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Genetic mouse models of brain ageing and Alzheimer's disease

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ABSTRACT

Progression of brain ageing is influenced by a complex interaction of genetic and environmental factors. Analysis of genetically modified animals with uniform genetic backgrounds in a standardised, controlled environment enables the dissection of critical determinants of brain ageing on a molecular level. Human and animal studies suggest that increased load of damaged macromolecules, efficacy of DNA maintenance, mitochondrial activity, and cellular stress defences are critical determinants of brain ageing. Surprisingly, mouse lines with genetic impairment of anti-oxidative capacity generally did not show enhanced cognitive ageing but rather an increased sensitivity to oxidative challenge. Mouse lines with impaired mitochondrial activity had critically short life spans or severe and rapidly progressing neurodegeneration. Strains with impaired clearance in damaged macromolecules or defects in the regulation of cellular stress defences showed alterations in the onset and progression of cognitive decline. Importantly, reduced insulin/insulin-like growth factor signalling generally increased life span but impaired cognitive functions revealing a complex interaction between ageing of the brain and of the body. Brain ageing is accompanied by an increased risk of developing Alzheimer's disease. Transgenic mouse models expressing high levels of mutant human amyloid precursor protein showed a number of symptoms and pathophysiological processes typical for early phase of Alzheimer's disease. Generally, therapeutic strategies effective against Alzheimer's disease in humans were also active in the Tg2576, APP23, APP/PS1 and 5xFAD lines, but a large number of false positive findings were also reported. The 3xtg AD model likely has the highest face and construct validity but further studies are needed.

Contents

1. Introduction

Post-industrial societies are growing old, which is one of the biggest challenges for their social and health care systems. The most intensive growth is observed in the number of persons above 85 who are close to the upper limit of human life, which is – as the Bible writes – 120 years: "And the Lord said, My spirit will not be in man for ever, for he is only flesh; so the days of his life will be a hundred and twenty years." (Genesis 6:3). Improved health services, thanks to the results of pharmacological research, have significantly contributed to this beneficial tendency. However, an ageing population means that the ratio of age-related diseases and thus, their burden to the health care system, increases, thereby changing the priorities of pharmacological research.

One of the biggest general concerns of getting old is the loss of independence. Decline in cognitive abilities is the primary cause of the need for external care to help with everyday activities. Although the search for prophylaxis and treatment of neurodegenerative diseases has significantly intensified in the past decade, an effective therapeutic strategy is still missing. Since getting old is by far the biggest risk factor for these disorders, understanding the process of ageing is a prerequisite

Abbreviations: AD, Alzheimer's disease; IIL, insulin/insulin-like growth factor signalling; mtDNA, mitochondrial DNA; POLG, DNA polymerase γ; ROS, reactive oxygen species; SAMP8, senescence-accelerated prone mouse 8; SOD1, Cu/Zn-superoxide dismutase; SOD2, Mn-superoxide dismutase.

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for a pharmacological intervention in order to prevent or delay the development of neurodegeneration. The aim of this review is to provide a general overview of the advantages and limitations of the available rodent models of normal and pathological brain ageing and assessing the validity of the models. We focus on the three most frequently considered validity criteria: face validity (the same symptoms are present in the model and in the disease); construct validity (the same pathophysiological mechanism is responsible for the disease and for the phenotype in the model organism); and predictive validity (the same treatments are active – and inactive – in the model as in the clinic).

2. Main determinants of the course of brain ageing

Ageing could be defined as an age-dependent decline in fitness. In humans, brain ageing is generally associated with decreased attention, working and episodic memory deficits, and impaired motor functions, which together may be responsible for deficits in higher-level cognitive functions (Glisky, 2007). This progressive functional decline partly results from ageing of the brain itself, but also partly from ageing of peripheral organs resulting in sensory deficits, cardiac and vascular pathologies, etc. The progression of brain ageing is largely determined by the balance between stochastic pro-ageing events (like mutations, oxidation of lipids and proteins, etc.) and the activity of anti-ageing defence systems (like DNA reparation systems, quality control of proteins, etc.) (Bilkei-Gorzo, 2012). Gene expression profile analysis of brain samples from old and young individuals strongly supported the role of cellular stress defences as major determinants in the progression of the ageing process (Ginsberg, 2007). Additionally, a recent publication about the molecular correlates of ageing showed the importance of epigenetic processes in brain ageing and the principal differences between normal and pathological brain ageing (Pavlopoulos et al., 2013). Lifestyle and nutrition critically influence both the activity of anti-ageing systems and the generation of non-functional/toxic macromolecules. Under experimental conditions, it is possible to control these environmental factors and to test the influence of individual genes or conditions on brain ageing. The generation of mouse lines showing accelerated ageing or resistance to age-related changes has significantly contributed to our understanding of the critical processes of ageing. Using selective breeding from an AKR founder line, Takeda developed mouse strains with a marked ageing phenotype (Takeda et al., 1981). One of these lines, the senescence accelerated mouse prone 8 (SAMP8) is generally used as a model of accelerated brain ageing. The age-related functional changes in SAMP8 mice show a high similarity to what is observed in humans: learning and memory deficits (Flood & Morley, 1998), abnormalities of circadian rhythm (McAuley et al., 2002), and premature loss of hearing abilities (Menardo et al., 2012). These functional deficits are accompanied by histological alterations typical of the aged human brain: enhanced lipofuscin (Flood et al., 1995) and amyloid deposition, as well as gliosis (Nomura et al., 1996) and loss of neurons (Kawamata et al., 1997) whereby the noradrenergic system is significantly affected (Wang et al., 2009). Because of the high face validity of the model, this strain was frequently used to test the physiological mechanisms underlying brain ageing. It was suggested that enhanced oxidative stress and thus the increased level of oxidised non-functional macromolecules have a main role in the early onset of brain ageing in SAMP8 mice (Sato et al., 1996; Butterfield et al., 1997). A possible reason for the high oxidative load is mitochondrial dysfunction (Nakahara et al., 1998) resulting in increased generation of reactive oxygen species (ROS). Autophagy abnormalities in this strain may further contribute to the elevated load of oxidised macromolecules by the impaired clearance of damaged macromolecules and organelles (Ma et al., 2011). The potential role of enhanced levels of oxidised, non-functional macromolecules in accelerated brain ageing shows that dietary antioxidants (Farr et al., 2003, 2004) or enhancement of autophagy by calorie restriction improved learning and memory functions and increased life span in SAMP8 mice (Choi & Kim, 2000; Kim & Choi, 2000). Thus, studies using SAMP8 mice identified an increased load of damaged macromolecules as one of the critical determinants of brain ageing. With the aid of genetically modified animals it was possible to analyse the impact of this process on brain ageing in detail (see Table 1 for an overview—interested readers will find details about the models such as onset of the pathological changes in the references cited in the table legend).

