Olfactory Bulbectomized Rat: A Model for What?

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Abstract

The olfactory bulbectomized rat has been used primarily as an animal model for the detection of anti-depressive properties of new chemical entities and their assessment against the currently available anti-depressants. This is mainly due to the fact that the chronic efficacy of anti-depressants and not the acute efficacy is detectable using the model which resembles the efficacy of such drugs in humans. This review covers the chronological process that led to this use of this animal model, revises the logical reasons that justify that use and suggests other diseases the OBX rat can be used as a model for, such as certain neurodegenerative disorders and traumatic brain injury. A special consideration is also included for the “golden hour” meaning the chemical changes in the brain which occur in the first hour after the initial impact of traumatic brain injury, during which medical intervention has the highest potential of decreasing the permanent damage. If used as soon as the surgery is complete, the OBX rat could be evaluated as a model for neuroprotective drugs.

List of abbreviations

MDD = Major depressive disorder

OBX = Olfactory bulbectomy

NE = Norepinephrine

TBI = Traumatic brain injury

AD = Alzheimer's disease

MCI = Mild cognitive impairment

Amyloid beta = Aβ

APOE = encoding apolipoprotein E

PD = Parkinson's disease

NFTs = neurofibrillary tangles

hAPP = human amyloid precursor protein

FTD = frontotemporal dementia

5-HIAA = 5-hyroxyindole acetic acid

NPY = Neuropeptide-Y

LPS = lipopolysaccharide

IL = interleukin

TNF = tumor necrosis factor

SSRI = selective serotonin reuptake inhibitor

TCA = tricyclic antidepressants

NSS = neurological severity score

Aim of the thesis

Aim of this thesis is to review the validity of the OBX rat as a model for major depressive disorder, discuss in detail the different aspects that justify it as a model of depression and suggest some aspects that support the justification to use OBX rats as a model for neurodegenerative disorders, traumatic brain injury in general and a separate aspect of traumatic brain injury namely, The golden hour.

Contents

I. Introduction

Animal models have been used extensively throughout the history of medical research to ensure the safety and efficacy of the tested drug before risking a human life. The choice of animal, method of administration, duration of exposure, observed biomarker and data analysis have always been based upon the intended use of the drug and aspect of the disease being studied and are decided upon per study. This has been a process of trial and error and has improved immensely over the decades, yet it is still an unnerving decision-making process on behalf of the scientist to omit as much as possible the waste of resources, unnecessary animal cruelty, unpredicted side effects, and non-representative data while at the same time still follow the legal guidelines and quotas.

This review intends to review the validity of the olfactory bulbectomized (OBX) rat as a model for major depressive disorder (MDD) summarized how it came to be used for this purpose and extrapolate those rationalizations to suggest other justifiable uses for this model such as the studying of certain characteristics of neurodegenerative diseases and several aspects traumatic brain injury.

To fully explore these possibilities we will first briefly examine the disease it is currently modeling for and the inception of the model.

A. Major depressive disorder in humans; what we know so far

Major Depression disorder is a broad syndrome with many theories on how to define it. The most renowned as well as among the earliest theories being the monoamine theory (Schechter et al. 2005, 590-611) The major identified symptoms are Anhedonia, poor self-image, suicidal thoughts, and poor concentration. Beyond these well-established symptoms there is a whole range of atypical disorders associated with depression. It is widely accepted that individuals who meet the criteria of MDD might still have different combinations of symptoms and even if they do have identical symptoms, different biological disorders might have the same end result.(Halbreich 2006, 16-22) For these reasons, diagnosis of MDD based on a descriptive phenomenological approach is only a departure point. From here, an evaluation of the relevance of underlying mechanisms should be considered along with factors such as family history, past history and treatment response. (Antonijevic 2006, 1-15)

MDD has been considered using a multidimensional analysis. Street *et al.* concluded four dimensions from a total of 27 theories addressing 99 factors. The first dimension included cognitions affecting communication both interpersonal and intrapersonal, the second dimension described behavior related to environmental stress. The third dimension encompassed the perception of a lack of control resulting from failing unrealistic goals pursued by the subject. The fourth dimension involves the self-attribution of the negative results of social and

environmental circumstances. These four dimensions provide a comparative understanding to the environmental and individual factors that can render an individual depressed. (Street, Sheeran, and Orbell 2001, 53-67)

A more hands on approach has been discussed in the Diagnostic and Statistical Manual of Mental Disorders, Fourth edition, Text revision ((DSM-IV-TR)) where it was suggested that if symptoms are not a result of a substance intake, no history of bipolar disorder is reported, symptoms are not caused by mourning and are causing significant functional impairment, any five of the following nine symptoms being present continuously for two weeks satisfy the criteria of major depressive disorder. The nine symptoms being: depressed frame of mind, Anhedonia, appetite and weight change, both increase and decrease in sleeping time, feelings of guilt and low self-worth, psychomotor agitation and retardation, fatigue and loss of energy, decreased concentration, and suicidal ideation (Soleimani, Lapidus, and Iosifescu 2011, 177-193)

The severity of MDD was investigated as well and rating scales were designed to quantitatively asses the disorder. The most renowned rating scales being the Montgomery-Asberg depression rating scale (MADRS) and the Hamilton Depression Rating Scale (HRSD). These rating scales are used to assess the efficacy of anti-depressant drugs in comparison to placebos in most antidepressant efficacy trials and to determine the progress of treatment with anti-depressants. A few drawbacks of these approaches have been discussed increasingly. Namely, the fact that on the individual level treatment response is interpreted successful if 50% of greater improvement is observed on one of the depression severity scales and the fact that during clinical trials, although an indication of the efficacy compared to the placebo will register, due to the nature of the approach, it does not provide information on whether the patients return to the well-state. (Zimmerman, Chelminski, and Posternak 2004, 1-7)

After the examination of the nature and the clinical picture of the disease the OBX rat is modelling for, it is necessary to also elaborate on the history of the animal model and how it came to be used for this purpose.

