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OLFACTORY MEMORY FUNCTION IN MICE EXPRESSING A MUTATED HUMAN APP TRANSGENE

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Alzheimer's disease (AD) is the most common cause of progressive decline of cognitive function in old people, and is characterised by the presence in the brain of senile plaques and neurofibrillary tangles accompanied by brain inflammation and neuronal loss. There is good evidence indicating that the accumulation of the â-amyloid protein (Aâ), a 4-kDa polypeptide derived by the proteolytic cleavage of the Aâ precursor protein (APP), is a primary event in the pathogenesis of AD. One of the central unanswered questions in AD is around the precise relationship between cerebral Aâ accumulation and the emergence of cognitive deficits. For the majority of sufferers the cause of the disease is unknown, however mutations have been found in three different genes, including the gene encoding APP, that irrevocably led to AD. We have created transgenic mice bearing one of these gene mutations (point mutation of Valine for Isoleucine at locus 717 of human APP, V717I see Mullan et al, 1993) and verified the pedigree using standard molecular genetic techniques. We have shown that there are high levels of transgene Aâ in the brains of these mice from an early age, in addition, *in vivo* brain microdialysis has shown specific regional changes in the basal and stimulated levels of a number of neurotransmitter systems, including acetylcholine. The work presented here examines memory function in these AD transgenic mice using the social transmission of food preference (STFP) task (Bunsey and Eichenbaum, 1995; Galef and Whiskin, 2000). In this test, mice use conspecifics as a source of information to guide future food choices. Thus, "demonstrator mice" are permitted to eat food mixed with a particular aroma (cued food) and test mice are subsequently allowed to interact with the demonstrator animal. In a preference test 24hr later, observer mice will eat more of the cued food than food mixed with another novel aroma, a behaviour that can be used to index the use of the olfactory memory formed during the previous demonstrator-observer mouse encounter. We have tested AD transgenic mice in the STFP at different ages (3, 6, 12, 18 months old) and shown that hemizygous and homozygous AD transgenic mice are impaired in this task relative to age-matched wild-type mice in a way that suggests mnemonic impairment from an early age. The data are discussed in terms of the relationship between the behavioural effects of the transgene expression and the underlying pattern of neuropathological and neurochemical deficits.

References

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