2.1. Increased load of damaged macromolecules and oxidative stress

The mammalian brain is practically a post-mitotic organ because neurons are non-dividing cells and there is a low level of adult neurogenesis which is largely restricted to the subgranular zone of the hippocampus and to the subventricular zone (Curtis et al., 2012). Thus, unlike cells of the periphery, neurons cannot dilute the amount of oxidised or otherwise damaged macromolecules they contain by cell division. The production of reactive oxygen species (ROS) and thus the risk of macromolecule oxidation are connected to the energy production of the mitochondria (Gemma et al., 2007). In higher organisms, the brain has a very high energy demand which makes it more susceptible to the impact of metabolic by-products, particularly to reactive oxygen species. In ageing, increases in the concentration of oxidised macromolecules (Finkel & Holbrook, 2000) and upregulation of genes involved in the oxidative stress response are detected (Yankner et al., 2008). It was proposed that generation of free radicals is the major force behind the ageing process (Harman, 1956) but analysis of transgenic lines having increased oxidative stress did not fully support this hypothesis (Table 1). The life span of mice with genetic deletion of antioxidant enzymes was reduced only in mice lacking the Cu/Zn-superoxide dismutase (SOD1) but not in other lines (Perez et al., 2009). The reduced life span of $SOD1^{-/-}$ is associated with ageing-like symptoms: early loss of hearing and visual abilities (McFadden et al., 1999; Hashizume et al., 2008), muscle atrophy (Sakellariou et al., 2011), and enhanced susceptibility to neoplastic changes in ageing (Elchuri et al., 2005). Although $SOD1^{-/-}$ mice have a higher susceptibility to central nervous system injury like ischaemia (Kawase et al., 1999), irradiation (Fishman et al., 2009), or high amyloid load (Murakami et al., 2011), no report about early onset of cognitive dysfunctions has been published. Null-mutant mice for the mitochondrial form of superoxide dismutase (Mn-superoxide dismutase, SOD2) die within the first week of life (Li et al., 1995). In heterozygous mutants the superoxide dismutase activity is decreased by 30–80% depending on the tissue tested without compensatory changes in expression of other antioxidant enzymes (Van Remmen et al., 1999). Although an elevated oxidative damage was detected in this line during ageing, neither the life span nor the biomarkers of ageing differed between wild-type and mutant $SOD2^{+/-}$ mice (Van Remmen et al., 2003). Nevertheless, the damage caused by brain ischaemia was elevated in $SOD2^{+/-}$ mice (Mehta et al., 2011) suggesting that reduced oxidative capacity is rather a risk factor for negative outcomes after stroke or head injury and not an important modulator of brain ageing. Increase in antioxidant capacity either by dietary antioxidants (Head, 2009) or by increasing expression of antioxidant enzymes via genetic manipulation (Hu et al., 2006) is beneficial against age-related cognitive deficits but does not necessarily influence life expectancy. Thus, genetic mouse models of increased oxidative load can be used to test this specific aspect of ageing but not as a general model of altered brain ageing.

2.2. Mitochondrial deficits

It was suggested that progressive dysfunctions in the mitochondria during ageing significantly contribute to the ageing process (Park & Larsson, 2011). Mitochondria, the primary energy producing organelles, are especially sensitive to oxidative damage because mitochondrial DNA (mtDNA) is located close to the inner mitochondrial membrane where reactive oxygen species are generated and there is no DNA repair mechanism in the mitochondria (Barja, 2004). Not surprisingly, mtDNA

Table 1
Ageing phenotype of genetically modified mouse strains having altered anti-oxidative defences, mitochondrial deficits or deficits in homeostatic cellular defences.

	Strain	Modification	Life span	Learning, memory deficit	Slowly progressive	Increased oxidative load in the brain
Altered anti-oxidative defence	CAT tg	Increased catalase expression	Increased[1]	No	Not applicable	Reduced[1]
	Gpx1$^{-/-}$	Lack of glutathione peroxidase 1	No change	Not applicable	Not applicable	Not, except[2]
	Gpx4$^{+/-}$	Reduced glutathione peroxidase 4	Increased	Not reported	Not applicable	Not reported
	Gpx4 tg	Increased glutathione peroxidase 1 levels	Not tested	Not reported	Not applicable	Not reported
	MsrA$^{-/-}$	Lack of methionine sulfoxide reductase	No change[3] except[4]	Yes	Not reported	Not, except[4]
	SOD1$^{-/-}$	Lack of Cu/Zn superoxide dismutase	Reduced	Not, except[5]	Not	Yes
	SOD1 tg	Increased Cu/Zn superoxide dismutase levels	Not tested	Not, except[6]	Not reported	Reduced[7]
	SOD2$^{+/-}$	Reduced Mn-superoxide dismutase	No change	Not reported	Not applicable	Yes
	SOD2 tg	Increased Mn-superoxide dismutase levels	Increased	Not	Not applicable	Reduced
	Trx2$^{+/-}$	Reduced thioredoxin 2	No change	Not reported	Not applicable	Yes
Mitochondrial deficit	Mito mouse	Large deletion in mtDNA	Reduced	Not, except[8]	Not reported	Not reported
	PstI tg	High expression of mitochondrial restriction endonuclease	Not reported	Yes	Yes	Not reported
	POLG deficient “mtDNA mutator”	Deficit in POL γ activity	Reduced	Not reported	Yes	Not
	MILON	Disrupted Tfam in hippocampal and cortical neurons	Not reported	Not reported	Yes	Not
Deficit in homeostatic cellular defence	UBB(+1)	Aberrant ubiquitin	Not	Yes	Yes	Not reported
	Atg7$^{-/-}$	Loss of autophagy-related protein	Reduced	Yes	Yes	Yes
	Ercc1$^{\Delta/-}$	Mutation in the excision repair cross-complementing group 1	Not reported	Yes	Yes	Not
	Anti-sense GH transgene rat	Reduced growth hormone levels	Reduced	Not reported	Not applicable	Not reported
	GHR$^{-/-}$	Loss of growth hormone receptor	Increased	Yes	Not reported	Not reported
	LI-IGF1$^{-/-}$	Loss of insulin-like growth factor 1 in the liver	Increased	Impaired	Yes	Not reported
	IGF-1R$^{+/-}$	Reduced insulin-like growth factor 1 receptor levels	Increased	Not reported	Not applicable	Reduced
	IRS1$^{-/-}$	Loss of insulin receptor susbstrate-1	Increased	Not reported	Not applicable	Not reported
	IRS2$^{-/-}$	Loss of insulin receptor susbstrate-2	Increased	Impaired[9], but improved if[10]	Not reported	Reduced

1: When expressed in the mitochondria (Schriner et al. (2005)); 2: when expressed in the mitochondria (Esposito et al. (2000)); 3: constitutive knockout (Salmon et al. (2009)); 4: under oxidative stress (Moskovitz et al. (2001)); 5: In Tg2576 mice (Murakami et al. (2011)); 6: when S100β is also over-expressed (Gahtan et al. (1998)); 7: In the microglia (Dimayuga et al. (2007)); 8: impaired memory at long retention delays (Tanaka et al. (2008)); 9: constitutive knockout (Martin et al. (2012)); 10: forebrain specific deletion (Irvine et al. (2011)).