B. OBX rat: A brief history

In 1971, Marks *et al.* investigated the rat model with the bilateral lesions of the olfactory bulbs to evaluate the proposition by Lindley *et al.* who claimed that anosmic rats had greater learning and performance deficits than rats that only had olfactory cues eliminated. (Lindley 1928) (Marks et al. 1971, 1-6) Marks did not directly support Lindley's claims. This was expanded upon by Thomas who reported an impairment in the development of passive avoidance response (Thomas 1973, 140-148). Soon after, in 1976, Van Riezen and Wren *et al.* speculated the behavioral changes of the olfactory bulbectomized rats could be used to detect novel anti-depressants(van Riezen, Schnieden, and Wren 1976, 426P-427P) and a year later proposed the olfactory bulbectomized rat as a model for depression.(Wren, van Riezen, and Rigter 1977, 96-100) verifying it's anti-depressant detection ability the same year. The behavioral changes were quantified and tested for reversibility using anti-depressant drugs (van Riezen, Schnieden, and Wren 1977, 521-528), using, among others, mianserin (brand names: Depnon , Lantanon,

Lerivon, Lumin , Norval, Tolvon) as the anti-depressant standard to be detected by the animal model (Rigter et al. 1977, 451P-452P).

Even before its suggestion as a model for depression, the OBX model has been studied for changes in sexual behavior (Sato et al. 1974, 301-309)(Larsson 1975, 195-199; Pollak and Sachs 1975, 337-343), food intake and preference(Leung, Larson, and Rogers 1972, 553-557)(Larue 1975, 491-493), as well as effects of handling(Loyber et al. 1977, 1393-1394), maternal behavior (Schwartz and Rowe 1976, 879-883)and nursing behavi()or(Singh and Tobach 1975, 151-164). After its proposal as an anti-depressive activity detecting animal model the research became more directed towards expanding on the paradigm. From studying its survival, growth and suckling behavior when the operation was performed neonatal (Teicher et al. 1978, 553-561) and the differences in effects when the operation was performed in different times in the rats life(Lumia, Meisel, and Sachs 1981, 497-509), to attempts to clarify how the anti-depressants resulted in the relief of some of the physiological effects caused by the bulbectomy.(Castagne et al. 2011, Unit 8.10A)

Looking at the depression-like effects a bilateral olfactory bulbectomy had on the rats; interests naturally focused on the brain chemistry of the animals (Tonnaer et al. 1980, 683-686) as well as mental functions and development.(Shibata, Watanabe, and Ueki 1980, 309-313) The stress induced by the handling of the rats in the lab and its resulting behavior in OBX rats became another major niche of research on the OBX rat (Shibata et al. 1981, 275-280). The social behavior of the animal model was also a main area of focus.(Shibata et al. 1984, 225-230; Beatty and Costello 1983, 525-528)

After reviewing the history of the OBX rat model, it became apparent that a uniform method for the bulbectomy has been establish and is therefore summarized below.

C. Established surgical procedure

The surgical removal of the olfactory bulbs of a rat has been established with little variety between the methods of different groups. Animals were anesthetized with either isoflourane gas anesthetic (3%-4%)(Breuer et al. 2007, 990-995), intraperitoneal with chloral hydrate(van der Stelt et al. 2005, 1061-1067)(Cairncross et al. 1977, 144P) or using Diabutal 50mg/kg (Wang and Hull 1980, 211-215) and were placed in a stereotaxic instrument. After the incision was made in the scalp above the olfactory bulbs, lidocaine (5%)(van der Stelt et al. 2005, 1061-1067)(Breuer et al. 2007, 990-995) and iodine(Breuer et al. 2007, 990-995) were added to the incision as anesthetic and antiseptic. Using of a burr, on either side a hole was drilled in the skull (2mm diameter, 8mm anterior to bregma) and 2 mm from the midline of the frontal bone overlying the olfactory bulbs. (van der Stelt et al. 2005, 1061-1067)(Breuer et al. 2007, 990-995) or were drilled down to the dura. (Wang and Hull 1980, 211-215). The olfactory bulbs were removed using a blunt hypodermic needle attached to a water pump(van der Stelt et al. 2005, 1061-1067) or a vacuum pump(Breuer et al. 2007, 990-995) or were excised using a sharp needle and a magnifying glass and the upper aspect of the cribriform plate was scraped (Wang and Hull 1980, 211-215).Blood loss was prevented by hemostatic sponges(van der Stelt et al.

2005, 1061-1067)(Breuer et al. 2007, 990-995) or foam along with sulphathiazole for potential infections.(Wang and Hull 1980, 211-215)The incisions were then sutured using resorb able material. Sham operated rats underwent the same procedure without removing the olfactory bulbs. Subcutaneous saline (5ml) and Rimadyl(5mg/kg) post operatively was administered with the purpose of pain reduction in some procedures (Breuer et al. 2007, 990-995) but it was widely customary that the recovery period postoperative was 2 weeks before participation of the animals in any behavioral tests.

So far the OBX model has been discussed on the disease it is used as a model for, its discovery and how its use has developed and standardized. However, there is a fundamental logical problem with using an animal model for a psychological disease which has to be brought into consideration when interpreting the data obtained from such in vivo experiments. Therefore the value of the data and to which extent it can be extrapolated to human conditions must be critically reviewed and contemplated.

D. Limitations on ideal criteria of an animal model for Major Depressive Disorder

It is safe to conclude that defining the criteria of an ideal model for major depressive disorder is already extremely problematic due to the complex nature of the disorder. To attempt an animal model that fits the ideal criteria is obviously impossible even if there was a clear definition of the disorder, because of the vast mental capacity difference between humans and animals, nevertheless efforts to define this ideal criteria for an animal model for depression were first conceived of by Mckinney and Bunney in 1969, They proposed that a model needs to meet three main requirements; namely, 1) a similarity in the behavior of the animal to the symptoms seen in patients with depression, called face validity, 2) that the behavioral changes occurring in the animal can be measured objectively, called construct validity and 3) that the behavioral changes can be reversed by any treatment that is therapeutically effective, I.E. pharmacological predictive validity. (Song and Leonard 2005, 627-647)(McKinney and Bunney 1969, 240-248)(Song and Leonard 2005, 627-647)

Furthermore, the changes brought to the rats with the olfactory bulbs removed are extensive and coincide with many symptoms of major depressive disorder. Of course not all changes correspond with the human condition which is why it is important to list those changes seen in the OBX rat separately as well as within the context of it being a model for MDD.

