alzheimer's research&therapy

REVIEW

Modeling Alzheimer's disease with non-transgenic rat models

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Abstract

Alzheimer's disease (AD), for which there is no cure, is the most common form of dementia in the elderly. Despite tremendous efforts by the scientific community, the AD drug development pipeline remains extremely limited. Animal models of disease are a cornerstone of any drug development program and should be as relevant as possible to the disease, recapitulating the disease phenotype with high fidelity, to meaningfully contribute to the development of a successful therapeutic agent. Over the past two decades, transgenic models of AD based on the known genetic origins of familial AD have significantly contributed to our understanding of the molecular mechanisms involved in the onset and progression of the disease. These models were extensively used in AD drug development. The numerous reported failures of new treatments for AD in clinical trials indicate that the use of genetic models of AD may not represent the complete picture of AD in humans and that other types of animal models relevant to the sporadic form of the disease, which represents 95% of AD cases, should be developed. In this review, we will discuss the evolution of non-transgenic rat models of AD and how these models may open new avenues for drug development.

Introduction

Alzheimer's disease (AD) is a progressive and irreversible debilitating form of dementia. It is characterized by progressive memory impairment and diminished cognitive performance. Non-cognitive neurological comorbidities often include depression, aggression, and/or psychosis. Histological alterations of the brain tissue include an early degeneration of the cholinergic network, nicotinic neurons in particular, that progressively extends to other types of neurotransmission, neuroinflammation, amyloid plaque deposition, neurofibrillary tangles, and loss of white matter. AD has become a major healthcare concern. It is expected that the number of patients suffering from AD in the United States and European Union, currently between 5 and 6 million, will double by 2040. The picture is even darker if we consider that this evaluation only includes the patients who have been or could be diagnosed, not those for whom the disease is still clinically silent, and does not include China and India, where information concerning AD is limited. The human cost goes well beyond the patients; it also includes the caregivers, with a ratio of three caregivers per patient. The financial cost for society is also exorbitant: US$200 billion for the United States in 2012. Current projections estimate an increase to US$1.1 trillion in 2050. In comparison, the financial stimulus package passed by the Obama administration in 2011 was $800 billion.

The history of drug development for AD is not a success story. For years, drug developers focused on compensating for the loss of cholinergic neurotransmission. This led to the development of acetylcholinesterase inhibitors, with tacrine as the class leader. This strategy was based on the hypothesis that inhibiting the enzyme that degrades acetylcholine (Ach) would restore physiological concentrations of Ach in the synaptic cleft and the functionality of cholinergic neurotransmission, resulting in therapeutic benefit. Tacrine, which was released to the market in the early 1990s, showed some modest activity in clinical trials; however, its therapeutic use was hampered by dramatic liver toxicity, which required close monitoring of patient liver function [1]. Tacrine was progressively replaced by a new generation of acetylcholinesterase inhibitors, namely galantamine, donepezil, and rivastigmine, which were devoid of liver toxicity but produced questionable therapeutic benefits [2]. In 2004, the non-competitive N-methyl-D-aspartate (NMDA) antagonist memantine was released to the market. Although the toxicological profile of memantine was excellent, the therapeutic benefits in AD were modest [3]. Since then, the AD pipeline has suffered numerous

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setbacks due to failed clinical trials of the vaccine AN1792, amyloid peptide ligand/plaque formation inhibitor tramiprozate, γ-secretase modulator tarenflurbil, γ-secretase inhibitor LY540139, anti-histamine latrepirdine, and more recently, humanized monoclonal antibodies bapineuzumab and solanezumab. Interestingly, all of these compounds demonstrated significant efficacy in transgenic animal models of AD.