has a very high mutation rate (Ames et al., 1993), which leads to compromised energy support in the ageing cell. Analysis of genetically modified mouse lines (Table 1) having extremely high mtDNA mutation rates due to mutated DNA polymerase γ (POLG) showed that these animals experience accelerated ageing and reduced life span but normal ROS production and were free from oxidative stress (Trifunovic et al., 2004; Kujoth et al., 2005). Although in humans deficit or mutation in POLG leads to severe neuropathies and progressive dementia starting in infancy (Isohanni et al., 2011), at the time of writing of this manuscript there was no publication about learning or memory deficits in POLG mutant mice. Similarly, mice having a larger deletion in mtDNA (mito mouse strain) show an early ageing phenotype, reduced life span but no gross cognitive deficits apart from impaired memory at long retention delay (Tanaka et al., 2008). To test the influence of mtDNA mutation specifically on the brain, a mouse line (named "MILAN") was created lacking the mitochondrial transcription factor A (TFAM) in forebrain neurons, which is necessary for the transcription and replication of mtDNA (Sorensen et al., 2001). A late-onset neurodegeneration characterised by neuronal loss and axonal degeneration leading to disruption of neuronal networks in the cortex first present in 5–6 months old MILAN animals. Unlike in normal ageing, the progression of pathological changes is extremely fast and the animals die within 1–2 weeks following onset of the first symptoms (Sorensen et al., 2001). Thus, this model recapitulates some but not every important aspects of brain ageing.

2.3. Impaired cellular stress defences

As shown above, increased ROS levels due to defective mitochondria or decreased levels of antioxidant enzymes do not necessarily alter the progression of cognitive ageing. However, one can speculate that the rate of clearance of oxidised macromolecules could counterbalance the negative consequences of increased ROS load. It is known that the efficacy of quality control and clearance mechanisms significantly influences the progression of brain ageing (Walter et al., 2011) and impaired clearance contributes to the development of neurodegenerative diseases (Komatsu et al., 2006; Rubinsztein et al., 2012). Supporting this possibility, mice from two independent genetic mouse models of impaired autophagy (UBB(+1) and Atg7$^{-/-}$ lines) show late-onset neurodegeneration, neurological, and memory deficits (Komatsu et al., 2006; Fischer et al., 2009).

Evolutionarily conserved signalling pathways are activated by cellular stress: DNA damage and/or low levels of nutrients activate homeostatic mechanisms which can critically influence the progression of brain ageing (Bishop et al., 2010). Mutant mouse lines defective in genome maintenance displayed symptoms of progeria (Hasty et al., 2003), including neurodegeneration and cognitive decline, when the mutation was neuron specific (Borgesius et al., 2011). These results suggest that accumulation of DNA damage and impaired clearance of damaged macromolecules specifically in neurons could contribute to age-related cognitive deficits.

Converging evidence suggests that insulin/insulin-like growth factor (IIL) signalling is a conserved mechanism connecting availability of nutrients with body growth and life span (Bishop et al., 2010). Reduced signalling due to reduction in insulin-like growth factor in transgenic rats (Shimokawa et al., 2002) or in growth hormone receptor knockout mice (Bartke, 2008), genetic inactivation of insulin receptor susbstrate-1 (Bartke, 2008), insulin receptor in adipose tissue (Holzenberger et al., 2004) or of insulin receptor susbstrate-2 in the brain of mice (Taguchi et al., 2007), all extend life span. IIL signalling is involved in brain development because brain myelin content is reduced in insulin-like growth factor-1 (IGF-1) knockout mice (Ye et al., 2002) whereas it is increased in IGF-1 transgenic mice (Carson et al., 1993). Genetically modified mice with reduced IGF-1 levels due to a liver-specific deletion of IGF-1 have disrupted long-term potentiation (Trejo et al., 2007) in the hippocampus and impairments in spatial learning and memory (Svensson et al., 2006). These data together suggest that reduced IIL signalling is beneficial in bodily ageing but may impair cognitive functions. However, the long living Ames dwarf mice have reduced IIL signalling but show enhanced spatial memory (Sharma et al., 2010). Thus, further research is needed to clear up the role of IIL signalling in brain ageing.

Getting old is the highest risk factor for neurodegenerative disorders. Thus, it is generally assumed that processes involved in normal, healthy ageing also contribute to the pathogenesis of major late-life neurodegenerative diseases like Alzheimer's disease (Jagust, 2013). It is still not fully known whether these diseases are accelerated forms of brain ageing, meaning that everyone who lives long enough will suffer from one of these disorders, or if separate pathological processes underlie them. Nevertheless, fMRI studies showed that medial temporal lobe pathologies are specific for patients having mild cognitive impairment or AD, which suggests that different brain regions are affected by normal and pathological brain ageing (Stoub et al., 2005).

3. Animal models of Alzheimer's disease

The most common form of dementia in the elderly is Alzheimer's disease (AD): the majority of patients above 65 suffering from dementia have AD (World Health Organization and Alzheimer's Disease International, 2012). Its prevalence is strongly age-dependent: a recent meta-analysis of global literature showed that in subjects between the ages of 60 and 64, 1.3% were diagnosed with AD, whereas in subjects over 90 this value was 63.9% (Prince et al., 2013). The clinical signs of AD are progressive learning and memory deficits affecting first short-term then, in later stages of the disease, long-term memories. Non-cognitive symptoms like disturbances in diurnal activity, aggressiveness, symptoms of affective and paranoid-schizophrenic disease are often associated with AD, which – unlike the cognitive symptoms – are not progressive (Reisberg et al., 1987). Histological diagnosis criteria of AD are the presence of extracellular amyloid-β plaques and intracellular neurofibrillary tangles (Claeysen et al., 2012). These histological changes are accompanied by decreased synaptic density, increased neuroinflammatory glial activity (Agostinho et al., 2010) and neuronal loss. In the first phase of AD the basal forebrain cholinergic neurons (Whitehouse et al., 1981) and adrenergic neurons in the locus coeruleus (German et al., 1992) are the most affected, whereas in later phases of the disease a massive loss of hippocampal and cortical neurons is also present. There are two forms of the disease: around 1% of patients have the familial form of AD, which has an earlier onset and more rapid progression. However, the clinical and histopathological features of this form are undistinguishable from the much more common sporadic form of AD (Brouwers et al., 2008). Molecular genetic studies have proved the central role of β-amyloid in the pathogenesis of AD: mutations associated with the familial form of AD were present in the amyloid precursor gene APP and in the presenilin genes 1 and 2, which are involved in the cleavage of APP and thus in the generation of β-amyloid (Cruts & Van Broeckhoven, 1998). Moreover, the product of the APOE gene, the major risk gene for late-onset sporadic AD, is a binding partner of β-amyloid (Strittmatter et al., 1993).