E. Physiological changes:

The surgical removal of the olfactory bulbs of a rat results in, among others, anosmia, the loss of the ability to detect pheromones and danger assessment. This affects many aspects of a rat's life including its reproductive behavior, social dominance among males, avoidance behavior gender recognition and other chemical cues. (Song and Leonard 2005, 627-647) these can be best explained per system. Nevertheless, one of the full body physiological changes seen after the

surgery that develops fast (2 days) and persists over a period of weeks is the body temperature increase during the nocturnal period. (Vinkers et al. 2009a, 39-46)

1. Immune system

Several studies have concluded interesting changes seen in the immune system after bulbectomy. The ratio of white blood cell count, specifically lowered lymphocytes and increased neutrophil percentages (Cai and Leonard 1994, 40-47), (Song and Leonard 2005, 627-647) increase in macrophage and monocytes activity (Song, Earley, and Leonard 1996, 1-16), decreased neutrophil phagocytosis (Cai and Leonard 1994, 40-47) and the observation that decreased the concentration of LyT 2-positive suppressor T cells relative to L3T4- positive T helper cells suggest that after the rats underwent the surgery, an activation of the immune system persisted.(Komori et al. 2002, 194-196)(Song and Leonard 2005, 627-647)

A study by Pistovcakova *et al.* demonstrated how the OBX induced deviating leukocyte differential count was reversed by administering tiagabine. (Pistovcakova et al. 2008, 54-59) Another study presented the inability of OBX rats to produce lipopolysaccharide (LPS)-induced interleukin (IL)-1beta and tumor necrosis factor (TNF) (Connor et al. 2000, 27-35) and yet a third study examined the performance of the immune system of OBX rats against periodontitis and discovered a significant loss of periodontal bone compared to sham operated rats.(Breivik et al. 2006, 469-477) Recently, Rinwa *et al.*noted the microglial neuroinflammatory response could be suppressed with quercetin. (Rinwa and Kumar 2013)

2. Endocrine

Hormone levels are also affected by the bulbectomy, most commonly reported; the corticosterone level increase in the circulation, (Song and Leonard 2005, 627-647; Breivik et al. 2006, 469-477) and the increase of vasopressin. IT is speculated that the increase in corticosterone concentration is due to the compensatory activity of the hypothalamus (Marcilhac et al. 1999, 89-92)

3. Neurochemistry

It is well established that the concentration of noradrenaline in the brain is decreased after bulbectomy. (van der Stelt et al. 2005, 1061-1067; van Riezen and Leonard 1990, 21-34; Jancsar and Leonard 1984, 263-269) The amount of beta-adreno receptors have been reported to be elevated on blood lymphocytes. This is thought to occur due to the relatively diminished available noradrenaline. (van Riezen and Leonard 1990, 21-34) Also serotonin concentration stays consistently decreased post-operatively, as well as its metabolite 5-hyroxyindole acetic acid (5-HIAA). (Jancsar and Leonard 1984, 263-269) These deviations were most prominent in the midbrain, frontal cortex, nucleus accumbens, basolateral amygdala, dorsal hippocampus and amygdaloid cortex. (Redmond, Kelly, and Leonard 1997, 355-359) (Connor et al. 1999, 125-133) (van der Stelt et al. 2005, 1061-1067)Both an increase in density of serotonin-2A receptors and a

decrease in receptor sensitivity to external serotonin were actual following bulbectomy. (Butler, Tannian, and Leonard 1988, 585-594) A reduction, reversible with mianserin, of muscarinic receptors in the brain was observed. (Earley et al. 1995, 559-570) Receptor density increased in the GABA-A receptors (Dennis, Beauchemin, and Lavoie 1993, 77-82) (Dennis, Beauchemin, and Lavoie 1995, 279-288).

F. Behavioral changes:

Even though it has been suggested that it lies in the manner the animals are handled, generally, an increase in irritability and aggression has been reported repeatedly.(Shibata et al. 1981, 275-280; van Riezen and Leonard 1990, 21-34; Kelly, Wrynn, and Leonard 1997, 299-316; Vinkers et al. 2009b, 39-46) inefficient muricide is also reported to be more frequent than sham operated rats(Leonard and Tuite 1981, 251-286) and female cannibalism, intermale and territorial aggression are elevated as well.(Lumia, Meisel, and Sachs 1981, 497-509). But to assess the validity of an animal model, a closer look must be taken at factors that resemble the disease being modeled. Therefore the behavioral changes seen in rats after an olfactory bulbectomy are objectively revised in detail here.

1. Circadian rhythmicity, stress and sleep

Olfactory bulbectomized rats exhibit altered circadian rhythmicity. Increased nocturnal body temperature, increased nocturnal activity, and decreased heart rate all appear within days of the surgery and proved to signify true olfactory bulbectomy induced changes. (Vinkers et al. 2009b, 39-46)(van Riezen and Leonard 1990, 21-34)Under minor stressors such as witness stress OBX rats exhibit an increased autonomic activation threshold along with an elevated locomotor response whereas with more intense stressors such as novel cage stress or open field stress the OBX and sham operated rats differ only slightly in response. (Vinkers et al. 2009b, 39-46) Sleep is also affected in post-op OBX rats as Sakurada *et al.* reported a decrease in REM sleep compared the base line assessed pre-operatively.(Sakurada et al. 1976, 509-511) This effect was normalized with the acute administration of fluoxetine. (Wang et al. 2012, 314-324)

2. Sexual pattern deviation

The most significant report of the effects of an olfactory bulbectomy on the sexual behavior of rats was concluded by Wang *et al*. when they stated a significant drop in the incidence average of ejaculation in males that was improved upon administering a pinch in the tail.(Wang and Hull 1980, 211-215) Another noteworthy study stipulated a marked elongated in ejaculation time was observed, mounted infrequently or failed to and more interestingly, the operated male rats failed to distinguish between receptive and non-receptive female rats.(Edwards, Griffis, and Tardivel 1990, 447-450)

3. Dietary pattern deviation

The dietary pattern deviation observed in OBX rats is considered part of the learning disability it develops post-op. This was reported by Leonard *et al.* by using a straight passage for the starved rats to pass through in order to reach the food. Olfactory bulbectomized rats consistently showed longer traveling times but this could be from either or both missing the olfactory cues or a learning deficit.(Egan, Earley, and Leonard 1979, 143-147) In any case, Leung *et al.* demonstrated that the olfactory bulb is not necessary for rats to control dietary intake and balance consumption of protein.(Leung, Larson, and Rogers 1972, 553-557)

