Cell Mol Neurobiol (2009) 29:859–869
DOI 10.1007/s10571-009-9367-5

ORIGINAL PAPER

Beyond the Rat Models of Human Neurodegenerative Disorders

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Received: 14 November 2008 / Accepted: 11 February 2009 / Published online: 5 March 2009

Abstract The rat is a model of choice in biomedical research for over a century. Currently, the rat presents the best "functionally" characterized mammalian model system. Despite this fact, the transgenic rats have lagged behind the transgenic mice as an experimental model of human neurodegenerative disorders. The number of transgenic rat models recapitulating key pathological hallmarks of Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, or human tauopathies is still limited. The reason is that the transgenic rats remain more difficult to produce than transgenic mice. The gene targeting technology is not yet established in rats due to the lack of truly totipotent embryonic stem cells and cloning technology. This extremely powerful technique has given the mouse a clear advantage over the rat in generation of new transgenic models. Despite these limitations, transgenic rats have greatly expanded the range of potential experimental approaches. The large size of rats permits intrathecal administration of drugs, stem cell transplantation, serial sampling of the cerebrospinal fluid, microsurgical techniques, in vivo nerve recordings, and neuroimaging procedures. Moreover, the rat is routinely employed to demonstrate therapeutic efficacy and to assess toxicity of novel therapeutic compounds in drug development. Here we suggest that the rat constitutes a slightly underestimated but perspective animal model well-suited for understanding the mechanisms and pathways underlying the human neurodegenerative disorders.

Keywords Rat models · Neurodegenerative disorders · Transgenesis · Alzheimer's disease · Tauopathies

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The Rat as a Powerful Tool in Biomedicine

The laboratory rat developed from the brown rat (*Rattus norvegicus*), represents the first mammalian species to be domesticated for scientific research. The first inbred rat strain was established by Helen Dean King in 1909. Since that time, a large number of rat strains were used to develop models for serious human diseases (Jacob 1999).

The rat exhibits physiological characteristics similar to those of humans and therefore it has become the most widely studied experimental animal model for biomedical research (Jacob 1999; Cozzi et al. 2008). It is one of the best functionally characterized mammalian model systems. The rat is being widely used because it allows experimental procedures, which could not be easily carried out in mice (Gill et al. 1989). The size of this animal allows many important experimental manipulations, such as microdialysis, intravenous cannulation, surgical manipulations, radiometric monitoring of blood pressure, chronic measurements of regional blood flows, cardiac output, and multiple blood collections of larger volumes than in mice (Report of the NIH Rat Model Repository Workshop 1999; Pravenec et al. 2003; Tesson et al. 2005).

Rats comprise 28% of all laboratory animals and are, in a number of instances, the most appropriate experimental

model of human disease (Report of the NIH Rat Model Priority Meeting; 1999). These animals offer exciting opportunities to understand human health and disease, to develop new therapeutic agents and to study responses to environmental agents. These animals are of utmost importance to several fields of biomedical research, such as aging, addiction, alcoholism, arthritis, autoimmune disease, blood diseases, cancer, cardiovascular disorders, dental diseases, diabetes, diseases of the skin and hair, endocrinology, eye disorders, gerontology, growth and reproduction, hematologic disorders, hypertension, immunology, infectious diseases, kidney diseases, learning and memory, metabolic disorders, neurological and neuromuscular disorders, nutrition, obesity, organ transplantation, parasitology, pharmacology, psychiatric disorders, pulmonary diseases, reproductive disorders, skeletal disorders, toxicology, and urological disorders (Gill et al. 1989; James and Lindpaintner 1997; Jacob 1999; Report of the NIH Rat Model Priority Meeting 1999; Aitman et al. 1999; Pravenec et al. 2001, 2008; Gibbs et al. 2004; Lu et al. 2007).