Despite the significant efforts of basic and pharmacological research, the present therapeutic repertoire only slows down disease progression and an effective treatment for AD is still missing. Thus, there is an enormous need for drugs capable of preventing disease, of modifying the pathogenic process in the early phase of AD and for effective alleviation of the symptoms in the middle and late phases of the disease.

AD has a long prodromal period starting with an increase in β-amyloid levels (Ashe & Zahs, 2010). High concentration of β-amyloid leads to the formation of amyloid plaques and intracellular neurofibrillary tangles from hyperphosphorylated tau proteins. Although both soluble amyloid and amyloid plaques are toxic for neurons, experimental evidence suggests that the presence of neurofibrillary tangles also plays a major role in neuronal loss. Cholinergic and noradrenergic neurons are highly sensitive to amyloid toxicity, therefore the decline in the number of these neurons starts in the early phase of the disease

(Tomlinson et al., 1981; Whitehouse et al., 1981). The reduced noradrenergic signalling probably contributes significantly to the pathological process in the later phases of AD by exacerbating ongoing neuroinflammation (Heneka et al., 2006). The biggest loss in the number of neurons can be observed in the cortex and hippocampus in the advanced phase of AD (Mann, 1996) leading to hypometabolism and atrophy in the affected brain areas. The presence of amyloid plaques and dying neurons activates the immune system leading to neuroinflammatory changes, which significantly contribute to the further progression of AD (Hensley, 2010). When dementia is diagnosed, the patients already show severe histopathological changes in the brain. Thus, animal models have a crucial role in understanding the early pathological process of the disease and in the development of disease modifying drugs (Epis et al., 2010; Van Dam & De Deyn, 2011). These models take on even more importance considering we are lacking widely available biomarkers for the prodromal phase of AD (Foster, 2007) which makes large clinical experiments impossible. Alzheimer disease-like pathological changes characterised by amyloid plaque deposition associated with cognitive impairment can be observed during ageing in some longer living species like monkey (Voytko & Tinkler, 2004) or dog (Cummings et al., 1996) but not in the mostly widely used model organisms in neuropharmacological research: rodents (Van Dam & De Deyn, 2011). The generation of transgenic mouse lines expressing genes associated with AD was the breakthrough that made possible modern Alzheimer's disease research. I will now briefly summarise the advantages and limitations of the most widely used or promising transgenic lines (a general overview is shown in Table 2—more details about the models such as onset of pathological changes are found in the references shown in the table legend). An exhaustive overview about the available transgenic mouse models can be found on the website of the Alzheimer Research Forum: http://www.alzforum.org/res/com/tra/.

3.1. Tg2576

This line expresses the 695-amino acid isoform of human Alzheimer beta-amyloid (Aβ) precursor protein containing the Swedish mutation (Lys670 → Asn and Met671 → Leu) under a viral (HCMV) promoter resulting in a fivefold increase in $Abeta_{40}$ and a 14-fold increase in $Abeta_{42/40}$ (Hsiao et al., 1996). Imaging studies showed an age-dependent accumulation of Aβ in brain areas also affected in AD patients (Opazo et al., 2006; Muller et al., 2013) with the caveat that not each tracer effective in clinical practice gives a positive signal in this model (Kuntner et al., 2009; Snellman et al., 2013). Histological analyses of the brains of aged Tg2576 mice reveal similar changes to those found in AD patients: a large number of amyloid plaques associated with apoptosis (Shirvan et al., 2009; Wati et al., 2009; Shevchenko et al., 2012) dystrophic neurons (Woodhouse et al., 2009) and ubiquitin, as well as alpha-synuclein positive neurites (Yang et al., 2000). In the brain of aged transgenic Tg2576 mice, a significant reduction in the number of cholinergic (Apelt et al., 2002; Luth et al., 2003; Wenk et al., 2004; Watanabe et al., 2013) and adrenergic (Guerin et al., 2009) neurons was detected. This type-specific neuronal loss was present in the early phase of the disease before the appearance of amyloid plaques and cognitive deficits similar to that occurring in humans during the prodromal phase of AD. A chronic elevation of pro-inflammatory cytokines (Benzing et al., 1999; Nichol et al., 2008) and microglial activation (Frautschy et al., 1998; Wegiel et al., 2001; Yan et al., 2003; El Khoury et al., 2007) was detected in aged Tg2576 mice, suggesting that in this model – like in AD – neuroinflammatory changes are present which may contribute to the progression of the brain pathologies. These histological and inflammatory changes are associated with learning and memory deficits in a wide range of models: Tg2576 mice have an age-dependent impairment in working (Corcoran et al., 2002) and spatial memory (Hsiao et al., 1996) as well as inferior hippocampus-dependent contextual (Corcoran et al., 2002) and amygdala-dependent cued fear learning ability (Barnes & Good, 2005) suggesting a wide-spread deficit in cognitive functions. The phenotypic changes in this line are not restricted to these higher functions: similar to AD patients (Reisberg et al., 1987), mice from this transgenic line have an abnormal diurnal cycle with sleep abnormalities (Wisor et al., 2005). Besides these similarities, there are significant differences between the symptoms in AD and the phenotype of Tg2576 mice: the cognitive deficits are never so debilitating as in human patients. In mice there is no widespread cell loss and the neurons remain free of neurofibrillary tangles (Yang et al., 2000) and advanced glycation endproducts (Munch et al., 2003). Imaging studies in AD patients revealed decreased glucose metabolism from the early phase of the disease, whereas in Tg2576 animals hypermetabolism was shown, which normalised with age (Luo et al., 2012). Thus, this transgenic line is probably a model of the early phase of AD but could not be used generally as an animal model of AD (Ashe & Zahs, 2010).

Despite these limitations, studies using the Tg2576 line have provided important information about the pathogenic processes in AD. It was shown that Aβ alone, without the presence of abnormal tau proteins, induces memory deficits because genetic deletion of β-secretase, the key enzyme responsible for Aβ production, rescues Tg2576 mice from temporal memory deficits (Ohno et al., 2006). Whether soluble or insoluble form of Aβ has higher toxicity is not clear from the experimental data: correlation between the onset of memory deficits and appearance of detergent-insoluble Aβ aggregates (Westerman et al., 2002) and extracellular soluble 56-kDa Aβ (Lesne et al., 2006) has also been reported. Nevertheless, memory deficits precede the generation of amyloid plaques (Jacobsen et al., 2006) suggesting that the plaques do not trigger the development of cognitive impairments but participate in the development of further pathological processes. This hypothesis was supported by the observation that amyloid plaques disrupted integration of synaptic signals (Stern et al., 2004). Using the Tg2576 model, it was determined that the number but not the size of the plaques increases during the progression of the disease (Christie et al., 2001). It was also shown that soluble Aβ peptide attenuates proteasome activity (Oh et al., 2005) that may contribute to increased protein ubiquitination (Yang et al., 2000). An important feature of AD is that the amyloid deposition is not restricted to the brain parenchyma, but also present in the vasculature of the brain thus impairing the local transport of nutrients and oxygen. It was shown in Tg2576 mice that Aβ is responsible for the amyloid deposition (McGowan et al., 2005; Han et al., 2008) and that Aβ elicits vascular oxidative stress by binding to CD36 scavenger receptors (Park et al., 2011). By testing the dynamics of the development of synaptic deficits in Tg2576, it was suggested that mitochondrial dysfunction is present in the early phase of the disease (S.H. Lee et al., 2012) and it may trigger the pathological changes on the level of synapses by activating caspase-3 (D'Amelio et al., 2011). When testing how known risk factors of AD contribute to the pathogenesis of the disease, it was found that both traumatic brain injury and behavioural stress accelerate Aβ deposition (Uryu et al., 2002) and plaque formation (Lee et al., 2009) by increasing oxidative stress and exacerbating neurodegeneration through a corticotropin-releasing hormone receptor-dependent mechanism (Carroll et al., 2011). The significant role of oxidative stress in the pathogenesis of AD was also shown when memory deficits were prevented by increasing the anti-oxidative capacity of the brain via overexpressing SOD2 (Massaad et al., 2009) or by the absence of 12/15-lipoxygenase (Yang et al., 2010) in Tg2576 mice.