4. Cognitive changes

Early on it was discovered that learning is permanently altered after an olfactory bulbectomy, increase in exploratory behavior, decrease in passive avoidance learning (Wieronska, Papp, and Pilc 2001, 517-525) (van Riezen and Leonard 1990, 21-34) extinction of conditioned taste aversion(Jancsar and Leonard 1984, 263-269) and decrease in active avoidance learning(Marks et al. 1971, 1-6) all indicate that a crucial processing portion of the brain is not functioning adequately and affects a rats ability to learn greatly. Passive avoidance deficits experiments have been set up as two- compartment box in which the rat has to remain in one so as to avoid receiving electrical shocks to the feet.(van Riezen, Schnieden, and Wren 1976, 426P-427P). Another approach is when the rat is required to remain on a wooden plateau to avoid the shocks. (Broekkamp, Garrigou, and LLoyd 1980, 643-646) However, active avoidance is tested for, using the two compartment set-up but instead the rat is initially placed in the room with the shocking floor. The time it takes to change rooms is considered the measure of active avoidance. (Cairncross, Schofield, and King 1973, 481-485) Spatial navigation has been studied using The Morris water maze where causal factor, the learning deficit, could be differentiated from the absence of olfactory cues. OBX rats still performed poorer than sham operated rats. (Redmond, Kelly, and Leonard 1997, 355-359)

G. The relation between OBX induced changes and symptoms of MDD

A model is only as useful as the parallels it draws with the human disease. Therefore it is appropriate to assess the similarities between the model and the disease in a comparative manner. All the similarities found in the information provided above are summarized in table 1. Naturally, any symptom that cannot be demonstrated in an animal are not included.

symptom	MDD	OBX	reference
Anhedonia	present	present	(Chambliss et al. 2004, 593-600)
Cognitive impairments	present	present	(Jaako-Movits et al. 2006, 1559-1570)
Altered GABA	present	present	(van der Stelt et al.

levels			2005, 1061-1067)
Altered norepinephrine levels	present	present	(Jancsar and Leonard 1984, 263-269)
Altered serotonin levels	present	present	(Jancsar and Leonard 1984, 263-269)
Altered dopamine levels	present	present	(van der Stelt et al. 2005, 1061-1067)
Hyper-reactivity to stress	present	varies	(Masini et al. 2004, 111-119)
Eating disorder	present	varies	(Masini et al. 2004, 111-119)
Decreased hippocampal volume	present	present	(McEwen and Olie 2005, 525-537)(Jaako-Movits et al. 2006, 1559-1570)
Memory malfunction	present	varies	(Kelly, Wrynn, and Leonard 1997, 299-316)
Increase corticosterone levels	present	varies	(Cairncross et al. 1977, 144P)
Decreased muscarinic receptor density	present	present	(Earley et al. 1995, 559-570)
Psychomotor agitation	present	rare	(Sobin and Sackeim 1997, 4-17)
Symptoms reversible with chronic use of anti-depressants	present	present	(Earley et al. 1995, 559-570)

Table 1.

It is obvious that the OBX rat model has many comparable symptoms and changes that resemble the human MDD. It's pharmacologically predictive validity has been the strongest argument to date, as only the chronic (as opposed to the acute) administration of anti-depressants are efficacious and show a steady improvement of most symptoms caused by the bulbectomy.

II. OBX model and antidepressants

A. Effects and results with established antidepressants

Mianserin was the first to cancel out the effects observed after rats underwent a bilateral olfactory bulbectomy and by that initiated a long series of studies confirming, expanding upon or utilizing this model for anti-depressant activity detection.(Rigter et al. 1977, 451P-452P)

The OBX model has been successfully detecting antidepressant drugs for decades now with the most reproducible effect, meaning the hyperactivity in the open field test. This effect is also the confirmation test of successful surgery when the testing drug is meant to affect a different parameter of the OBX rats. (Breivik et al. 2006, 469-477)Many effects of the bulbectomy are reversible with the administration of antidepressant drugs and fail to return to baseline when given a drug lacking antidepressant acitivty. (Song and Leonard 2005, 627-647) Such effects include decrease in passive avoidance learning (Wieronska, Papp, and Pilc 2001, 517-525), deviating leukocyte differential count (Pistovcakova et al. 2008, 54-59) and the microglial neuroinflammatory response(Rinwa and Kumar 2013). These effects are reversible upon chronic administration of both selective serotonin reuptake inhibitors (SSRI) and tricyclic antidepressants (TCA). (van Riezen and Leonard 1990, 21-34) (Breuer et al. 2007, 990-995)

There are some very compelling arguments that plea for the use of the OBX rats to test for antidepressant activity of novel drugs, but beyond that, due to the similarities seen between it and the clinical picture of depression, it has been regarded met the criteria as a model for the major depression disorder and even its association with drug abuse has been stipulated by Holmes *et al.* who observed the obx rats learning to self-administer low doses of amphetamines more rapidly than the control and sham operated rats (Holmes et al. 2002, 4-10)

Nevertheless, not all effects return to pre-operative levels after chronic administration of antidepressants. Fluvoxamine failed to increase extracellular serotonin level in such way.(van der Stelt et al. 2005, 1061-1067) and MK-801, a non-competitive NMDA receptor antagonist ,even increased the open field hyperactivity,(Ho et al. 2004, 641-646)(Breuer et al. 2009a) which is a good reminder of the fact that no animal model is perfect and results always have the possibility to contradict predictions.

Appendix A contains a summary of antidepressant drugs that successfully decrease OBX rat hyperactivity in the open field test.

B. Long term effects and behavioral changes after cessation of chronic antidepressant treatment

Further investigations have been carried out by Breuer *et al.* on the OBX rat to understand why chronic but not acute treatment with antidepressants and efficacious and to study the extent antidepressants affects the bulbectomy induced symptoms, including onset time and duration of efficacy after ceasing

the treatment. The study concluded that sub chronic (7 days) and chronic (14 days) successfully normalized the hyperactivity and the reversible effects of the highest dose of imipramine in the OBX faded after 10 weeks after which the hyperactivity was again higher than the sham operated rats. (Breuer et al. 2007, 990-995) It was noted in a later publication that the duration of treatment is directly proportional to the duration of the absence of symptoms.(Breuer et al. 2009b)

C. Research opportunity: relapse incidence during chronic antidepressant treatment and repeated relapse time difference.

Interesting results might be obtained if the duration of the absence of symptoms is compared to each other while repeatedly confronting olfactory bulbectomized rats to periods of treatment and treatment cessation and whether the time taken for the bulbectomy induced become longer or shorter, E.I. whether the antidepressant has a cumulative healing effect and causes semi-permanent changes in brain plasticity or whether the rat develops a resistance to the treatment. To fully examine this phenomenon, not only the hyperactivity effect should be examined, instead all previously reported effects of bulbectomy should be considered.