Rat is the first organism with a dense, single integrated map, offering means to integrate all previously mapped genes and quantitative trait loci onto a single backbone (Jacob 1999). Moreover, compared to mice, the rat genome showed an enrichment of genes involved in immunity, chemosensation, detoxification, or proteolysis (Gibbs et al. 2004). Interestingly, laboratory rats possess a higher diversity than inbred mice strains (Canzian 1997), which allows the monitoring of a broad spectrum of biological responses (Tesson et al. 2005). More than 1000 strains, substrains and genetically modified rats are currently used to display a wide range of biochemical and physiological phenomena and serve as models for various diseases (Aitman et al. 2008).

Production of Transgenic Rats

To date, germline-competent rat embryonic stem (ES) cells have not been established in the rat system (Aitman et al. 2008). Therefore, the existence of truly totipotent embryonic stem cells have given the mouse a clear advantage over the rat in the rapid generation of knock in and knock out transgenic models (Tesson et al. 2005). Furthermore, rat transgenic technology possesses additional drawbacks that may have an undesirable effect on the efficiency of transgenic rat production, for example: the superovulation is less effective in rats than in mice (Popova et al. 2004), the survival rates of microinjected zygotes are relatively lower in rats (Filipiak and Saunders 2006; Popova et al. 2002), rat embryo culture systems are slightly less developed (Popova et al. 2004), the entire microinjection process is more difficult than in mice (Popova et al. 2004) and breeding rats is much more expensive than breeding mice (Tesson et al. 2005). Despite these limitations, almost 200 transgenic rat models have been generated within the last two decades (http://www.ifr26.nantes.inserm.fr/ITERT/transgenese-rat/Documents/Table%20trans-genic%20.doc). To obtain transgenic rats, several techniques have been developed, including DNA microinjection, viral vector-mediated DNA transfer and sperm-mediated DNA transfer (Wall 2002; Tesson et al. 2005; Cozzi et al. 2008) (Table 1).

The technique most commonly used to generate transgenic animals is traditional microinjection of foreign DNA into one or both pronuclei of a single-cell stage embryo (zygote) (Houdebine 2005a). Pronuclear DNA microinjection is the most convenient approach to produce transgenic rats (Bagis et al. 2002, Hirabayashi et al. 2008). In the rat, this method was used in 1990 for the first time (Mullins et al. 1990). The transgene usually includes the coding sequence of a gene (cDNA) and an efficient widespread or tissue-specific gene promoter. Generally, transgenic efficiency after DNA microinjection is rather low in rat, usually up to 5% (Hirabayashi et al. 2001), however, in some instances it can reach up to 41% (Filipiak and Saunders 2006). Recently, several modification of these techniques have been developed to increase the efficiency of the transgenesis, such as microinjection with an artificial chromosome vector (Takahashi et al. 2000) or microinjection with a transposon system (Lu et al. 2007). Transposons, transposable DNA elements, represent a promising genetic tool for the generation of novel transgenic rat models for several human disorders. DNA transposons, which possess an intrinsic capability to change their genomic position, are known to be efficient carriers of foreign DNA into cells. Currently, they have emerged as new integrating gene vehicles with applications in transgenesis, mutagenesis, or gene transfer (Miskey et al. 2005; Dalsgaard et al. 2008).

Another approach is viral vector-mediated DNA transfer, where retroviral vectors are usually injected into the perivitelline space (between the zona pellucida and the cytoplasmic membrane) of the embryos (Michalkiewicz et al. 2007) or, alternatively, by incubating zona-free embryos in a viral solution (Cozzi et al. 2008). Retroviral vectors derived from oncoretroviruses or lentiviruses are able to efficiently integrate DNA sequences into the genome (Tomanin and Scarpa 2004). While viral gene transfer of prototypic retroviruses can only occur in host cells which are actively replicating at the time of infection, lentiviruses can be actively transported into the nucleus of non-dividing cells (Pfeifer 2004). In the rat, very high efficiencies of transgene insertion have been reported (13%–59%) (Dann 2007). The major drawback of the retroviral vectors is their relatively restrictive capacity (up to around 10 kb) for the insertion of expression cassettes (Pfeifer 2004; Cozzi et al. 2008).