One of the most important features of a model for pharmacological research is its predictive validity. Therapeutic strategies used in clinical practice for the prevention or treatment of AD are generally effective in Tg2576 mice suggesting that there is a low risk of obtaining false negative results with this model. Acetylcholinesterase inhibitors (Dong et al., 2005), memantine, and galantamine (Unger et al., 2006), are all drugs with proven clinical efficacy (Kavanagh et al., 2011; Wilkinson et al., 2012) that improved cognitive functions and reduced Aβ deposition in these mice. Also, physical exercise (Parachikova et al., 2008), *Ginkgo biloba* treatment (Stackman et al., 2003) and an omega-3 fatty acid

Table 2
Validity of the most widely used genetic mouse models of Alzheimer's disease.

		Tg2576	APP23	APP/PS1	3xtg AD	5xFAD
Face validity	Late onset, progressive	Yes	Yes	No late onset	Yes	No late onset
	Learning/memory impairment	Yes	Yes	Yes	Yes	Yes
	Diurnal cycle disturbances	Yes	Yes	Yes	Not tested	Not tested
	Increased anxiety level	No	Yes	Yes	Yes	No
Constructive validity	Amyloid plaques	Yes	Yes	Yes	Yes	Yes
	Tau-hyperphosphorylation	No	Yes	Yes	Yes	No
	Neurofibrillary tangles	No	No	No	Yes	No
	Neuroinflammation	Yes	Yes	Yes	Yes	Yes
	Loss of noradrenergic neurons	Yes	Yes/no	Yes	Yes	Yes
	Loss of cholinergic neurons	No	Yes/no	Yes	Yes	Yes
	Massive neuronal loss in cortex, hippocampus	No	No	No	No	No
Predictive validity	Free from false negative findings	Yes	Yes	Yes	Yes	Yes
	Free from false positive findings	No	No	No	No	Not known

enriched diet (Lim et al., 2005), which are all thought to be beneficial for the prevention and slowing the progression of AD, were effective against the pathological changes in Tg2576 animals. The presence of false positive findings using this line is, however, noteworthy. There are a number of reports about treatment strategies that effectively diminished or even stopped the progression of AD-like pathologies in Tg2576 mice that gave either inconsistent or even negative results when tested in the clinic. It is important to note that inefficacy of a treatment in a clinical trial could be the result of a suboptimal dose or treatment regime and does not necessarily prove a drug is not effective. Nevertheless, in this manuscript, a treatment that provided positive results in animal experiments but remained ineffective in clinical trials is described as a false positive.

Several studies showed the efficacy of ibuprofen in Tg2576 mice, showing that it alters Aβ processing (Yan et al., 2003), suppresses the release of inflammatory mediators (Morihara et al., 2005) and reduces Alzheimer-like pathologies (Lim et al., 2001b). Clinical studies on the other hand gave inconsistent results, reporting both negative (Pasqualetti et al., 2009) and positive outcomes (Babiloni et al., 2009) of the treatment. Also, experiments using rosiglitazone, a proliferator-activated receptor γ agonist, provided very promising results (Pedersen et al., 2006; Denner et al., 2012) in mice but the ensuing clinical trials did not support these positive preclinical findings (Tzimopoulou et al., 2010; Harrington et al., 2011). Another example is immunisation with Aβ which effectively reduced amyloid deposition (Wilcock et al., 2003), cleared the existing amyloid deposits (Wilcock et al., 2004), reduced amyloid angiopathy (Thakker et al., 2009) and reversed memory loss (Kotilinek et al., 2002) without producing notable side effects. In the clinic, however, the same treatment led to enhanced incidence of encephalitis, which led to the abrupt termination of the trial (Gilman et al., 2005). Nevertheless, followup studies with these patients suggested a positive effect of passive immunisation (Vellas et al., 2009) therefore clinical trials using new, humanised anti-Aβ antibodies are currently under way (Blennow et al., 2012; Farlow et al., 2012; Winblad et al., 2012).

Despite the relatively high incidence of false positive findings, a number of new compounds and treatments were tested using the Tg2576 line. These preclinical studies hinted at the efficacy of β-secretase inhibitors against learning and memory deficits (Fukumoto et al., 2010; May et al., 2011) and cholinergic dysfunction (Ohno et al., 2004).

Substances with diverse mechanisms of action like the curry spice curcumin (Lim et al., 2001a), the phosphatidyl-inositol kinase inhibitor wortmannin (Haugabook et al., 2001), the metal chelator DP-109 (Lee et al., 2004) and pharmacological inhibition of activin-like kinase-5 (Town et al., 2008) have also proved to be effective in reducing Aβ pathology in Tg2576 mice.

3.2. APP23

Mice from the APP23 line express the same mutant human amyloid protein with the Swedish mutation as Tg2576 mice, but here the murine Thy-1 promoter drives the expression (Sturchler-Pierrat et al., 1997). Thus, Tg2576 and APP23 lines were created using the same strategy: overexpression of a human mutant amyloid protein associated with the familial form of Alzheimer's disease in the mouse brain. Not surprisingly, these models have very similar properties and limitations; they also gained a similar popularity within neuroscience research. Aβ deposits appear in the brain of APP23 mice at the age of 6 months. The progression of amyloidosis was visualised by high-resolution positron emission tomography (PET) (Higuchi, 2009). Histological evidence of glial activation, degeneration of neurites and synapses as well as tau hyperphosphorylation is detected (Sturchler-Pierrat & Staufenbiel, 2000) in close vicinity to plaques. Neuronal loss is moderate in the neocortex and in the hippocampus (Bornemann & Staufenbiel, 2000; Bondolfi et al., 2002) but is prominent in the locus coeruleus leading to reductions in noradrenaline signalling (Heneka et al., 2006). Similar to AD patients and Tg2576 mice, APP23 mice show prominent amyloid deposition in the cerebral vessels (Calhoun et al., 1999) leading to amyloid angiopathy (Beckmann et al., 2003). A magnetic resonance imaging (MRI) study proved the presence of focal microvascular lesions in the cortical and thalamic regions (Beckmann et al., 2011). Mice from the APP23 line show age-related cognitive deficits in a broad range of memory models (Kelly et al., 2003; Hellweg et al., 2006; Vloeberghs et al., 2006b; Van Dijck et al., 2008) associated with anxiety (Lalonde et al., 2002), aggression (Vloeberghs et al., 2006a), and altered circadian rhythm (Vloeberghs et al., 2004) which are all symptoms commonly present in AD patients.