III. OBX rat could be used to model:

A. Neurodegeneration in chronic studies:

It is reasonable to assume some form of healing of the neuronal tissue after the removal of the olfactory bulbs. But it was Shoenfeld *et al.* who first studied this process and observed a degenerative time course as a result of bulbectomy, during which the severed projections previously connected to the olfactory bulbs. (Schoenfeld and Hamilton 1977, 951-967) This happens in stages, anterograde degeneration is seen first, in the first two weeks, after which the retrograde degeneration follows within the first three weeks, finally transneural degeneration completes after eight weeks from the day of the surgery.(Schoenfeld and Hamilton 1977, 951-967)(Breuer et al. 2009a) However, Heimer *et al.* reported transneural degeneration as early as 8 days after surgery in the pre-piriform cortex and death of cortical neurons.(Heimer and Kalil 1978, 559-609) and according other studies, 4 days was already sufficient for terminal degeneration to become apparent in areas such as the piriform cortex, the hippocampal formation and the basolateral amygdala complex.(Breuer et al. 2009a) These stages resemble neurodegeneration processes that occur in human diseases, many of which may benefit from the information that could be learned from using the OBX rat to model neurodegeneration. For example, it has been reported that imipramine stimulated neurogenesis.(Santarelli et al. 2003, 805-809)

1. Alzheimer's disease

Alzheimer's disease (AD) is a mental affliction with three stages of severity but the cascade of events leading to the characteristic neuronal and synaptic losses begin at the genetic level.(Hall and Roberson 2012, 3-12) It affects 35 million people today and continues to frustrate the search for new cures. The clinical feedback identifies the preclinical, mild cognitive impairment (MCI) and dementia as the main stages of AD. Preclinical AD is differentiated from MCI by the absence of clinical symptoms but detectable AD biomarkers and the line between MCI and dementia is crossed when the clinical symptoms become functional impairments.

One of these biomarkers is the accumulation of amyloid beta (Aβ) and is linked to structural and functional alterations in the brain. Aβ-modifying therapies have been trialed and proved to be relatively much more effective before the onset of neuronal degeneration. (Sperling et al. 2011, 280-292) The pathology of AD is described as senile plaques as a result of the extracellular Aβ deposits and the

intracellular neurofibrillary tangles (NFTs) which are aggregates that appear as filaments and are composed of hyperphosphorylated tau protein.(Lewis et al. 2001, 1487-1491)

Animal models for AD have been primarily based on disease-causing mutations; we will therefore expand on the genetics of AD and their physical manifestations. The genes that are correlated with AD can be divided into two groups, one group causes autosomal dominant AD when mutated; polymorphism in the other group is believed to increase the risk of developing AD. (Hall and Roberson 2012, 3-12) Due to the fact that the pathophysiology of both types are similar, the current animal models for AD have been focusing on the expression of the disease-causing mutations of autosomal dominant AD even if it is not the bulk of AD cases clinically. (Harvey, Skelton-Robinson, and Rossor 2003, 1206-1209) Although the *APOE* (encoding apolipoprotein E) gene is the most influential risk factor gene with the Ɛ4 allele of *APOE* being thought to be linked to early onset and increased risk of AD, (Schmechel et al. 1993, 9649-9653) mutation in APP or presenilins PS-1 and PS-2, which are among the main players causing the autosomal dominant form of AD, are the gene that are manipulated most in transgenic mice to model the senile plaques of the disease.(Lewis et al. 2001, 1487-1491)

One of the aims of this thesis is to suggest the OBX rat as a potentially useful model for the neurodegenerative nature of AD complementing the available animal models of AD and gaining more complete nature of the disease in humans and possibly even discover new drug targets to suspend the neurodegeneration. For this reason, even if both the disease and most of the current animal models are genetic based, the OBX rat could still prove useful by modeling the stages where the neurodegeneration are pronounced.

a) Existing models

The existing models on Alzheimer's disease are mentioned here briefly to illustrate their difference and accuracy to the disease itself. The main reason, however, is to underline the importance of an animal model that has a neurodegenerative distinction, something the following models all lack. There are three main types of mouse models for Alzheimer's disease: The hAPP transgenic models, the Aβ transgenic models and the animal models modeling the role of tau.

The Human APP (hAPP) transgenic lines are the earliest and most used mouse models and model the synaptotoxicity of autosomal dominant AD with relatively little neuronal loss. (Hall and Roberson 2012, 3-12)The types of this line are differentiated according to the mouse strain, hAPP expressing promoters and expressed mutations and isoforms. It is the hAPP expressing promoters that enable us to control factors such as strength of expression, expression onset delay and can even sometimes be neuron specific. (Sasahara et al. 1991, 217-227) An increase in KPI-positive APP isoforms however, is correlated with cognitive deficits (Fukuchi et al. 1996, 219-227) and similar specificities are dependent on isoform differences which makes the expressed APP isoform important in considering an AD model. The variety and specificity in the hAPP transgenic model lines makes it either a very difficult choice or an enormous amount of laboratory work to obtain conclusive results.

The Aβ transgenic models are a quite recent addition and so far have not shown data regarding cognitive deficits.(Hall and Roberson 2012, 3-12) There are the directly expressing Aβ lines to study the effect of Aβ but there are also lines that combine sequences such as BRI protein or other APP fragments with the Aβ proteins and produce BRI- Aβ42 fusion protein. This fusion protein causes a very similar pathology to the aggregate pathology of Aβ in humans.(Lewis et al. 2001, 58-62)

Animal models modeling the role of tau do not cause AD in the mice, instead these mice have mutated genes encoding for human tau and develop frontotemporal dementia (FTD). To model the separate aspects of AD in one mouse model, both mutant APP and mutant tau are expressed so as to develop first the Aβ plaques and then independently develop the tangle pathology which resemble human AD greatly. (Oddo et al. 2003, 1063-1070)

A fourth type of model that depends on expressing human apoE stressing endogenous promoters and other regulatory factors are also available, and cause cognitive defects. Expression can be in either the neurons or in the astrocytes which is where they are produced primarily.(Xu et al. 2006, 4985-4994)(Hall and Roberson 2012, 3-12)