Animal models of disease are a cornerstone of the drug development process. Their function is to closely mimic the disease or an aspect of the disease in humans and translate the results obtained *in vitro* to clinical applications. The need for animal models of pathologies affecting the central nervous system has been recognized since 1980 [4]. An attempt to establish criteria for such animal models was made the same year [5]. The first tools described as animal models of AD were based on etiological considerations of the disease, whether chronic aluminum intoxication [6] or excitotoxic lesions of cholinergic neurotransmission [7] was thought to be at the origin of the neurodegeneration. The early 1990s saw the appearance of the first transgenic mouse models of AD, nearly a decade after the discovery of the first mutation in the gene encoding the amyloid precursor protein (APP) and its central role in the familial form of AD. These models, which carried a mutated form of the human *APP* gene, were found to be unsatisfactory, and double transgenic mice carrying two human mutated transgenes, *APP*/*PS1* [8] or *APP*/*tau*, were developed [9]. This was soon followed by the APP/PS1/tau triple transgenic mouse model [10]. The strategy behind the development of these models was to reproduce pathological features observed in AD, including the sporadic form, rather than tackle the etiology of AD. This consideration justified the use of the transgene *tauP301L*, a mutation of the gene encoding the tau protein that is not encountered in AD but pertains to the frontotemporal dementia with Parkinsonism linked to chromosome 17.

Although the rat has been the animal of choice for drug development and fundamental research for decades, it progressively faded away in favor of mice, a species in which genetic manipulation is much easier and for which there is a greater variety of research reagents available. These transgenic models contributed tremendously to our understanding of the molecular mechanisms involved in the onset and progression of the disease. Transgenic mouse models of AD helped decipher the secretory pathway of APP and the production of $A\beta_{42}$ through APP cleavage by β- and γ-secretases [11], thus improving our understanding of AD pathogenesis. In addition, these animal models provided evidence about the physiological role played by APP, APP fragments and α-secretase in processes like neurogenesis [12,13] and the mechanism underlying memory consolidation [14].

It is undeniable that transgenic mouse models of AD led the way of the fundamental research so far conducted on understanding the disease. Moreover, it is critical to mention the primordial role played by the transgenic mouse models in the development of tracers for magnetic resonance imaging (MRI) and positron emission tomography (PET) imaging and in the characterization of new biomarkers [15,16]. However, transgenic mouse models have some limitations [17,18]. First, unlike the human neuropathology, which displays massive neurodegeneration, only very few models show neuronal death and on a scale that does not compare to what is seen on postmortem human brains. Second, the way the genetic manipulation translates into the histological and clinical recapitulation of the disease highly depends on the promoter used to insert the transgene and on the genetic background of the recipient animal. This actually makes any comparison between transgenic mouse models difficult. And last, but certainly not the least, due to their nature, these models only relate to the familial early-onset form of AD (FAD), which represents a mere 5% of AD diagnoses. The remaining 95% are sporadic late-onset forms (SAD), the causes of which remain elusive.

Although SAD and FAD clinical phenotypes are very similar, SAD does not involve mutations and the cause for amyloid accumulation and aggregation remains to be established. In that sense, transgenic mouse models are unfitted for unveiling SAD etiopathogenesis. In addition, the only true validation of an animal model used for drug development purposes is whether it led to successful testing in human trials and thus to the subsequent release of a drug to the market. From discovery to Food and Drug Administration (FDA) approval for release, it takes an average of 15 years to complete a drug development program. The first transgenic mouse model of AD was developed 22 years ago. Based on the current condition of the AD drug pipeline, the limitations of these transgenic models of AD in drug development are apparent. The obstacles to drug development require creation of novel animal models focusing on the etiology rather than symptomatology of the disease using a pharmacological approach rather than a genetic approach.

In this review, we will discuss the historical genesis of various non-transgenic rat models of AD that have been established, the re-appearance of the rat as a potential tool for drug development for AD, and how pharmacologically induced rat models may help overcome the challenges of AD research and drug development.