Table 1 Current transgenic procedures used for the generation of transgenic rats

Transgenic techniques	Advantage	Disadvantage	Proportion of transgenic pups	References
Pronuclear microinjection of DNA				
(1) Microinjection of foreign DNA	The principle of these techniques is simple	Manipulation skills required to perform DNA microinjections	0.4%–5%	Charreau et al. 1997
	They are widespread and firmly established	Low embryo survival		Hirabayashi et al. 2001
	Most reproducible and straightforward method	Low efficiency of transgene integration		Pfeifer 2004
		Enormous production costs		Popova et al. 2004
		The odds of single copy integration are very low		Popova et al. 2005
		Higher stickiness and flexibility of cytoplasmic and pronuclear membranes		Tesson et al. 2005
		A considerable portion of zygotes undergoes lysis immediately after injection		Filipiak and Saunders 2006
		Embryo culture technique is not well adapted for use in rats		Dann 2007
		Injected DNA often results in random insertion of concatamers		Hirabayashi et al. 2008
				Popova et al. 2008
(2) Microinjection using an artificial chromosome vector	Cloning capacity of the chromosome vector is more than 1 Mb	The efficiency is usually low	1%–25.5%	Takahashi et al. 2000
		The technique is labor-intensive		Moreira et al. 2004
	With this technique transgenic animals carry single or few copies of the transgene	Purification and injection of large DNA fragments into single cell embryos are difficult		Cozzi et al. 2008
Retroviral vectors				
(1) Lentiviral transgenesis into the perivitalline space	Subzonal injection into the perivitalline space is much less invasive than DNA microinjection	Relatively reduced capacity (up to 10 kb) for the insertion of expression cassettes	13%–59%	Lois et al. 2002
	Lentiviral transgenesis is several times more efficient than DNA microinjection	There is no control over the integration site and the number of copies of the transgene		Wall. 2002
	This transfer is not dependent on the size, localization or visualization of the nucleus	Transgene insertion site may also modify the expression of genes at and around the site of integration		Pfeifer. 2004
	Single integrations of DNA are more often achieved	High rates of mosaicisms		van den Brandt et al. 2004
	Lentiviviral vectors are able to transduce dividing and nondividing cells			Dann et al. 2006
				Dann 2007
				Robl et al. 2007
				Cozzi et al. 2008
				Kanatsu-Shinohara et al. 2008

Table 1 continued

Transgenic techniques	Advantage	Disadvantage	Proportion of transgenic pups	References
(2) Lentiviral transduction of spermatogonial stem cells	Higher efficiency of transgene insertion	Relatively reduced capacity (up to 10 kb) for the insertion of expression cassettes	5.8%–52%	Hamra et al. 2002 Ryu et al. 2007
		Complexity of this process		Kanatsu-Shinohara et al. 2008
Sperm-mediated transgenesis				
(1) In vitro incubation of DNA and intracytoplasmic sperm injection	Relatively simple and low cost method	Manipulation skills required to perform intracytoplasmic sperm injection (ICSI)	0.9%–17%	Wall 1999
	Higher survival rates of rat oocytes	Lack of reproducibility in some laboratories		Wall 2002
		Low number of born progeny		Hirabayashi et al. 2002a Hirabayashi et al. 2002b Kato et al. 2004 Hirabayashi et al. 2005 Houdebine. 2005b Tesson et al. 2005 Lavitrano et al. 2006 Hirabayashi et al. 2008
(2) Testis mediated gene transfer (used Plasmid DNA-liposome complexes)	Manipulation of embryos is not required	When plasmid DNAs are introduced, they often exist extrachromosomally	Approximately 9.5%	Chang et al. 1999
	Much simpler and more convenient method Low cost method	Occacional mosaicism		Smith and Spadafora 2005

Sperm-mediated DNA transfer is based on the ability of sperm cells to bind and internalize exogenous DNA (thus, they can act as vector for exogenous DNA) and transfer it into the egg during fertilization under in vitro or in vivo conditions (Lavitrano et al. 2006, Smith and Spadafora. 2005). A perspective modification of this technique is testis-mediated gene transfer, where plasmid DNA–liposome complexes are injected into the testis (Chang et al. 1999). We can reasonably expect that with the improvement of the transgenic technology rats will expand their usefulness to the pharmaceutical industry and fundamental research even more.