A more detailed list of the various animal models for Alzheimer is included in Appendix B.

b) Justifications to use the OBX rat as a model for Neurodegeneration in Alzheimer's disease

> *"It is important to emphasize that no existing animal model exhibits all features of AD. The ideal model of AD would develop the full range of clinical and pathological features of AD, including cognitive and behavioral deficits, amyloid plaques and neurofibrillary tangles, gliosis, synapse loss, axonopathy, neuron loss and neurodegeneration."* (Hall and Roberson 2012, 3-12)

The similarities between the models used for AD and the disease itself vary per model. The signs and symptoms of AD has been studied separately instead and reproduced in the mouse models to obtain a clear clinical picture. Therefore it is reasonable to examine how many characteristics the OBX model shares with the other models. Table 2 contains the most important symptoms in AD.

symptoms	OBX	hAPP	Aβ	tau	Human apoE	references
Cognitive deficiency	present	present	absent	present	present	(Fukuchi et al. 1996, 219-227)(Jaako-Movits et al. 2006, 1559-1570)(Hall and Roberson 2012, 3-12)
Formation of amyloid plaques	absent	present	present	present	present	(Fukuchi et al. 1996, 219-227)(Lewis et al. 2001, 58-62)(Oddo et al. 2003, 1063-1070)(Hall and Roberson 2012, 3-12)
Memory loss	present	absent	unknown	unknown	unknown	(Kelly, Wrynn, and Leonard 1997, 299-316)(Hall and Roberson 2012, 3-12)
Neurodegeneration	present	absent	unknown	unknown	unknown	(Schoenfeld and Hamilton 1977, 951-967)(Hall and Roberson 2012, 3-12)

Table 2.

So far the OBX exhibits equal validity as the commonly used models of AD. It is important to consider the fact that each of these models are studied for a specific aspect of AD, which is why we propose the use of the OBX model for the study of the neurodegenerative aspect of AD.

2. Traumatic brain injury

TBI is a group of pathological conditions that occur sequentially, the severity of the cognitive deficiency depends on the severity of the initial injury. TBI can be classified according to the type of external force (penetrating or closed) or type of injury mechanism (primary and secondary injury mechanisms) (Xiong, Mahmood, and Chopp 2013, 128-142) The damage is a result of both direct and indirect mechanisms beginning at the time of the injury to, sometimes weeks after the initial injury. The primary injury mechanism can be divided in three types according to duration of application into: impulse loading occurring as a result of a different body part receiving the impact and the head moves as a consequence, static loading is when the skull is compressed for longer than 200ms and impact loading which is of high magnitude and short duration directly to the head. The latter two are sometimes accompanied with skull deformation. (Davis 2000, 1-13) Secondary injury mechanisms initiate as a result to the primary mechanical tissue deformation and implicate diffuse neuronal depolarization and the release of glutamate and aspartate among other excitatory neurotransmitters causing an influx of calcium.(Lee et al. 2004, 70-78) the calcium influx causes both mitochondrial damage and the upregulation of cytokines and chemokines. These processes lead to the release of reactive oxygen species and reactive nitrogen

species. This in turn translates into the clinical picture with symptoms such as blood brain barrier damage, ischemia and hypoxia, increased intracranial pressure and edema. (Xiong, Mahmood, and Chopp 2013, 128-142)

a) Existing models

To establish a need for a new model, it is desirable to examine the current models for traumatic brain injury. The available models of this condition all depend on causing physical damage to the exterior of the head of the testing animal using some form of pre-calculated force. Relatively reproducible, these models exhibit many similarities with the clinical picture and serve their purpose well. The main classes of animal models of TBI can be divided according to method of applying the injury. These methods include Feeney's weight drop model (Feeney et al. 1981, 67-77), where the severity of the injury can be manipulated by increasing or decreasing the weight used in the apparatus, models obtained by fluid percussion(Thompson et al. 2005, 42-75), which does not cause a blow to the head of the animal but instead has a more forceful pulse through a craniotomy modeling TBI when the skull is not fractured, controlled cortical impact injury model, which causes widespread damage and degeneration reaching even the hippocampus(Hall et al. 2005, 252-265) and penetrating ballistic like brain injury models which resemble gunshot wounds and modeled accordingly.(Williams et al. 2005, 313-331)

A comprehensive list of the currently used animal models for TBI is included in appendix C.

b) Justifications to use the OBX rat as a model for Traumatic brain injury

The OBX model can serve to study separate aspects of TBI since the brain damage is not resultant from an impact but instead from surgery. The effect of neuroprotective drugs could be tested to see to what extent the characteristic OBX effects will develop. Another interesting aspect of this proposition is to study the decreased hippocampal neurogenesis, being reversible with citalopram (Jaako-Movits et al. 2006, 1559-1570); it might hold the key to finding new ways to stimulate neurogenesis after TBI. Table 3 exhibits some key features of the existing models and compares them to the OBX rat model.

symptoms	OBX	Feeney's	Fluid percussions	ccii	references
Primary injury mechanism	absent	present	present	present	(Breuer et al. 2007)(Xiong, Mahmood, and Chopp 2013, 128-142)
Secondary injury mechanism	undocumented	present	present	present	(Xiong, Mahmood, and Chopp 2013, 128-142)(Lee et al. 2004, 70-78)
inflammation	limited	Present	Present	Present	(van der Stelt et al. 2005, 1061-1067)(Wei et al. 2013)(Hall et al. 2005, 252-265)
Functional deficits	present	present	present	present	(Jaako-Movits et al. 2006, 1559-1570)(Xiong, Mahmood, and Chopp 2013, 128-142)
Accuracy of reproducibility	surgical	Impact controlled	Pulse controled	widespread	(Breuer et al. 2007)(Feeney et al. 1981, 67-77)(Thompson et al. 2005, 42-75)(Hall et al. 2005, 252-265)
Unnecessary pain	limited	undocumented	undocumented	undocumented	(Breuer et al. 2007)

Table 3.

It is safe to assume there maybe significance to the OBX when it comes to TBI studies. The absence of primary injury mechanism and limited inflammation also means the site of injury will be very clean and therefore easily monitored for physiological changes. The surgical precision ensures that the injuries are identical in all samples and the maximum reduction of unnecessary pain could facilitate the approval for such experiments from the animal experimentation approving establishment.

