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Transgenerational transmission of an anticholinergic endophenotype with memory dysfunction

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ABSTRACT

Impaired cholinergic neurotransmission associated with cognitive dysfunction occurs in various mental disorders of different etiologies including Alzheimer's disease and postalcoholic dementia and others. To address the question whether there exists a common endophenotype with a defined genetic and/or epigenetic signature causing mental dysfunction in these disorders, we investigated 2 generations of offspring born to alcohol-treated mothers. Here, we show that memory impairment and reduced synthesis of acetylcholine occurs in both F1 (exposed to ethanol in utero) and F2 generation (never been exposed to ethanol). Effects in the F2 generation are most likely consequences of transgenerationally transmitted epigenetic modifications in stem cells induced by alcohol. This clearly documents the role of ancestral history of drug abuse on the brain development of subsequent generations. The results further suggest an epigenetic trait for an anticholinergic endophenotype associated with cognitive dysfunction which might be relevant to our understanding of mental impairment in neurodegenerative disorders such as Alzheimer's disease and related disorders.

1. Introduction

Structural-functional organization principles of the cholinergic system, that is, nerve cells releasing acetylcholine, the first neurotransmitter that had been identified (Dale, 1914), have long been a leading paradigm to conceptualize the brain-behavior relationship against the background of chemical neuroanatomy (van der Zee et al., 2011). Earlier psychopharmacological evidence for a role of cholinergic function in cognition together with biochemical findings on reduced cholinergic marker enzymes and degeneration of cholinergic basal forebrain neurons in Alzheimer's disease (AD) eventually culminated in formulating the "cholinergic hypothesis" of memory dysfunction (Bartus et al., 1982).

While in the light of more recently gained knowledge, its original formulation might require some updating, the cholinergic hypothesis has been of tremendous heuristic value over the last 30 years, providing the basis for the todays leading strategy to ameliorate cognitive dysfunction in AD by cholinesterase inhibitors (Seltzer, 2006). Still, degeneration of cholinergic neurons in the basal forebrain resulting in a dysfunction of cholinergic neurotransmission at the sites of its axon terminals in the cerebral cortex and hippocampus is not specific to AD. It also occurs in a variety of developmental and other neurodegenerative diseases which all are associated with cognitive dysfunctions such as Parkinson's disease, Down's syndrome, Creutzfeldt-Jakob's disease, dementia pugilistica, progressive supranuclear palsy, olivo-ponto cerebellar atrophy or postalcoholic Korsakoff's disease (for review, see Bigl et al., 1990).

Degeneration of cholinergic basal forebrain neurons providing the sole source of the cholinergic fiber network of the cortical mantle (Bigl et al., 1982; Saper and Chelimsky, 1984) results in a functional cholinergic deafferentation of the entire cortex. This leads to impaired gaiting of sensory input and information processing as a critical prerequisite for learning and memory (Fuller et al., 2011; Grunwald et al., 2001; Hasselmo and Giocomo, 2006; Ma and Luo, 2012; Richter et al., 2014). To conceptualize the pathophysiological meaning of degeneration of cholinergic basal forebrain neurons in the etiology of cognitive impairment, we have

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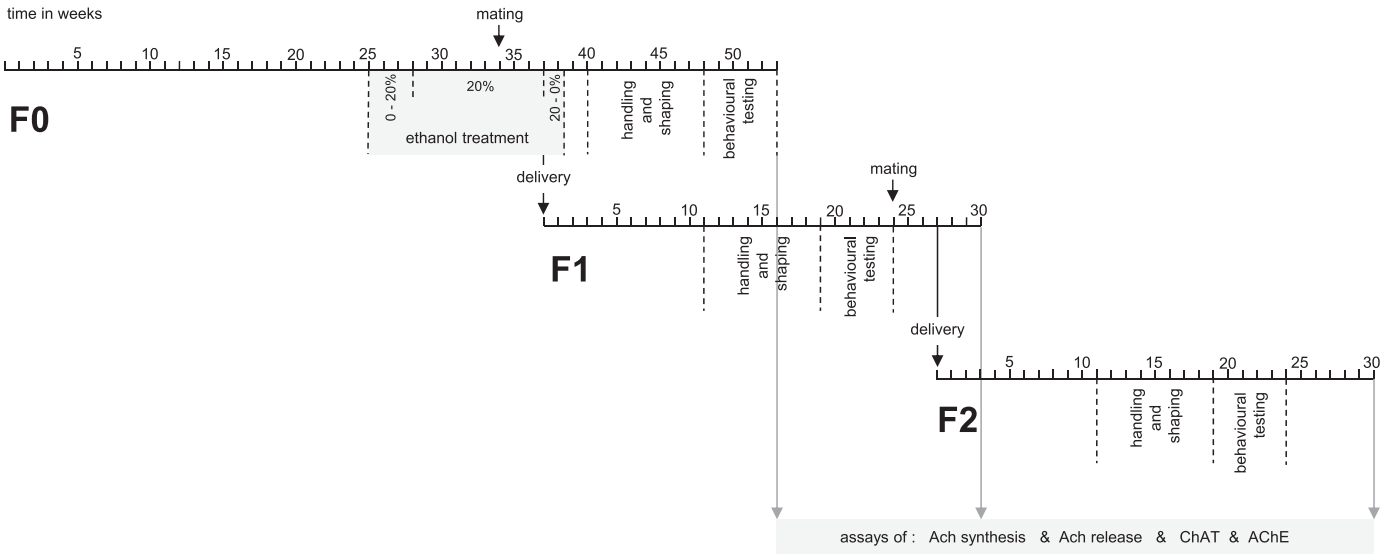