It is still unclear whether elevated Aβ levels also lead to impaired noradrenergic and cholinergic signalling in APP23 mice. Marked loss of cholinergic neurons (Choi et al., 2013), small differences between wild-type and APP23 mice (Diez et al., 2003), and no change in the number of cholinergic neurons but a reduced length of cholinergic fibres (Boncristiano et al., 2002) were all reported. Whether the noradrenergic system is affected in the APP23 mice is also unclear (Van Dam et al., 2005b; Szot et al., 2009). Nevertheless, a reduced noradrenalin signalling elicited by degeneration of the locus coeruleus with dsp-4 treatment exacerbated Aβ pathology by increasing amyloid deposition and glial activation (Heneka et al., 2006). This same study, using high-resolution magnetic resonance imaging-guided micro PET, also demonstrated reduced cerebral glucose utilisation and diminished acetylcholinesterase activity. Interestingly, reduced cholinergic signalling did not influence the course of amyloidosis and thus the progression of the disease (Boncristiano et al., 2002). Also, the hypothesis that decreased oestrogen levels in women are a possible risk factor for AD was supported by the analysis of double mutant APP23/aromatase knockout mice (Yue et al., 2005). It was also possible using the APP23 mice to investigate in detail the course of amyloidosis (Eisele et al., 2009) and the changes in extracellular size and geometry (Sykova et al., 2005) as well as the role of BDNF in the histopathological changes observed in the close vicinity of plaques (Burbach et al., 2004).

Drugs used for the treatment of AD are generally effective in APP23 mice improving their performance in models of learning and memory (Van Dam et al., 2005a; Vloeberghs et al., 2006a). Risperidone, which is used to reduce behavioural and psychological symptoms of dementia, reduced aggression in APP23 mice supporting the predictive validity of this model (Vloeberghs et al., 2008). Non-pharmacological strategies to alleviate symptoms of AD by both cognitive and physical training are also used. In this model, environmental enrichment, which is an analogue of cognitive training, improved the performance of mice in the water-maze test, upregulated neurogenesis, and elevated BDNF levels (Wolf et al., 2006). On the other hand, daily wheel running as physical activity remained ineffective (Wolf et al., 2006). Using APP23, diverse therapeutic strategies were tested, mostly focusing on the reduction of Aβ toxicity. Vaccination using non-viral Aβ DNA vaccines effectively diminished Aβ levels and pathology (Okura et al., 2006). Increasing the clearance of Aβ by upregulating transthyretin expression also proved to be effective against the development of neuropathological changes (Buxbaum et al., 2008; Li et al., 2011). Reducing Aβ levels is probably a prerequisite to stop or at least decrease the progression of AD. However, to improve cognitive abilities, the restoration of neuronal numbers in the affected brain areas is crucial. A possible strategy to reach this goal is the implantation of human neuronal stem cells. A study using APP23 mice showed that application of the acetylcholinesterase inhibitor phenserine enhanced neuronal differentiation of stem cells by reducing amyloid precursor protein levels (Marutle et al., 2007). Finally, as written above, it was suggested that decreased noradrenergic signalling is involved in the pathogenesis of AD. Unexpectedly, treatment with the α_1 adrenoreceptor antagonist prazosin prevented memory deficits by reducing pro-inflammatory processes and increasing the release of anti-inflammatory cytokines and apolipoprotein E (Katsouri et al., 2013).

J20 is nowadays one of the most popular mutant human amyloid protein expressing mouse lines. Mice from this strain express human amyloid protein with the Swedish mutation together with the Indiana mutation (Val717 → Phe) (Mucke et al., 2000). Since it is a relatively new model, there is less known about the features of this line compared to the Tg2576 or APP23 strains. Nevertheless, amyloid deposition is detected as young as 5–7 months old animals accompanied with reduced synaptophysin levels (Mucke et al., 2000). Histological examinations revealed alterations in the dendrite structure (Moolman et al., 2004) and an early neuronal loss accompanied by astrocytosis and microglial activation (Wright et al., 2013). Similar to other transgenic mice expressing mutant human amyloid protein, J20 mice show severe learning deficits (Sun et al., 2008; Karl et al., 2012; Kim et al., 2013). Most of the studies using the J20 line have focused on the immune therapy of Alzheimer's disease (Seabrook et al., 2004; Seabrook et al., 2007; Frenkel et al., 2008).