The OBX model will have to be assessed using the neurological severity score (NSS), brain water content and histopathological deficits and tested with a neuroprotective drug standard for ameliorated neurological injury, NO levels and iNOS mRNA levels.

It must be noted that so far no neuroprotective drug that was successful with an animal model has passed clinical trials. (Xiong, Mahmood, and Chopp 2013, 128-142)

B. Golden hour of TBI in acute studies

It is important to note first of all that the Golden hour in TBI does not mean literally 60 minutes after the trauma occurs. Instead it is a metaphor for the fact that the sooner medical intervention is applied the larger the chance of a full recovery a patient has. It has been argued previously that an irreversible process occurs after the golden hour that may not be fatal to the patient, but much more severe and permanent repercussions do result without medical attention.(open source 2013) However, no peer reviewed paper has been published (before 2002) that claims there is a particular time limit after which medical treatment would be futile. (Bledsoe 2002, 105)But as mentioned above the secondary injuries can cause as much damage to the brain tissue as the initial blow and paramedics strive to decrease the intracranial pressure and inflammation as much as possible in the clinical practice for this reason. (Tepas et al. 2009, 368-372) To study the underlying mechanism and develop a pharmacologically predictive model is therefore of significant value.

Not much is known of the Golden hour. This is logical because TBI in humans is completely unpredictable when it occurs. So research on human TBI can never ethically take place from T=0. On animals, however, we do have the chance to study the phenomenon up close from the start or even administer neuroprotective drugs or anti-inflammatory drugs previous to the trauma.(Xiong, Mahmood, and Chopp 2013, 128-142) It may be unhelpful for humans because patients will not have the chance to use these drugs prior to an accident but this does not mean such data cannot be helpful in the quest to understand the underlying mechanisms and potentially the search for a damage minimizing treatment.(Davis 2000, 1-13)

1. Justifications to use the OBX rat as a model for Golden hour in TBI

The OBX rat provides a clean cut, minimally inflamed and reproducible model with a steady and well documented rate of neurodegerenation. The fact that it is not as inflamed as TBI models could serve an important purpose such as the studying of underlying mechanisms causing long lasting, preventable damage to the brain. The reproducibility of the models also offers the chance for reliable research. The OBX rat, being a relatively old and well documented rat model for other disorders, allows it for new use in TBI and golden hour studies, to minimize extra cost of verifying results or eliminating discrepancies that come from unexpected results within a study that uses a newer animal model.

IV. Conclusion

In the absence of a better animal model, the OBX rat is a justified method of detecting anti-depressant activity of drugs and on several different levels model human MMD. Adding the facts that it responds to chronic treatment and not acute,(van der Stelt et al. 2005, 1061-1067) that many of the bulbectomy induced effects are reversible with antidepressant treatment(Earley et al. 1995, 559-570), it exhibits enough to establish it as a valuable pharmacologically predictive model. Even if not every aspect of this model is understood, with many benefits and few drawbacks, it appears to be a cheap and effective way of screening for anti-depressant properties that perform favorably in the clinical trials phase. Moreover, the bulbectomy shows effects in the rats that are reproducible that can be utilized to understand more about the stages of neurodegeneration in neurodegenerative diseases and shed light over the action of neuroprotective drugs in both acute and chronic studies.

The range of changes following the bulbectomy surpasses it status for a single use. This model is very specific in the way it affects the brain and it shows particular aspects that have partial counter parts in other human diseases. One of the more interesting of those aspects is the neurodegeneration (van der Stelt et al. 2005, 1061-1067) without the often accompanied inflammation or even crushed brain tissue. Therefor we have included a provisional comparative study to other models used to model for diseases that include neurodegeneration and found it reasonable to investigate further whether it is practically useful to use the OBX for this purpose. Alzheimer's disease and Traumatic brain injury have been the focus of this thesis as examples of neurodegenerative diseases. Compared to the existing models and their predictive validity, the OBX rat model seems to qualify and offer certain advantages.

In Alzheimer's disease, as with any human disease, no ideal animal model exists and each existing model offers a different aspect of the disease to study (Hall and Roberson 2012, 3-12). With each of these models offering a different advantage, the OBX rat's advantage is that it includes memory loss, cognitive deficits and neurodegeneration without the presence of the amyloid plaques. This may be advantageous for experiments that were designed to test for late stage Alzheimer's disease.

As for Traumatic brain injury, the currently available models mainly depend on recreating the physical impact to the animals in one way or another. These methods all share the problem that they are less reproducible than a surgical procedure and cannot be used to study only a part of the injury alone. It seems that the OBX rat model offers this advantage. It is highly reproducible due to the surgical nature of the bulbectomy and inflammation occurs only minimally. It is therefore worthy to investigate in full its pharmacologically predictive value with neuroprotective drugs as well as examine the possibility of partial mechanisms of neurodegeneration.

Finally, the golden hour in TBI has been a previously controversial topic due to a claim that the time limit is actually 60 minutes. However that does not take away the fact that the sooner a patients is under medical care after TBI the higher the chances are for a full recovery, depending of course on many other factors as well(Bledsoe 2002, 105). The OBX rat offers a unique advantage with its minimally inflamed cranial tissue and surgical reproducibility. It could offer a better understanding of the various

mechanisms involved in cognitive impairment caused by TBI. It could also be used to study different aspects of neuroprotective drugs that currently used TBI models do not offer.

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VI. Appendices

1. Appendix A: Antidepressants and other drugs shown to reduced OB activities in the open field test

Copied from:

The olfactory bulbectomized rat as a model of depression. Cai Songa, Brian E. Leonard. Department of Biomedical Science, AVC, University of Prince Edward Island and National Institute of Nutrisciences and Health, Charlottetown, Canada. Department of Pharmacology, National University of Ireland, Galway and Department of Psychiatry and Neuropsychology, University of Maastricht, The Netherlands.2005(Song and Leonard 2005, 627-647)

Antidepressants and other drugs shown to reduce OB activities in the open field test