Modeling Neurodegenerative Disorders in the Rat

Human neurodegenerative diseases are chronic disorders of the central nervous system. Many of these disorders display characteristic proteinaceous aggregates, such as amyloid plaques and neurofibrillary tangles in Alzheimer's disease, Lewy bodies in Parkinson's disease (PD), neuronal intranuclear inclusions in Huntington's disease, Bunina bodies in amyotrophic lateral sclerosis, glial cytoplasmic inclusions in multiple system atrophy (MSA), etc. (Cha 2007). These neurodegenerative diseases are often referred to as protein misfolding disorders—foldopathies or conformational diseases (Kosik and Shimura 2005; Zilka et al. 2008). This results from the presence of misfolded proteins in CNS lesions. The proteins are not in the proper functional conformation and are devoid of biological activity and even worse, they can gain novel toxic functions.

Currently, there is no effective therapy for the vast majority of common neurodegenerative foldopathies, because their primary cause remains poorly understood. To unravel the causative factors behind the neurodegeneration several transgenic rodent models have been developed. Rodent models have significantly contributed to the understanding of basic molecular mechanisms of neurodegeneration (Spires and Hyman 2005; Götz and Ittner 2008; Turner and Talbot 2008). To date, most of the available information has been generated in mouse models. Although these models have been of great use, the potential of mice for the study of neurodegenerative pathways is limited because of the brain size and problematic behavioral testing. In fact, the rats have several advantages that make them superior to mice. The rat is the model of choice in neurobehavioral and stereotaxic neurological studies. The size of the rat brain offers unique possibilities for the application of microsurgical techniques, intrathecal administration of drugs, stem cell transplantation, serial sampling of the cerebrospinal fluid, in vivo nerve recordings, and neuroimaging procedures (Howland et al. 2002; von Hörsten et al. 2003; Matsumoto et al. 2006). Moreover, the CSF volume of a rat is 10- to 20-fold greater than that of a mouse (Nagai et al. 2001). Therefore, transgenic rats make studying the CSF proteome, even in an age-dependent manner, possible. Furthermore, the rat is routinely employed both to demonstrate therapeutic efficacy and to assess the toxicity of novel therapeutic compounds in drug development. For this reason, the rat still remains a major model system inside the pharmaceutical industry (Jacob 1999). This makes the rat an ideal animal model for the development of novel disease modifying drugs for human neurodegenerative disorders.

The Rat Models for Human Neurodegenerative Disorders

To date, several transgenic rat strains have been generated to model familial Alzheimer's disease (Echeverria et al. 2004; Ruiz-Opazo et al. 2004; Flood et al. 2007; Folkesson et al. 2007; Agca et al. 2008), human tauopathies (Zilka et al. 2006), Huntington's disease (von Hörsten et al. 2003), or amyotrophic lateral sclerosis (Nagai et al. 2001; Howland et al. 2002) (for details see Table 2).

Alzheimer's disease (AD) is a degenerative dementia that destroys the higher structures of the brain. The disease leads to deficits in cognitive function that cause a decline in memory, learning ability and language, inability to perform purposeful movements; they are accompanied by concomitant behavioral, emotional, interpersonal, and social deterioration. These cognitive and behavioral alterations are always associated with difficulties in daily life (Burns et al. 2002). The majority of AD cases correspond to the sporadic form of this disorder. Mutations in the amyloid precursor protein (*APP*), presenilin-1 (*PS1*), and presenilin-2 (*PS2*) genes are linked to the familial form of AD. However, these pathogenic mutations account for less than 1% of AD cases (Delacourte et al. 2002). Prominent neuropathologic features of AD are senile plaques consisting of the amyloid ß peptide (Aß), which is derived from the amyloid precursor protein (APP) (Masters et al. 1985) and neurofibrillary tangles that are composed of hyperphosphorylated and truncated forms of tau protein (Grundke-Iqbal et al. 1986; Wischik et al. 1988; Novak et al. 1991; 1993).