3.3. APP/PS1

In the APP/PS1 line, two strategies are combined to reach elevated Aβ levels: overexpression of the human amyloid precursor protein encoding gene with the Swedish mutation (the same as used in the previously discussed lines) together with the mutant presenilin-1 gene, which additionally impairs amyloid protein processing leading to elevated $A\beta_{42}$ levels (Kurt et al., 2001; Radde et al., 2006). The stable genetic background (Radde et al., 2006), the early onset of pathological changes, and the presence of two separate pathological mechanisms have made this model popular in the past decade. Cerebral amyloidosis is present early on, in 6–8 weeks old mice. PET imaging studies in this strain also supported the presence of progressive amyloidosis (Manook et al., 2012; Poisnel et al., 2012a). Aβ toxicity related pathologies develop in ageing APP/PS1 mice characterised by intensive gliosis (Malm et al., 2007; Yan et al., 2009; Jardanhazi-Kurutz et al., 2011), presence of dystrophic excitatory synaptic boutons (Mitew et al., 2013) and tau-positive neuritis (Kurt et al., 2003; Leroy et al., 2012). The pathological changes in APP/PS1 mice show a number of further similarities with AD: the abundant age-dependent severe neuropathology (Wirths et al., 2006) is associated with global brain atrophy (Delatour et al., 2006) and decreased glucose metabolism in the hippocampus (Sadowski et al., 2004). This later point was however challenged by an imaging study, which suggested an increased hippocampal glucose uptake, especially close to the amyloid plaques (Poisnel et al., 2012b). The reason for these conflicting results is unclear and needs further investigation. Although similar to the previously discussed models there is no general massive neuronal loss, some neuronal populations which are also affected in the early phase of AD show significant deficits. The number of catecholaminergic neurons in the locus coeruleus is reduced in ageing (O'Neil et al., 2007), which is suggested to contribute to the pathogenic changes (Jardanhazi-Kurutz et al., 2010; Rey et al., 2012; Hammerschmidt et al., 2013). Also, the number of interneurons together with the level of calcium-binding proteins in the hippocampus is reduced (Popovic et al., 2008; Takahashi et al., 2010). All these changes, similar to those shown in human imaging studies, lead to significantly reduced bilateral functional connectivity in different brain regions (Bero et al., 2012). Testing the cognitive abilities of these mice revealed that the loss in working memory, similar to humans suffering from AD, is present from the early phase of the disease (Huntley & Howard, 2010; Lagadec et al., 2012). In the later phase of the disease, deficits in spatial memory (Ferguson et al., 2013) and in taste aversion learning (Pistell et al., 2008) also appear in the APP/PS1 mice. As non-cognitive symptoms associated with Alzheimer's disease, irritability, disturbances of the diurnal cycle and of motor functions, depression, and, anxiety are reported (Pugh et al., 2007). A further similarity between the model and Alzheimer's disease is that female APP/PS1 mice develop amyloid deposits at younger ages than male mice (Wang et al., 2003) since the incidence of AD is higher in women. Similarly, the discrepancies between this model and AD are similar to that of APP23 mice: phospho-tau appears much later than the amyloid deposition, the level of hyperphosphorylated tau remains low, it is differently distributed as in AD patients and does not form neurofilaments (Kurt et al., 2003). It was suggested that the lack of tau pathology is responsible for the limited neuronal loss and lower amyloidogenic processing of the amyloid precursor protein (APP) as is typical in humans and in the above mentioned transgenic mouse models of AD (Leroy et al., 2012). The crucial role of Aβ in the progression of AD-like pathology was proven by showing that genetic deletion of BACE, the enzyme responsible for the amyloidogenic processing of APP, rescued memory deficits in APP/PS1 mice, similar to the Tg2576 line (Ohno et al., 2006). Interestingly, Aβ deposition was significantly correlated with decreased glucose transporter-1 levels and hippocampal atrophy (Hooijmans et al., 2007) but not with synaptic and cognitive deficits (Trinchese et al., 2004). There is a bidirectional interaction between Aβ deposition and early pathological events: increasing Aβ levels lead to deficits in lysosomal proteolysis and axonal transport as well as to reduced functional connectivity in brain regions, which then facilitate amyloidogenic APP metabolism and deposition (Bero et al., 2012; Torres et al., 2012). It is heavily discussed in the Alzheimer research community whether amyloid plaques have a pathogenic role or whether it is a late event and rather soluble Aβ is responsible for the toxic changes. Using this line, it was possible to prove that formation of amyloid plaques is an early event in the pathogenic process preceding neuritic changes and neuroinflammation (Meyer-Luehmann et al., 2008). Similar to other transgenic models of AD, the disease progression was strongly related to the level of neuroinflammation in APP/PS1 mice (Fonseca et al., 2004; Biscaro et al., 2012). The oxidative damage caused by overactivation of microglia combined with defects in mitochondrial activity (Trushina et al., 2012) significantly contributes to the observed reduction in neurogenesis and cognitive deficits (Choudhry et al., 2012; Hamilton & Holscher, 2012). An important regulator of glial activity is noradrenalin, thus the selective loss of noradrenergic neurons in the locus coeruleus may also contribute to disease progression. This hypothesis was also supported in APP/PS1 mice showing that deletion of locus coeruleus neurons exacerbated the progression of AD-like symptoms (Hammerschmidt et al., 2012; Rey et al., 2012). The influence of environmental risk factors

on the development of the disease was also assessed using this line: aluminium load, similar to early studies using rats (Bilkei-Gorzo, 1993), accelerated the decline of cognitive abilities (Zhang et al., 2012). On the other hand, physical exercise prevented memory decline (Liu et al., 2011), as in humans (Roach et al., 2011) and in Tg2576 mice (Parachikova et al., 2008). Generally, treatments effective against AD in the clinic were also effective in this line: the NMDA receptor blocker memantine improved spatial learning (Minkeviciene et al., 2004) and reduced amyloid levels both in vivo and in neuronal culture (Alley et al., 2010). Blocking acetylcholinesterase activity is one of the first therapeutic strategies for the treatment of AD. In APP/PS1 mice, the acetylcholinesterase inhibitor IQM-622 effectively decreased Aβ deposits and protected neurons (Antequera et al., 2012). Lastly, disturbed iron homeostasis was also implicated in the pathogenesis of AD. The iron chelator desferrioxamine slowed down the progression of the disease both in humans (McLachlan et al., 1993) and in APP/PS1 mice (Guo et al., 2013). When assessing the predictive validity of this model one should keep in mind that in a number of cases clinical trials could not fully support the positive preclinical findings using this strain. Quetiapine decreased Aβ levels and prevented memory impairment in APP/PS1 mice (Centonze et al., 2009) and in AD patients a preliminary retrospective study reported an improvement in behavioural symptoms (Rocca et al., 2007). However, a more extensive randomised double-blind placebo-controlled study failed to find any improvement in agitation and there was significantly greater cognitive decline in the treated group (Ballard et al., 2005). Similarly, rosiglitazone proved to be effective in APP/PS1 mice (O'Reilly & Lynch, 2012), whereas phase 3 clinical studies failed to find evidence of efficacy (Gold et al., 2010; Harrington et al., 2011). Supplementation of diet with the antioxidant Coenzyme Q10 (Li et al., 2008) or docosahexaenoic acid (DHA) (Hooijmans et al., 2009) delayed the development of AD-like pathology in APP/PS1 mice. In the clinic, antioxidant therapy has remained ineffective (Galasko et al., 2012) and clinical trials with DHA provided inconsistent results (Quinn et al., 2010; Yurko-Mauro et al., 2010). Even with these caveats, there is an impressive list of publications about strategies which proved effective in slowing down the pathological process or in improving the health status of the APP/PS1 mice: stem cell therapy (H.J. Lee et al., 2012), caloric restriction (Mouton et al., 2009), and treatment with retinoic acid (Ding et al., 2008), with the α2-adrenoreceptor antagonist fluparoxan (Scullion et al., 2011), with the calpain inhibitor BDA-140 (Trinchese et al., 2008) or with the extract of the plant *Withania somnifera* (Sehgal et al., 2012), amongst others.