The genesis and the evolution of AD rat models

In 1980, WJ Hadlow wrote 'Even though finding an animal model embodying the total picture of senile brain disease with dementia is unlikely, efforts should be made to identify in some animal each of the several aspects of

the aging process and dementia' [5]. In the early 1980s, the progressive degeneration of cholinergic neurotransmission was thought to be the pathological pathway, if not the origin of AD, and at least a major contributor to the disease. During this decade, consistent with the cholinergic hypothesis and WJ Hadlow's statement, the first animal models of AD were developed based on impairing central cholinergic function to reproduce the alterations of cognitive performance seen in clinics. A prominent strategy was the use of the choline mustard aziridium AF64A in many cases. AF64A is a chemical that preferentially triggers degeneration of cholinergic neurotransmission. AF64A was used in various protocols, including *in situ* injection into the dorsal hippocampus [19], the frontal cortex [20], or the nucleus basalis magnocellularis [21] or administration through an intracerebroventricular route [22]. These procedures were primarily aimed at inducing degeneration of the cholinergic neurons in the nucleus basalis magnocellularis. Another strategy consisted of using a glutamatergic agonist to induce the excitotoxic degeneration [23] of a subpopulation of cholinergic neurons. Thus, ibotenic acid [24], an agonist of the NMDA receptor, and kainic acid [25], a kainate receptor agonist, were both used by local injection into the nucleus basalis magnocellularis or in the cortex to induce a deficit in cholinergic neurotransmission. More anecdotic were the injection of diphtheria toxin into the nucleus basalis magnocellularis [26] or the grafting of AD patient brain tissue into the rat occipital cortex [27]. In addition to histological traits similar to those described in AD patients, these cholinergic-based rat models commonly displayed memory deficits and learning impairment.

The 1990s saw a downturn in the development of rat models, as they became progressively overshadowed by the emerging transgenic mouse models of AD. These transgenic mice became the dominant animal models for fundamental research and drug discovery in the field of AD. However, the emphasis on the nicotinic receptor as a target for AD [28] encouraged the use of the well-characterized cholinergic-based rat models for nicotine and nicotine derivative drug development programs [29]. Although the transgenic models were taking over the field of *in vivo* experimentation in AD, rats were still considered a useful model organism for development of AD models. The 1990s saw the beginning of a shift toward animal models reflecting the hypothesis that amyloidogenesis underlies the disease. As previously mentioned, the deposition of amyloid plaques in brain parenchyma is a hallmark of AD. An attempt to reproduce this histological alteration was conducted in rats for the first time by Frautschy and colleagues in 1992 by injecting purified amyloid plaques extracted from human AD brains into the cortex and hippocampus of adult rats [30]. This resulted in plaque formation and vascular amyloidogenesis in the rat brain. This first attempt paved the way for a new generation of rat models of AD. Two years later, Ingram and colleagues [31], who clearly identified the need to go beyond the cholinergic hypothesis to establish other animal models that would help answer questions pertaining to AD not strictly related to cholinergic neurotransmission, advocated the use of such models. In the meantime, efforts were still made to refine cholinergic-based rat models using 192 IgG-saporin, a toxin linked to an immunoglobulin that selectively targets cholinergic neurons [32].

The shift initiated in the 1990s took full shape during the next decade, when most of the rat models developed reflected the attempt to reproduce the amyloidogenic cascade and related amyloid peptide pathological pathways. The general principle was to inject a form of amyloid peptide into the rat brain so the animal would develop one or several of the pathological features documented in clinics. Various forms of the amyloid peptide (Aβ) were used in acute injection or chronic infusion. $A\beta_{1\text{-}40}$ [33,34] and $A\beta_{1\text{-}42}$ [35,36] were most commonly used either by intracerebroventricular infusion or by intrahippocampal injection. These peptides were used as the sole disease-triggering agents, with the exception of the ferrous amyloid buthionine (FAB) rat [35], a rat model in which the AD phenotype is induced by the infusion of a solution containing the amyloid peptide $A\beta_{1\text{-}42}$, the inhibitor of glutathione synthesis buthionine sulfoximine, and ferrous sulfate over 4 weeks. We will discuss the FAB rat in more detail below.