Drug names	Classes	Dose (mg/kg)	Routes of treatments	References
Amitriptyline	Tricyclic antidepressant	10.0	i.p	Kelly et al. (1997)
Lofepramine	Tricyclic antidepressant	20.0–30.0	i.p	O'Connor and Leonard, 1988 and Kelly and Leonard, 1999
Desipramine	Tricyclic antidepressant	7.5–10.0	i.p	Paul and Purdy, 1992, Connor et al., 2000, Song and Leonard, 1997, Mudunkotuwa and Horton, 1996 and Kelly and Leonard, 1999
Imipramine	Tricyclic antidepressant	5.0	i.p	Stockert et al., 1988 and Otmakhova et al., 1992
Mianserin	Atypical antidepressant	2.0–5.0	i.p	Leonard and O'Connor (1987)
Tianeptine	Serotonin reuptake enhancers	2.5–5.0	i.p	Kelly and Leonard (1994)
Milnacipran	NE and 5-HT reuptake inhibitor	30.0	p.o	Redmond et al. (1999)
Trazodone	Serotonin reuptake inhibitor	50.0	i.p	Takeuchi et al., 1997 and Otmakhova et al., 1992
Moclobemide	monoamine oxidase A inhibotor	10.0	i.p	Kelly et al. (1997)
Nomifensine	NE and DA reuptake blocker	3.0	i.p	Bellver et al. (1990)
Fluvoxamine	Serotonin reuptake inhibitor	10.0	i.p	Song and Leonard (1994)
Reboxetine	NE reuptake inhibitor	10.0	i.p	Harkin et al. (1999)
Sertraline	Serotonin reuptake inhibitor	5.0–20.0	i.p	Song and Leonard, 1994b and Song and Leonard, 1994c
Venlafaxine	Serotonin reuptake inhibitor	7.5–20.0	i.p	Song et al., 2002 and McGrath and Norman, 1998
Fluoxetine	Serotonin reuptake inhibitor	10.0–30.0	i.p	Possidente et al., 1996 and Butler and Leonard, 1990
Paroxetine	Serotonin reuptake inhibitor	10.0	i.p	Cryan et al. (1998)
Lithium	Anti-manic antidepressant	3.0 mMol	i.p	Song and Leonard (1994)
Metyrapone	antiglucocorticoid	50	i.p	Healy et al. (1999)
Alnespirone	5-HT1A receptor agonist	10	i.p	McGrath and Norman (1999)
Flesinoxan	5-HT1A receptor agonist	1–3	s.c	Cryan et al. (1997)

Drug names	Classes	Dose (mg/kg)	Routes of treatments	References
Flibanserin (BIMT 17)	5-HT1A agonist and 5-HT2A antagonist	10	i.p	Borsini et al. (1997)
Yohimbine	[a]α-2 adrenoceptor antagonist	1.0	i.p	Jancsar
Sulpiride	[a]DA receptor antagonist	20.0	i.p	Kelly et al. (1997)
Adinazolam	[a]GABA agonist	2.5	i.p	O'Connor et al. (1985)
Progabide	[a]GABA agonist	150.0	i.p	Lloyd et al. (1987)
Rolipram	[a]Phosphodiesterase 4 inhibitor	0.5–1.0	i.p	Song et al. (2002)
NPY	[a]Neuropeptide	0.5 nMol	i.c.v	Song et al. (1996)
Interleukin-2	Cytokine	10 IU	i.c.v	Song and Leonard (1995)

i.p., intraperitoneal injection; s.c., subcutaneous injection, i.c.v., intracerebroventricular injection.

a

Drugs in these categories have not been established as antidepressants but there is clinical evidence to indicate that they have antidepressant activity.

2. Appendix B: Mouse models of AD

Copied from:

Mouse models of Alzheimer's disease. Alicia M. Hall, Erik D. Roberson. Center for Neurodegeneration and Experimental Therapeutics, Departments of Neurology and Neurobiology, University of Alabama at Birmingham, Birmingham, AL 35294, United States. 2012. (Hall and Roberson 2012, 3-12)

Representative mouse models of AD.

Tg line	Gene/isoform	Mutation	Promoter	Plaques (mo)	Cognitive deficits (mo)	Vendor number	Reference
hAPP models							
PDAPP	hAPP695 < 751,770[a]	Ind	PDGF-B	6–9	6	n.a.	[27], [41], [49],[73] and [110]
J20	hAPP695 < 751,770[a]	Swe, Ind	PDGF-B	6	4	JAX 006293	[114] and [126]
Tg2576	hAPP695	Swe	HamPrP	9	10	Taconic 1349	[5],[162] and [176]
APP23	hAPP751	Swe	Thy1	6 CAA: 12	3	n.a.	[21] and [91]
TgCRND8	hAPP695	Swe, Ind	HamPrP	3 CAA: 11	3	n.a.	[29] and [79]
TASD-41	hAPP751	Swe, Lon	Thy1	3 CAA: 7	6	n.a.	[140]
R1.40	hAPP YAC[a]	Swe	hAPP	14–15	16–17	JAX 005300	[66],[93] and [94]
Aβ Models							
BRI-Aβ42A	BRI-Aβ42	n.a.	MoPrP	3	?	JAX 007182	[106]
hAPP/PS1 models							
PSAPP	hAPP695	Swe	HamPrP	6	4	n.a.	[4], [40] and [67]
(Tg2576xPS1)	PSEN1	M146L	PDGF-B				
APPswe/PS1ΔE9	m/hAPP695[c]	Swe	MoPrP	6	6	JAX 004462	[82],[83] and [145]
	PSEN1	ΔE9	MoPrP				
5xFAD	hAPP695	Swe, Lon, Flo	Thy1	2	6	JAX 008730	[89], [118],[122] and [123]
	PSEN1	M146L, L28V	Thy1				
2xKI	m/hAPP[c]	Swe	mAPP	6	9–12	n.a.	[25] and [183]
	PSEN1	P264L	mPS1				
Models with hTau							
TAPP	hAPP695	Swe	HamPrP	8–15	Motor deficits	Taconic 2469	[100]
(Tg2576xJNPL3)	hTau-4R0 N	P301L	MoPrP				
3xTg	hAPP695	Swe	Thy1	6	4.5	JAX 004807	[12],[120] and [121]
	hTau-4R0 N	P301L	Thy1				
	PSEN1	M146V	mPS1				
vhtau	hTau PAC[d]	Wild-type	hTau	–	12	JAX 005491	[3],[44] and [128]

This list is not comprehensive, but includes important prototypes, some commonly used models, and those that are available from repositories and thus are most easily available.

A APP minigene expressing all three isoforms, mostly KPI-positive APPs.

B Yeast artificial chromosome, expressing entire human APP gene, including all isoforms.

C Humanized mouse APP, in which three amino acids in Aβ are changed to the human sequence.

D P1 artificial chromosome, expressing entire human tau gene, including all isoforms (H1 haplotype).