Neuroscience and Biobehavioral Reviews 36 (2012) 1357–1375

Contents lists available at SciVerse ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

APP transgenic mice for modelling behavioural and psychological symptoms of dementia (BPSD)

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ARTICLE INFO

Article history:
Received 7 December 2011
Received in revised form 10 February 2012
Accepted 13 February 2012

Keywords:
Amyloid
Alzheimer's disease
Open-field
Spontaneous alternation
Elevated plus-maze
Emergence test
GABA
Aggression

ABSTRACT

The discovery of gene mutations responsible for autosomal dominant Alzheimer's disease has enabled researchers to reproduce in transgenic mice several hallmarks of this disorder, notably Aβ accumulation, though in most cases without neurofibrillary tangles. Mice expressing mutated and wild-type *APP* as well as C-terminal fragments of APP exhibit variations in exploratory activity reminiscent of behavioural and psychological symptoms of Alzheimer dementia (BPSD). In particular, open-field, spontaneous alternation, and elevated plus-maze tasks as well as aggression are modified in several *APP* transgenic mice relative to non-transgenic controls. However, depending on the precise murine models, changes in open-field and elevated plus-maze exploration occur in either direction, either increased or decreased relative to controls. It remains to be determined which neurotransmitter changes are responsible for this variability, in particular with respect to GABA, 5HT, and dopamine.

Contents

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doi:10.1016/j.neubiorev.2012.02.011

1. Pathobiology of Alzheimer's disease

1.1. Cognitive symptoms of Alzheimer's disease

Probable Alzheimer's disease is diagnosed when progressive loss in remembering new items (anterograde amnesia) occurs in conjunction with a deficit in language (aphasia), object use (apraxia), form recognition (agnosia), or step-by-step planning (McKhann et al., 1984). In general, memory and verbal fluency deficits are the initial symptoms (Amieva et al., 2005), progressive amnesia sometimes being the only sign over a period of several years (Weintraub and Mesulam, 1993). A loss of factual information (declarative memory) is found for verbal and spatial items (Amieva et al., 2005; Graham et al., 2004; Helmes and Ostbye, 2002; Jacobs et al., 1995; Kessels et al., 2005; Lee et al., 2003), whereas procedural memory is relatively spared, evaluated in pursuit-rotor (Eslinger and Damasio, 1986; Jacobs et al., 1999) and either verbal (Karlsson et al., 2002) or spatial (Kessels et al., 2005) priming tasks. However, some procedural tasks are impaired, such as prepulse inhibition of the acoustic startle response, implying a deficit in sensory gating (Ueki et al., 2006), as well as delay or trace conditioning of the eyeblink response (Woodruff-Pak and Papka, 1996; Woodruff-Pak et al., 1996).

In addition to amnesia, patients with Alzheimer's disease are susceptible to constructional apraxia, characterized by a difficulty in copying geometric figures or reproducing them with building blocks (Graham et al., 2004; Helmes and Ostbye, 2002; Henderson et al., 1989; Nielson et al., 1996). Impaired flow perception (Kavcic et al., 2006; Tetewsky and Duffy, 1999), visual search (Parasuraman et al., 2000; Tales et al., 2004), abstract reasoning (Helmes and Ostbye, 2002), and executive functions (Collette et al., 1999; Graham et al., 2004; Rainville et al., 2002b) may contribute to this symptom. As a result, they are more likely than controls to be disoriented in a maze (Rainville et al., 2002a), a circular arena (Hort et al., 2007), a hospital ward (Monacelli et al., 2003), and in the streets when driving a motored vehicle (Uc et al., 2004).

1.2. Behavioural and psychological symptoms of Alzheimer's disease

Among emotional symptoms, apathy is one of the most common features of Alzheimer dementia, sometimes accompanied by dysphoria, social withdrawal, and depression (Chung and Cummings, 2000; Daffner et al., 1992; Frisoni et al., 1999; Hart et al., 2003; Lanari et al., 2006; Lyketsos et al., 2002; Petry et al., 1988; Senanarong et al., 2004). But sometimes agitation is the predominant feature, accompanied by disinhibition and inappropriate euphoria. These opposite signs often overlap in the same patient, as apathy scores have been found to be linearly correlated with disinhibition (Holthoff et al., 2005; Lyketsos et al., 2002). Apathy/anxiety scores, on one hand, and disinhibition/euphoria scores, on the other, were both correlated with caregiver non-compliance (Senanarong et al., 2004), underlying their importance in day-to-day activities. Symptoms may differ from one patient to another with respect to inhibition or disinhibition. Alzheimer patients may either be excessively inhibited due to anxiety, or else display a loss in inhibitory control, often accompanied by irritability and hostility (Chung and Cummings, 2000; Daffner et al., 1992; Frisoni et al., 1999; Hart et al., 2003; Lyketsos et al., 2002; Petry et al., 1988; Senanarong et al., 2004). Excessive aggression may be due to degeneration of brainstem 5-hydroxytryptamine (5HT) neurons, known to influence this symptom (Hardy et al., 1985; Lyness et al., 2003; Whitford, 1986).

1.3. Behavioural symptoms linked with metabolic markers

Insight into the neurobiological factors underlying dementia symptoms may be obtained by measuring regional brain metabolism. Alzheimer patients characterized by apathy had lower fluorodeoxyglucose (FDG) uptake in medial prefrontal cortex than a subgroup not displaying this sign (Holthoff et al., 2005; Marshall et al., 2007). These results indicate that apathy may be the result of dysfunction at the level of medial prefrontal cortex. In addition, FDG uptake was lower in temporal neocortex of Alzheimer patients suffering the most from anxiety (Hashimoto et al., 2006). Moreover, Alzheimer patients with misidentification delusions had lower glucose utilization in orbitofrontal, medial temporal, and striate cortex but higher utilization in sensory association cortices (superior temporal and inferior parietal) than those without this symptom (Mentis et al., 1995). Likewise, demented patients with delusions had higher glucose utilization in inferior temporal but lower utilization in medial occipital cortex than those without them (Hirono et al., 1998). In addition to glucose, regional brain metabolism may be estimated by brain perfusion on single photon emission computed tomography (SPECT) scans by measuring the uptake of hexamethylpropelenamine oxime (HMPAO). The HMPAO technique dissociated between patient groups on the basis of emotional reactivity (Hirono et al., 2000). In particular, a mixed group of patients with Alzheimer's or vascular dementia displaying marked aggression had lower neocortical HMPAO uptake than a demented group not displaying this symptom.