Other amyloid species used included $A\beta_{25\text{-}35}$ [37], a neurotoxic non-amyloidogenic fragment, and $A\beta_{1\text{-}43}$ [34]. These various amyloid fragments did not induce similar pathological phenotypes. While histological alterations similar to those seen in AD patients were consistently found in most of the models (although the exact histopathology varied from one to another), reproducing the decline of cognitive performance was highly dependent on the experimental protocol. The amyloid peptide infusion site and regimen used were of particular importance. Another strategy developed during this decade was based on the hypothesis that AD may be a type 3 diabetes [38]. This hypothesis was based on post-mortem histological observations of the brains of AD patients, which showed a consistent decrease in expression of insulin, insulin-like growth factor, and their corresponding receptors [38]. It was then assumed that injecting streptozotocin, a glucosaminenitrosourea toxic to pancreatic β cells, into rat brain would result in the same pattern. Streptozotocin administration induced the phosphorylation of the tau protein, amyloid deposits, cognitive impairment, insulin desensitization, and neuronal death [39,40].

The beginning of the current decade saw an increasing number of preclinical studies using AD rat models characterized during the 2000s to implement drug development programs. In particular, rat models faithfully reproducing amyloid pathogenesis were used to assess the efficacy of drug candidates as diverse as steroid analogs [41-43], fatty acids [44], polyphenols [45], non-steroidal anti-inflammatory drugs [44], plant extracts [46,47], γ-secretase inhibitor [48], stem cell proliferative agents [49], naturally occurring compounds [43,50,51], and plaque formation inhibitors [52]. Other than the type of amyloid peptide used in these models, a major difference was the injection regimen into the brain. The solution containing the amyloid peptide was administered either by chronic infusion or locally in a very specific part of the brain, mainly the hippocampus [41,42,47,49]. Intra-amygdala injection [52] or acute intracerebroventricular injection [46,50,52] have also been reported. Chronic infusion was achieved through intracerebroventricular administration using an Alzet® type of osmotic micropump, generally over a 2- to 4-week period of time [43-45,48]. The resurgence of interest in the rat as an animal model of AD led other investigators to use various other types of rat models to investigate the effect of molecules of potential therapeutic interest. These models included, but were not restricted to, specific cholinergic deficits [53], streptozotocin injections [54,55], okadaic acid-induced tau protein hyperphosphorylation [56], and aluminum salt administration [57].

This combination of circumstances during the past decade, including the failure of transgenic models to fulfill expectations and an increased diversity of experimental reagents, redefined the rat as a very useful tool to develop new models of AD. In the next section, we will focus on a particular AD rat model we developed in our laboratory that is used by us and others in drug development programs.

The ferrous amyloid buthionine (FAB) rat model

The FAB rat was developed in response to our need to have available an animal model of AD that corresponds to the sporadic form of the disease. The choice of the rat strain was made carefully so that it would contribute to the development of the model. Long-Evans rats were selected for these studies because of their high susceptibility to neurodegenerative diseases. Indeed, the Long-Evans strain carries a mutation of the *Cblb* gene that has been demonstrated to render the encoded protein inactive, and *Cblb*-deficient mouse strains are highly sensitive to experimental encephalomyelitis after immunization with myelin basic protein [58]. Because the rodent protein is 96% homologous with the human protein, findings from this rat strain are extremely pertinent to human neurodegenerative diseases [59]. The Long-Evans strain also possessed another advantage: they are not albino rats and therefore do not have the impaired sight of albino strains. Indeed, impaired sight was a factor that we identified as a potential problem when animals would be involved in cue recognition-related experiments (for example, a water maze) in which the distance between the animal and the cues may exceed vision capacity.