3.4. 3xtg AD

Transgenic mice with enhanced Aβ recapitulate some, but not all, of the important aspects of AD. In 2003, a new triple-transgenic model of Alzheimer's disease was presented, which expresses the mutant human tau protein, the human APP with the Swedish mutation and the mutant presenilin (Oddo et al., 2003b). This model shows probably the highest face validity with AD, because the presence and dynamics of the pathological changes is very similar to the human situation. Accumulation of intracellular Aβ is the first step of the events followed by tau protein hyperphosphorylation, extracellular deposition of Aβ protein and appearance of paired intracellular neurofilaments from hyperphosphorylated tau (Oddo et al., 2003a; Mastrangelo & Bowers, 2008). These changes on the molecular level are accompanied by significant loss of noradrenergic (Manaye et al., 2013) and cholinergic neurons (Girao da Cruz et al., 2012), and upregulation of microglial activity (Mastrangelo & Bowers, 2008). Furthermore, an imaging study highlighted disturbances in glucose uptake in brain areas similar to those of AD patients even in the early phase of the pathogenic process (Nicholson et al., 2010). The behavioural phenotype of 3xtg AD mice shows a number of similarities to those observed in AD patients: cognitive deficits (Billings et al., 2005; Oddo et al., 2006; Guzman-Ramos et al., 2012), where episodic memory loss appears first (Davis et al., 2013), circadian changes, and, anxiety and restlessness (Sterniczuk et al., 2010a,b). Aβ accumulation and development of learning deficits are exacerbated in ovariectomised female mice (Carroll et al., 2007). Ovariectomy induces oestrogen depletion, which is thought to be a significant risk factor for AD in postmenopausal women. The large number of similarities between this model and AD suggests a high level of face validity of the 3xtg AD line. However, there is no neuronal loss in the hippocampus of 3xtg AD mice, whereas in AD patients, massive cell loss is detected in this area (Manaye et al., 2013). It is assumed that the presence of mouse, non-mutant tau protein protects neurons from excessive generation of hyperphosphorylated tau, neurofibrillary tangles, and cell death. Also, unlike in humans, a MRI study found no differences in white matter densities between control and 3xtg AD animals (Kastyak-Ibrahim et al., 2013). Nevertheless, this model offered the first possibility to test the interaction between amyloid and tau protein. It was shown that Aβ triggers and contributes to the development of tau pathology by inhibiting proteasome activity whereas tau does not influence Aβ pathology (Oddo et al., 2007; Tseng et al., 2008). The hyperphosphorylated tau is further responsible for the formation of neurofibrillay tangles, for the activation of apoptotic processes, and thus, for cell death (Rohn et al., 2008). The findings concerning the mechanism of interaction between AD and inflammation using other transgenic models of AD were supported further by the work of Sy et al. showing that tau pathology is potentiated by inflammation (Sy et al., 2011). This finding suggests that infection in the elderly is a potential risk factor for AD. The high face and construct validity of the model helped to investigate how known risk factors like high-fat diet, diabetes and traumatic brain injury influence the development of AD-like pathology on a molecular level (Ma et al., 2009; Julien et al., 2010; Tran et al., 2011). When testing the predictive validity of this model using compounds with known efficacy (or inefficacy) in AD therapy, this model was again not quite free from false positive findings. Ibuprofen (McKee et al., 2008), DHA (Arsenault et al., 2011), pioglitazone (Miller et al., 2011; Sato et al., 2011), nicotinamide (Rainer et al., 2000; Demarin et al., 2004; Green et al., 2008) and treatment with muscarinic M1 receptor agonist (Caccamo et al., 2006) all effectively reduced AD-like pathology in this line, whereas they have provided inconsistent results in the clinic. Nevertheless, as with the previously presented transgenic models, therapeutic strategies with known efficacy are also effective in 3xtg AD mice including mental (Billings et al., 2007) and physical training (Garcia-Mesa et al., 2011), dietary supplementation with S-adenosyl methionine (Remington et al., 2009; S. Lee et al., 2012) and pharmacological treatment with memantine (Martinez-Coria et al., 2010). Also, novel and promising therapeutic approaches, which were effective in other transgenic models like passive immunisation (Oddo et al., 2004), stem cell implantation (Blurton-Jones et al., 2009) or induction of autophagy via rapamycin treatment (Majumder et al., 2011), all alleviated the AD-like symptoms in 3xtg AD mice.

3.5. 5xFAD

The late onset of pathological changes in the above mentioned transgenic models shows their face validity since they recapitulate the late onset of Alzheimer's disease starting in the second half of human life. The late onset of the symptoms, however, is responsible for technical disadvantages like high animal housing costs, problems in animal facilities with limited housing capacities, long delays between planning and performing the experiments, etc. For this reason, in 2006, a new transgenic line was developed bearing five mutations: the double Swedish mutation (K670N/M671L), which is responsible for the enhanced amyloid production, and mutations which are responsible for altered amyloid precursor protein processing leading to a higher ratio of the more amyloidogenic Aβ production such as the Florida (I716V) and London (V717I) mutations in APP and the mutant presenilin 1 (M146L + L286V) (Oakley et al., 2006). Intracellular Aβ starts to

accumulate in 1.5 month old mice while the extracellular deposition is present in mice as young as 2 months. Obviously, the construct validity of this model is lower than in the 3xtg AD line but the face validity – not counting the very early onset of the disease – is similar to the Tg2576, APP23 or APP/PS1 models. Mice from the 5XFAD line first display amyloid accumulation (Oakley et al., 2006) followed by selective loss of noradrenergic (Kalinin et al., 2012) and cholinergic (Devi & Ohno, 2010) neurons. All these changes are leading to cognitive impairments (Girard et al., 2013) and non-cognitive behavioural abnormalities (Jawhar et al., 2012). To test the pathological mechanisms underlying AD, the 5xFAD line is perhaps not the best choice, but the crucial role of β-secretase activity in the development of AD-like pathology (Ohno et al., 2007; O'Connor et al., 2008) and the mechanism of insulin deficiency in amyloidosis are both studied using this line (Devi et al., 2012). The predictive validity of this model is still unclear because there are only a few reports published about drug and treatment effects on 5XFAD mice. Ibuprofen treatment remained ineffective in 5XFAD mice (Hillmann et al., 2012) in agreement with the findings of a recently published meta-analysis (Jaturapatporn et al., 2012). Three reports evaluating possible therapeutic strategies are published with positive outcome using the 5XFAD line: genetic reduction of BACE1 activity, the herbal tonic medicine icariin and the phosphokinase C ε-specific activator, DCP-LA, each improved synaptic plasticity and reduced the histological consequences of high Aβ levels (Kimura et al., 2010; Urano & Tohda, 2010; Hongpaisan et al., 2011).

Analysis of mouse strains showing accelerated and delayed brain ageing suggested that the balance between the generation and clearance of degraded macromolecules, efficacy of DNA repair, and mitochondrial activity are the major determinants of cognitive ageing. With the help of genetic mouse models it has been possible to dissect, on a molecular level, the intracellular processes influencing the progression of ageing. Phenotype analysis of these genetically modified mouse strains has provided evidence for similarities but also for striking differences between bodily and brain ageing (Table 1). Transgenic mouse models have played a major role in understanding the pathophysiology of Alzheimer's disease and contributed to the development of therapeutic strategies. Nevertheless the most widely used models—Tg2576, APP23 and APP/PS1 only mimic the initial phase of AD and they are prone to give false positive results when testing therapeutic strategies (Table 2). The 5xFAD model has less face validity as the previously mentioned lines but the early onset of symptoms and thus the reduced housing costs have made this strain popular in AD research. The 3x-tg AD line is probably the genetic mouse model with the highest face and construct validity. However, further experiments are needed to decide whether it also has superior predictive validity.

Conflict of interest statement

The author declares that there are no conflicts of interest.

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