found in the literature	Reduced number of Reelin-expressing pyramidal cells in EC; reduced Reelin levels in Hp [129] Early inflammation in EC [130]	MW Mz: deficit (rescued by AF267B) [40, 131, 132]; females are transiently worse than males [133] Ctxt fear Cond: deficit (not sensitive to AF267B) [131, 133] T-Mz : WM deficit [134, 135]

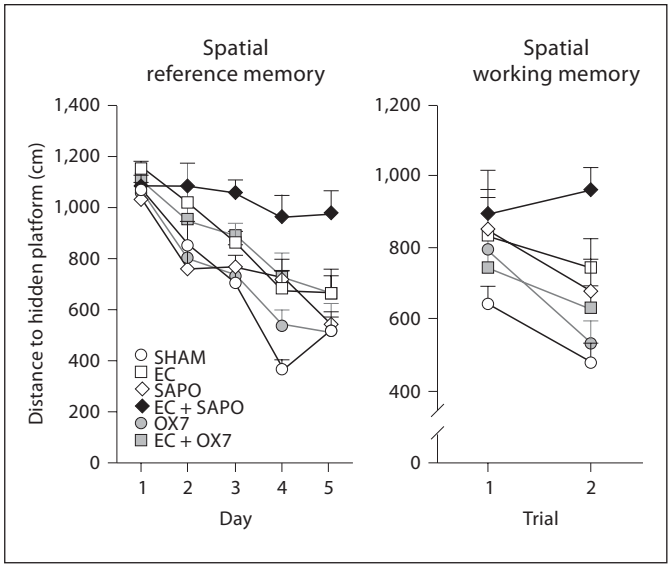

Fig. 1. Spatial reference memory and working memory performance in the Morris water maze in which the rat swims to the location of an escape platform hidden just beneath the opaque water surface. Performance is expressed as the mean distance (±SEM) to find the hidden platform in rats subjected to sham-operations (SHAM), neurotoxic entorhinal cortex lesions (EC) or intracerebral injections of 192 IgG-saporin (SAPO) or OX7-saporin (OX7). EC + SAPO and EC + OX7 rats sustained combined lesions. Intracerebral 192 IgG-saporin severely depletes the CBF neurons, but can also influence the integrity of Purkinje cells in the cerebellum, as the latter also bear the target receptors of 192 IgG-saporin. OX7-saporin injections provide a selective control for the potential effects of cerebellar damage. For the reference memory task, rats were given 4 consecutive trials from different start points on each day and allowed to find the platform positioned always in the same location; reduction of the distance traveled demonstrates learning. Note the absence of improvement in EC + SAPO rats. Such deficits failed to appear when the platform was visible (not shown). For the working memory test, the rats were given 2 consecutive trials (with different starting places) on each day, but the platform location was changed from day to day. This figure has been adapted from Traissard et al. [151].

Recent evidence suggests a more crucial role for the dorsolateral band of the entorhinal cortex, at least in spatial memory processes, but rats with such lesions are still able to learn a new spatial location in a water-maze task and their primary deficit concerns the failure to retrieve a location that had been acquired prior to lesion surgery [148].

This brief summary on the contribution of lesion approaches [for further details, see 15, 16, 149] leads to the conclusion that neurodegeneration in the transentorhinal region and isolated cholinergic depletion of the hippocampus (and/or cortex) are similarly insufficient to cause major memory deficits [16, 150]. Although entorhinal cortex degeneration begins well before severe episodic memory loss or frank dementia become obvious, it is expected that substantial loss in this region would have a significant influence on memory. It remains, however, highly plausible that it is a combination of severe neurodegenerative changes in both the entorhinal cortex and the CBF that constitutes a central issue for episodic memory loss in AD.

Evidence pertinent to this question has recently been published by Traissard et al. [151] in a study in which adult male rats were subjected to selective immunotoxic lesions of basal forebrain cholinergic neurons and fibre-sparing lesions of the entorhinal cortex, either separately or in combination. CBF lesions were made by intracerebroventricular injections of the low affinity nerve growth factor receptor-specific cholinergic immunotoxin 192 IgG-saporin [152, 153], while entorhinal cortex lesions were produced by multiple intraparenchymal injections of small amounts of N-methyl-D-aspartate. As illustrated in figure 1, rats with selective cholinergic damage alone showed little deficit on two widely used spatial memory tasks in the water maze, which tax reference and working memory, respectively, while those with entorhinal cortex lesions alone also showed only minor deficits. But there was a striking contrast in the rats that received the combination of 192 IgG-saporin and entorhinal cortex lesions as these rats showed a dramatic impairment on both spatial memory tasks and little evidence of being able to learn at all. These findings suggest that selective cholinergic lesions may severely tip the balance against an already failing medial temporal lobe memory system. Recent functional imaging studies suggest that many limbic and cortical brain regions in addition to the medial temporal lobe are associated with severe memory decline in dementia and its early progression [e.g. 36, 154, 155]. Nonetheless, we suggest that an improved understanding is required on the importance of the concurrent changes to these two key regions and their relationship to the dramatic memory decline observed in dementia. A greater and more specific focus on the combined, rather than isolated, loss of these two critical regions in clinical cases may therefore provide an improved approach to identify at risk cases, to understand the progressive decline of episodic memory and perhaps to encourage better treatments for the key problem of the cortical and subcortical disconnection of the hippocampal system in dementia.

Transgenic and Lesion Models Are Complementary: Let's Combine Them!