The AD phenotype was induced by administering a solution containing the human form of the 42-residue amyloid peptide ($A\beta_{1-42}$), ferrous sulfate, and buthionine sulfoximine via the intracerebroventricular route over a period of 4 weeks [35]. $A\beta_{1-42}$ was chosen because of its superior aggregating properties and because, at that time, it was thought to constitute the nucleus of any amyloid plaque formation. Ferrous sulfate was added to the solution as a pro-oxidative agent known to trigger oxidative stress through the Fenton reaction and induce the oxidation of various components of the cell membrane and subcellular compartments. In addition, the presence of iron deposits was described in amyloid plaques observed post-mortem in patients' brain tissue. Buthionine sulfoximine, an inhibitor of glutathione synthesis, was used to reduce the natural antioxidant defense of the brain and facilitate oxidative stress. Oxidative stress is a deleterious process that, since the late 1980s to early 1990s [61-63], has been unanimously recognized to play a role in AD pathogenesis [60]. It is generally admitted that oxidative species are generated either from, but not restricted to, neuroinflammation, mitochondria respiratory chain impairment [64,65] or from a direct effect of the amyloid peptide [66]. Many compounds are currently being developed aiming at the oxidative pathway as a potential treatment for the disease and oxidative profiling has gained interest as a biomarker of disease progression and for diagnostics purposes [67], and in this regard, the FAB rat may constitute an interesting model to test these approaches in preclinical development.

The solution was infused in the left ventricle using an Alzet® 2ML4 osmotic micropump. Four weeks of infusion resulted in the appearance of an AD phenotype that included cognitive impairment and development of a related histopathology [35]. The animals displayed significant impairment of spatial memory as measured in a Morris water maze task. Histological alterations included amyloid plaque deposits in the hippocampus and cortex, hyperphosphorylated tau protein, and formation of neurofibrillary tangles. Hyperphosphorylated tau protein was evidenced by positive immunoreactivity to Ser-199/202 and to Thr-181 epitopes [68,69] using AT-8 and AT-270 monoclonal antibodies, respectively [43]. Phosphorylated Ser-199/202 and Thr-181 are biomarkers commonly used in the clinic to measure hyperphosphorylated tau levels in the cerebrospinal fluid of AD

patients [69,70]. However, the exact subcellular localization of the neuronal hyperphosphorylated tau protein has not yet been determined. Neurodegeneration occurring in the cortex and hippocampus, neuroinflammation in the form of intense astrogliosis and microgliosis, and DNA oxidation were also reported. In addition, vascular amyloidosis was also observed. The AD phenotype developed only when the three components of the FAB solution were used together. No histopathological features or alterations of cognitive performance occurred when the amyloid peptide was used alone or in combination with only one of the other two compounds, highlighting the key role played by oxidative stress in amyloid peptide pathogenesis. Although others reported the occurrence of an AD-like phenotype after injection of amyloid as a sole pathological agent, this disparity may be explained by differences between rat strains. The neuronal phenotype vulnerability exhibited by these animals remains to be determined and at present this represents a limitation of this particular model.

Since then, the FAB model has been the centerpiece of our drug development programs. In particular, it successfully contributed to the characterization of the anti-AD properties of caprospinol, a naturally occurring steroid analog [43,71,72] for which an investigational new drug application has been submitted to the FDA. The FAB model has been reproduced by others and was recently commercialized by Taconic Farms, Inc. [73-76]. A summary of the experimental protocol used to develop the FAB model, the phenotype obtained as well as the effect of caprospinol on the FAB phenotype are outlined in Figure 1.