Fig. 1. Synopsis of the overall experimental design of the entire study providing the schedule of ethanol treatment (F0) and behavioral testing (F0, F1, F2). Abbreviations: Ach, acetylcholine; AChE, acetylcholinesterase; ChAT, choline acetyltransferase.

proposed a "syndrome of the partial cholinergic deafferentation of the cortical mantle" as a "least common denominator" common to all these different pathological entities (Arendt et al., 1989a,b). In an attempt to validate this concept, we developed a rodent model which allows to reproduce the cognitive dysfunction through neurotoxic interference with the cholinergic system by chronic alcohol application (Arendt et al., 1988). Restoring cholinergic function in this model through pharmacological inhibition of acetylcholine esterase or through transplantation of precursor cells of cholinergic neurons allows to reverse cognitive dysfunction (Arendt et al., 1988, 1989a,b).

The observation that cholinergic dysfunction associated with cognitive impairment is a common element of a large variety of mental disorders of quite different etiologies raises the question whether there might exist a common endophenotype with a defined genetic and/or epigenetic signature. To tackle this question, we extended our neurotoxic model of cholinergic damage by chronic ethanol toward the investigation of subsequent generations. Here, we show that cholinergic dysfunction associated with memory impairment can be observed in animals with a family history of alcoholism while never been exposed to alcohol either directly or indirectly. These results clearly document that there

Table 1
Synopsis of F and *p*-values for statistical analysis of the behavioral testing of the F0, F1, and F2 generation (2-way ANOVA; Holm-Sidak post hoc test)

Blocks of 4 trials	Fig. 4		Fig. 5 left panels		Fig. 5 right panels						Fig. 6	
	F0 versus Contr.		F1 versus Contr.		m_F2 versus Contr.		f_F2 versus Contr.		m_F2 versus f_F2		Control versus physostigmine	
	WM	RM	WM	RM	WM	RM	WM	RM	WM	RM	WM	RM
F_I	74.599	3.101	32,537.019	21,043.688	3661.673	5678.894	3661.673	5678.894	3661.673	5678.894	1702.065	8950.645
p	<0.001	0.079	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
F_{II}	5362.827	8586.974	3061.818	4047.185	5030.047	6484.423	5030.047	6484.423	5030.047	6484.423	5218.317	12,120.689
p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
F_{III}	11.965	1.553	54.564	144.688	15.434	23.163	15.434	23.163	15.434	23.163	13.880	61.241
p	<0.001	0.075	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
1	0.019	0.081	<0.001	<0.001	<0.001	<0.001	<0.001	0.030	0.148	0.036	0.031	0.062
2	0.006	0.168	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.011
3	<0.001	0.054	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.016	<0.001	<0.001	<0.001
4	<0.001	0.119	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.215	0.015	<0.001	0.006
5	<0.001	0.462	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.335	<0.001	<0.001	<0.001
6	<0.001	0.003	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.063	<0.001	<0.001	<0.001
7	0.002	1000	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.113	0.018	<0.001	0.021
8	0.030	0.081	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.002	0.013	<0.001	0.077
9	0.259	0.520	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.039	<0.001	<0.001	0.026
10	0.572	0.713	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.335	0.031	1000	0.125
11	0.295	0.098	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.113	<0.001	0.193	0.091
12	0.333	0.646	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.271	0.251	<0.001	0.077
13	0.375	0.581	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.099	0.280	0.053	0.127
14	0.333	0.646	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.085	0.026	0.032	0.021
15	0.747	0.854	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.485	<0.001	0.268	0.006
16	0.628	0.713	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.301	<0.001	0.297	0.125
17	0.687	0.520	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.622	<0.001	0.434	0.125