Transgenic models, especially the use of multiple transgenic mouse lines, have been valuable in studying the progression and interactions of amyloid plaques and NFTs. However, as outlined above, the reported cognitive deficits, CBF dysfunction and degenerative changes in the entorhinal cortex still fail to reach the severity of the neuropathological and cognitive alterations found in dementia. Conversely, the recent demonstration of the dramatic impact of combined CBF and entorhinal cortex lesions on cognitive abilities brings together two key pieces of the dementia process and points to the value of paying greater attention to the combined changes to these two regions, rather than to either in isolation. However, this new model does not of course mimic the presence of amyloid plaques and NFTs. Single lesions of the CBF fail to induce amyloid plaques in rats, even after a prolonged postsurgical delay [156], but some vascular amyloid deposits have been reported in rabbits [157]. Evidently, transgenic and lesion approaches have generated models which appear complementary. Transgenic mice bearing amyloid plaques and NFTs, but only mild cognitive deficits and modest CBF and entorhinal cortex alterations on one hand, and lesioned rats reproducing CBF and entorhinal cortex degeneration and severe memory deficits, but no plaques or NFTs on the other hand. Therefore, we propose that the two approaches be combined by making lesions in both the CBF and the entorhinal cortex in transgenic mice known to robustly exhibit amyloid plaques and NFTs. The resulting model would exhibit dramatic cognitive deficits, histopathological hallmarks and degeneration of two key regions of the disease, in other words, it would show more complete AD pathology than is currently available. Furthermore, we might also predict that the double lesions will not only have an additive effect on the transgenic phenotype, they could also worsen the amyloid and/or tangle burdens. Indeed, there are some indications that lesions of the CBF or the entorhinal cortex influence APP and tau metabolism in their target regions as reported in rabbits and rats [e.g. 157, 158]. Therefore, one might suggest that applying the double lesion to transgenic mice might amplify the amyloid and tangle pathologies. Recent work has suggested a new significance for cholinergic depletion and dementia progression in terms of both tau hyperphosphorylation and the production of Aβ; the latter products may in turn disrupt acetylcholine synthesis and cholinergic neurotransmission by altering axon terminals and synaptic integrity [15, 127]. Therefore, the proposed lesion plus transgenic model may also help to elucidate how cholinergic dysfunction and entorhinal cortex degeneration interact with the histopathology of the disease. In addition, the extent of the lesions as well as the timing of both entorhinal and CBF lesions could be easily controlled and a wide range of transgenic mouse models of AD are now available. Thus, this transgenic plus lesion model offers enough flexibility to study behaviorally relevant interactions between the expression of one or more transgenes and the time course of the impact of more or less extensive lesions, both in terms of neuropathology (e.g. enhanced amyloid deposits, increased NFTs, exacerbation of the lesion extent) and cognitive consequences (e.g. potentiation of deficits). Evidence on the influence of basal forebrain or parahippocampal lesions in robust transgenic models is also highly relevant to the evaluation of different therapeutic agents in these genetically compromised animals. For example, the proposed model might be particularly relevant to test new therapeutic strategies, and probably multiple therapies, targeting amyloid plaques and/or NFTs, as well as the symptoms or the progress of two of the key neurodegenerations found in dementia.

One caveat at this point in time that stands against the idea of developing the transgenic plus lesion model is that transgenic and lesion models have been developed in different species, respectively mice and rats. Thus far, there is only one exception in which AD-related genetic manipulations have been performed in the rat [159], whereas the majority of lesion studies have been performed using rats. This difference raises the question of whether results from lesion studies in rats can be generalized to mice, but this seems highly likely as it is already accepted that information from rat studies are informative as to the basic neurobiology of learning and memory, including that found in humans. Moreover, it is feasible to perform selective CBF lesions and entorhinal cortex lesions in mice. Concerning the entorhinal cortex, such lesions have been conducted in mice for some time [e.g. 160]. And there now exists a selective cholinergic immunotoxin claimed to be an equivalent to 192 IgG-saporin which is used for rats, namely mu p75-saporin. Although the older version of this murine immunotoxin had some severe drawbacks [161], an improved version of mu p75-saporin is now available (see http://www.atsbio.com/catalog/catalogframe.html). Our first experiment with this improved murine cholinotoxin found that it is able to induce both selective and extensive damage to CBF neurons (medial septum, diagonal band of Broca and nucleus basalis mag-

nocellularis) and to produce behavioral effects comparable to those described in rats with 192 IgG-saporin lesions [162]. Thus, this murine cholinotoxin may be used in transgenic models of AD to induce selective cholinergic lesions at different developmental time points.

It is also encouraging that the idea of combining lesions with a transgenic approach has already begun. In one study, Heneka et al. [163] showed that DSP-4 lesions of the noradrenergic neurons of the locus coeruleus greatly augmented the development of cortical amyloid pathology in APP23 mice and also exacerbated the cognitive deficits displayed in episodic-like memory tasks. The authors interpreted these findings in relation with the consequences of the lesions on the regulation of intracerebral inflammatory process. More relevant to the emphasis of the current review, Chauhan [164] has found substantially greater impairments after selective mu p75-saporin CBF lesions in Tg CRND8 mice, together with increased tau phosphorylation and tangle-like inclusions. These initial observations support the idea of critical interactions between the presence of localized degeneration or injury and the expression of the transgene(s). It seems highly likely, then, that lesions of the CBF and the entorhinal cortex will produce larger cognitive deficits in transgenic mouse models than in unlesioned transgenic mice. The developmental timing of the lesion intervention in the transgenic mice is likely to be critical, as there may be very different answers that may vary as a function of the specific issue under question. For example, the double lesion could be made before the onset of plaques or NFTs to examine if they accelerate the expression of the transgene. Alternatively, the lesion could be performed only once the plaque or NFT burden is already high (more advanced age) to investigate whether the presence of the latter exacerbates existing memory deficits or induces new ones. In line with the progression of dementia pathology, the lesions could be made in series, starting with the entorhinal cortex and adding the cholinergic one only later.

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