The transgenic rat models of Alzheimer's disease

Increasing knowledge in molecular biology allowed overcoming the complexity to undertake transgenesis studies in the rat. The concept applied was identical to the one used to develop transgenic mice and relied on the expression of one or several mutated human genes involved in the familial form of AD. One can argue that transgenic rats may not offer more interest than the transgenic mice available considering that they only represent another transgenic rodent model for the familial form of AD. In addition, the generated transgenic rats only reflect the amyloidogenesis hypothesis of Alzheimer's physiopathology. On the other hand, rats have always been regarded as a more robust tool for cognitive assessment, being capable, unlike mice but like primates, of higher order cognitive processes like metacognition. In that sense, rats are capable of cognitive processes at a higher level compared to mice, closing further the gap with humans. The first AD transgenic rat was produced in 2004 and carried the human APPswe mutated gene [77]. This model did not display any of the known AD histological alteration and, surprisingly, performed better in cognitive tasks than the age-matched control animals. Transgenic rat models developed thereafter included McGill-R-Thy1-APP [78], UKUR25 [79], Tg6590 [80], Tg478 [81], Tg1116 [81], Tg11587 [82], APP21 [83] and APP31 [83]. These models were built on various backgrounds, Sprague-Dawley, Wistar and Fisher-344, using various gene promoters like PDGF, murine Thy-1, synapsin-1 or ubiquitin-C. They all carry one or several mutations of the human *APP* transgene. Not all the models display histological modifications or cognitive impairment, and as for most of the mice models, there is no correlation between reduced cognitive performance and brain tissue histological alteration.

Similarly to mice, rats were used to mimic the tauopathy seen in AD. A major difference is that instead of using a human mutated transgene that is not relevant to the disease, rats express a truncated form of the normal human tau protein. These models displayed cognitive impairment associated to hyperphosphorylated tau protein and formation of tangles [84-86]. However, none of them show any sign of neuronal death [84,86].

Few rat models were developed using viral vectors. Adenoviral-associated viral vectors were locally injected in the hippocampus of Wistar rats to express a transgene encoding the fusion protein BRI-Aβ_{42} or BRI-Aβ_{40} [87,88]. Animals co-transfected with both BRI-Aβ_{42} and BRI-Aβ_{40} displayed a mild cognitive impairment. In these animals plaque formation in the brain was observed only in rats expressing BRI-Aβ_{42} alone. In addition, no pathological alterations of the brain histology were reported. One possible explanation could be found in the nature of the transgene itself. Mutation of the *BRI* gene results in the expression of the amyloid protein ABri and is linked to familial British dementia [89]. ABri precursor is cleaved by furin and furin-like proteases in order to release the peptide. However, ABri is not a substrate for the carboxypeptidase secretases that process APP. Likewise, the fusion protein undergoes furin-controlled cleavage, and unlike APP, does not follow the carboxypeptidase secretory pathway to release Aβ_{42} [87]. Such a 'hybrid' metabolic pathway may lead to the mild pathological profile described and raise questions about the capacity of the model to reproduce, at least in part, the AD phenotype. Another approach consisted in using a lentivirus-based vector to transfect the parkin-Aβ_{42} transgene [90] in the motor cortex of Sprague-Dawley rats [91]. The treated animals exhibited intraneuronal amyloidosis, Tau protein hyperphosphorylation and neuronal death. However, a major limitation of this model is the lack of cognitive impairment due to the site chosen by the investigators to inject the lentiviral construct. Indeed, no alteration of the motor cortex, an area not primarily affected in AD, would affect cognitive