Recently, several transgenic rat strains that express either human wild type (Clarke et al. 2007) or mutant APP (Echeverria et al. 2004; Ruiz-Opazo et al. 2004; Flood et al. 2007; Folkesson et al. 2007; Agca et al. 2008; Liu et al. 2008) have been generated. Strikingly, the majority of these models failed to develop β-amyloid plaques with aging because of low and inadequate expression levels of soluble Aβ. To increase the expression level of mutant APP and of soluble Aβ it was necessary to breed two

Table 2 Transgenic rat models of human neurodegenerative tauopathies

Disease	Transgene	Rat model	Rat strain	Literature
Huntington's disease	Truncated huntingtin with 51 CAG repeats	Transgenic line tgHDrat	Spraque Dawley	von Hörsten et al. 2003 Bauer et al. 2005 Cao et al. 2006 Kantor et al. 2006 Nguyene et al. 2006 Temel et al. 2006 Winkler et al. 2006 Petrasch-Parwez et al. 2007 Bode FJ et al. 2008
Amyotrophic lateral sclerosis	Mutated SOD1 (G93A or H46R)	Transgenic lines G93A-39 H46R-4	Spraque Dawley	Nagai et al. 2001 Aoki et al. 2005. Kato et al. 2005 Vermeiren et al. 2006
Amyotrophic lateral sclerosis	Mutated SOD1 (G93A)	Transgenic line SD-TgN(SOD1G93A)L26H	Spraque Dawley	Howland et al. 2002 Xie et al. 2004 Ludemann et al. 2005 Turner et al. 2005 Herbik et al. 2006 Lladó et al. 2006 Matsumoto et al. 2006 Rafałowska et al. 2006 Fendrick et al. 2007 Jokic et al. 2007 Suzuki et al. 2007 Thonhoff et al. 2007 Yin et al. 2007
Human tauopathies	N and C terminally truncated protein tau	Transgenic lines SHR318 SHR72	SHR	Zilka et al. 2006 Hrnkova et al. 2007 Korenova et al. 2008 Koson et al. 2008
Familial form of Alzheimer's disease	Mutated APP (K670N/M671L/V717F) Mutated PS1 (M146V)	Transgenic lines single transgenic rat Tg478 Tg1116 Double transgenic ratTg478/Tg1116 Triple transgenic rat Tg478/Tg1116/Tg11587	Spraque Dawley	Flood et al. 2007 Liu et al. 2008
Familial form of Alzheimer's disease	Mutated APP (K670N/M671L)	Transgenic lines 6601 6590	Spraque Dawley	Folkesson et al. 2007
Familial form of Alzheimer's disease	Mutated APP (K670N/M671L/V717F) Mutated PS1 (M146V)	Transgenic lines Single transgenic rat Tg UKUR28 Tg UKUR19 Double transgenic rat Tg UKUR25	Wistar	Echeverria et al. 2004

Table 2 continued

Disease	Transgene	Rat model	Rat strain	Literature
Familial form of Alzheimer's disease	Mutated APP (K670N/M671L)	Transgenic line 17 TgAPPswe	Fischer 344	Ruiz-Opazo et al. 2004
Familial form of Alzheimer's disease	Mutated APP (K670N/M671L/V717F)	Transgenic lines	Fischer 344	Agca et al. 2008
		APP21		
		APP31		
Alzheimer's disease	APP695	Transgenic line hAPP695	Wistar	Clarke et al. 2007

SOD1 superoxide dismutase 1. Mutations in this gene cause familial amyotrophic lateral sclerosis

APP amyloid precursor protein. Mutations in this gene cause familial forms of Alzheimer's disease

PS1 presenilin 1. Mutations in this gene cause familial forms of Alzheimer's disease

independent APP transgenic lines together and bring them to double homozygosity. Finally, the triple homozygous transgenic rat expressing human amyloid precursor protein (APP) with the familial AD (FAD) mutations K670N/M671L and K670N/M671L/V717I and human presenilin-1 (PS-1) transgene with the FAD M146V mutation displayed extracellular Aβ deposits in the brain (Flood et al. 2007).