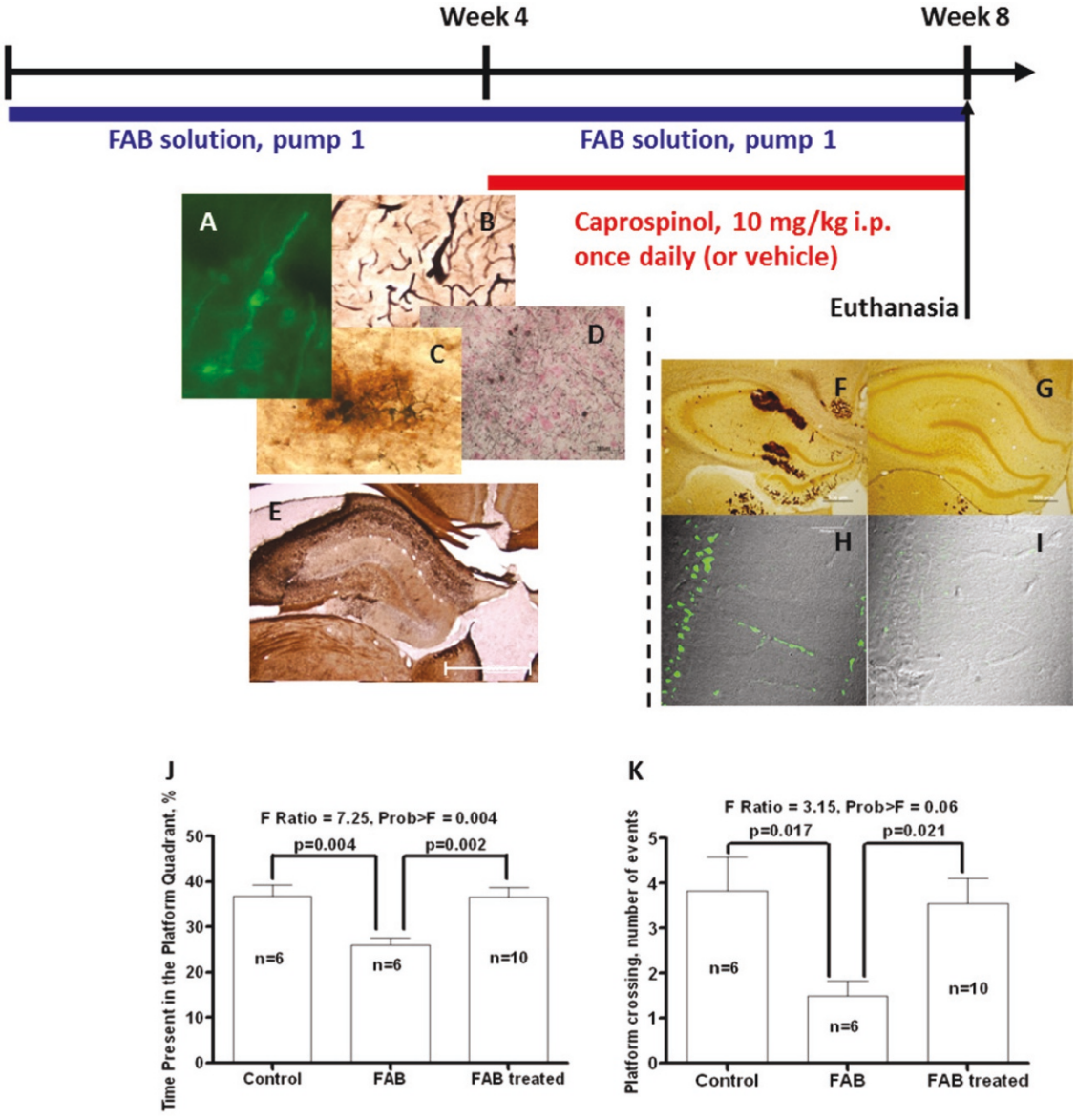

Figure 1. Experimental protocol used to assess the anti-Alzheimer's disease properties of caprospinol. The procedure used to induce the Alzheimer's disease (AD) histopathological phenotype in rats has previously been described [35]. The phenotype was induced by administering a solution containing $FeSO_4$ (1 mM), $A\beta_{1-42}$ (15 μM), and buthionine sulfoximine (12 mM) at pH = 5.1 ± 0.1 into the left ventricle of male Long-Evans rats via an osmotic micropump (2ML4; Durect Corp., Cupertino, CA, USA) over 4 weeks. This solution was named ferrous amyloid buthionine (FAB). At the end of the 4 weeks, the pump was replaced with a new one that contained the same solution for an additional 4-week infusion. In a subset of animals, caprospinol was administered intraperitoneally (10 mg/kg/day) during the final 4 weeks of FAB infusion, starting the treatment at a moment when the animals manifested the clinical phenotype. At the end of the 8-week period, cognitive processes were assessed using a Morris water maze task. **(A)** Histopathological features of the FAB rat at week 4. Hyperphosphorylated tau protein (clone AT-8) in the hippocampus. **(B)** Campbell-Switzer silver staining revealing vascular amyloidogenesis. **(C)** Campbell-Switzer silver staining revealing amyloid plaque containing neuritic debris in the cortex. **(D)** Cortical neurodegenerative processes revealed by De Olmos silver staining. **(E)** Amyloid deposits revealed in the hippocampus by Campbell-Switzer silver staining. **(F,G)** Histopathological features of the FAB rat at week 8 and the effect of caprospinol: Campbell-Switzer silver staining of amyloid deposits in the hippocampus of untreated (F) and caprospinol-treated (G) FAB rats. **(H,I)** Degenerating neurons labeled with FluoroJade C in the hippocampus of untreated (H) and caprospinol-treated (I) FAB rats. **(J)** Assessment of FAB rat cognitive performance in the Morris water maze task at week 8. FAB rats displayed dramatic cognitive impairment as shown by the much lower score obtained in the probe trial compared to the control rats (26.06 ± 1.49, n = 6, versus 36.81 ± 2.48, n = 6, $P = 0.004$). FAB-infused rats chronically treated with caprospinol at 10 mg/kg/day displayed cognitive performance equivalent to that observed in the control group (36.56 ± 2.09, n = 10, versus 36.81 ± 2.48, n = 6), demonstrating that chronic caprospinol treatment eliminated the cognitive impairment observed in the FAB-infused rats (36.56 ± 2.09, n = 10, versus 26.06 ± 1.49, n = 6, $P = 0.002$). **(K)** In addition, caprospinol-treated FAB rats crossed the platform more times than the untreated group. Parts of this figure were reprinted with permission from [49] and [63].

performances, and this should be regarded as a major setback.

Conclusion

AD is a devastating disease that takes a tremendous toll on western societies and beyond. Unfortunately, despite decades of effort and billions of dollars spent, no real treatment has been brought to the market. However, all of the drug candidates that failed in clinical trials showed anti-AD activity in various transgenic animal models. Until recently, drug development research programs exclusively used transgenic mouse models to assess the properties of drug candidates. Transgenic models still represent the golden standard. However, if we consider contributions to drug development and release to the market the ultimate validation of an animal model, we must admit that there is room for different types of animal models. It is especially crucial to stress that rat and mouse transgenic models of AD address only the familial form of the disease, which barely represents 5% of AD cases. We discussed the potential of pharmacologically induced rat models of AD, which are more relevant to the sporadic form of AD, the FAB rat in particular, and the increasing role they may play in the current drug development for AD effort. Indeed, because these models represent the sporadic form of AD, they may, if successful, change the regulatory framework needed to proceed to AD trials and bring value to clinical trial design. The rat, despite been the most widely used animal model in pharmacological and toxicological studies, has long been neglected as a tool for drug discovery in the field of AD. A better understanding of rat strains, an increasing variety of available reagents specific to the rat, and the understanding that there is an urgent need for a model relevant to the most frequent form of AD may lead to a new era of animal models that drive future successful drug development.

Abbreviations

Aβ, amyloid peptide; Ach, acetylcholine; AD, Alzheimer's disease; APP, amyloid precursor protein; FAB, ferrous amyloid buthionine; FAD, familial early-onset form of Alzheimer's disease; FDA, Food and Drug Administration; NMDA, N-methyl-D-aspartate; PS1, presenilin-1; SAD, sporadic late-onset form of Alzheimer's disease.

Competing interests

The authors declare that they have no competing interests.

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