Human tauopathies represent a heterogeneous group of neurodegenerative disorders that are characterized by the presence of intracellular accumulations of abnormal filaments of protein tau. A number of neurological diseases are known to have prominent filamentous tau inclusions including Alzheimer's disease (AD), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), Pick's disease (PiD), frontotemporal dementia with Parkinsonism linked to chromosome 17 (FTDP-17), and many others (Lee et al. 2001). Currently, a sole transgenic rat model of human tauopathy has been developed (Zilka et al. 2006). The model expressing non-mutated truncated tau derived from sporadic Alzheimer's disease displayed the AD-characteristic tau cascade consisting of argyrophilic and phospho-tau positive neurofibrillary tangles, mature sarcosyl insoluble tau complexes and extensive axonal damage in the brain stem and spinal cord. Surprisingly, transgene expression does not cause neuronal loss in the transgenic rat brain (Koson et al. 2008). Axonopathy led to neurogenic muscular atrophy, which was the primary cause of progressive muscle weakness. This resulted in the bradykinesia and paraparesis, progressive reduction in weight and finally to wasting and death of transgenic rats (Zilka et al. 2006; Hrnkova et al. 2007).

Huntington's disease (HD) is a devastating autosomal dominant neurodegenerative disease caused by an expansion of cytosine–adenine–guanine (CAG) repeats in the huntingtin gene which leads to neuronal loss in the striatum and cortex and to the appearance of neuronal intranuclear inclusions of mutant huntingtin. Huntington's Chorea is characterized by uncoordinated and awkward body movements, cognitive impairment and psychiatric symptoms (Gil and Rego 2008). The first transgenic rat model for Huntington's disease was generated by von Hörsten et al. (2003). The rat model expressing a truncated huntingtin with 51 CAG repeats displayed symptoms similar to the late-onset form of Huntington's disease. Rats developed a progressive phenotype characterized by emotional, cognitive, and motor deterioration. Neuropathological examination revealed nuclear inclusions and neuropil aggregates in the striatum. The most important feature of this model was its suitability for in vivo metabolic (PET) and structural imaging (MRI).

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease characterized by paralysis of motor function due to a combination of voluntary muscle weakness, atrophy, and spasticity (Turner and Talbot 2008). Approximately 10% of ALS cases are inherited, usually as an autosomal dominant trait. In 25% of familial cases, the disease has been linked to mutations in the gene encoding cytosolic copper–zinc superoxide dismutase (*SOD1*) (Aoki et al. 1993; Rosen et al. 1993). Based on these mutations, transgenic rats that express a human *SOD1* transgene with two different ALS associated mutations (G93A and H46R) have been generated (Nagai et al. 2001; Howland et al. 2002). These transgenic rat models reproduce the major phenotypic features of human ALS, such as selective motor neuron loss, ubiquitination, hyaline inclusion, vacuolation, and reactive astrogliosis. Several differences between the rat and mouse ALS models have been described including more rapid progression of disease and the transient appearance of vacuoles in the transgenic rat. Compared to transgenic mice, the larger size of rat models makes it possible to detect the concentration of amino acids or SOD1 in the cerebrospinal fluid (Nagai et al. 2001; Turner et al. 2005) and to intrathecally infuse a Ca^{2+}-permeable AMPA channel blocker (Yin et al. 2007).

Conclusion

The rat has become the most widely studied experimental animal model for biomedical research. However, the lack of efficient tools for the manipulation of the rat genome has dramatically limited the use of the rat as model for human neurodegenerative disorders. Therefore, the number of transgenic models recapitulating key pathological hallmarks of neurodegeneration is still limited. Despite this fact, transgenic rats have greatly expanded the range of potential experimental approaches. The larger size of rats compared to that of mice facilitates studies involving implantation of intrathecal catheters for chronic therapeutic studies; serial sampling of the cerebrospinal fluid and neuroimaging. Thus, transgenic rat models could become an important platform for revealing the molecular mechanisms underlying human neurodegenerative disorders, as well as designing novel therapeutic approaches.

Acknowledgment This work was supported by research grants APVV 0631-07 and LPP-0363-06.

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