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Cognitive and emotional abnormalities in cerebellar mutant mice

Kognitivní a emoční abnormality u myších mozečkových mutantů

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CONTENTS

LIST OF ABBREVIATIONS

Agtpbp1 – ATP/GTP binding protein 1 gene [*Mus musculus*]

ATXN2 – human ataxin-2 gene [*Homo sapiens*]

ATXN2 – ataxin-2 protein [*Homo sapiens*]

CCP1 – cytosolic carboxypeptidase 1 (known as Agtpbp1)

GluR*δ2* – δ2 glutamate receptor

Grid2 – glutamate receptor δ2 gene [*Mus musculus*]

Lc – Lurcher

pcd – Purkinje cell degeneration mice

SCA2 – spinocerebellar ataxia type 2

SUMMARY

Hereditary cerebellar ataxias represent a heterogeneous group of neurodegenerative disorders. Variability of human hereditary ataxias is also reflected in animal models of cerebellar disorders. The most frequently used animal models are *Lurcher* and *Purkinje cell degeneration* (*pcd*) mutant mice.

The main aim of this thesis was to analyze and compare the spatial and emotional behavior of these cerebellar mutants. Additional aims were to study the impact of abnormal behavior on breeding capacity in *Lurcher* mice and to assess the applicability of cerebellar mutants as models for experimental therapy of cerebellar degeneration.

We have confirmed several behavioral impairments in both *Lurcher* and *pcd* mutant mice. Nevertheless, we have found that the manifestation of spatial behavior deficit is different in these two cerebellar mutants. Based on our findings, we propose that the deficit of spatial performance in cerebellar mutants may potentially arise from a combination of 1) cognitive disturbances, 2) sensory deficits, 3) motor impairments, and finally, 4) affective disorder. Moreover, resulting spatial behavior could also be modified by the specific effect of mutation, genetic background, and sex. We have also shown that abnormal behavior, e.g. maternal infanticide leads to decreased breeding capability in *Lurcher* females. Although we have shown that embryonic cerebellar grafts survive well in both *Lurcher* and SCA2 mice, the morphology of the graft did not promise any strong specific behavioral effects.

SOUHRN

Hereditární mozečkové ataxie představují heterogenní skupinu neurodegenerativních onemocnění. Variabilita dědičných ataxií je také reflektována v širokém spektru zvířecích modelů. Nejčastěji používanými jsou mutantní myši typu *Lurcher* a *Purkinje cell degeneration* (*pcd*).

Hlavním cílem této práce bylo analyzovat a porovnat prostorové a emoční chování u myší typu *Lurcher* a *pcd*. Dalšími cíli bylo zkoumat vliv abnormálního chování myší typu *Lurcher* na jejich reprodukční úspěšnost a ověřit využitelnost mozečkových mutantů jako modelů pro experimentální terapii olivocerebelární degenerace.

Výsledky této práce potvrdily řadu behaviorálních poruch u myší typu *Lurcher* a *pcd*. Nicméně ukázali jsme, že poruchy prostorového chování se u těchto mutantů liší. Na základě našich výsledků se domníváme, že deficit v prostorovém chování u mozečkových mutantů může vznikat kombinací těchto faktorů: 1) kognitivního deficitu, 2) senzorických poruch, 3) motorických obtíží a 4) afektivních změn. Výsledné projevy prostorového chování mohou být navíc dále determinovány specifickým efektem mutace, genetického pozadí a/nebo pohlavím. Ukázali jsme také, že abnormální chování, např. mateřská infanticida u samic myší typu *Lurcher* vede k jejich sníženému reprodukčnímu potenciálu. Navzdory dobré schopnosti embryonálního transplantátu přežívat v mozečku myší typu *Lurcher* i SCA2, morfologie transplantátu nenaznačovala žádný silný specifický behaviorálně-funkční efekt.

1 INTRODUCTION

Cerebellum, “little brain” in Latin, has always been seen as a distinct subdivision of the brain (Glickstein et al., 2009). It is located in the posterior cranial fossa, underneath the occipital and temporal lobes of the cerebral cortex. The internal organization of the mammal cerebellum is similar to the cerebral hemispheres. It consists of three major parts: 1) cortex, repeatedly folded around, 2) the four-pairs of cerebellar nuclei deeply buried 3) in the middle of cerebellar white matter.

The cerebellar cortex is functionally built from Purkinje cells that are large projection neurons, and several types of interneurons: granule cells, Golgi cells, stellate cells, basket cells, unipolar brush cells, Lugaro cells and candelabrum cells (Jaarsma et al., 1998; Laine and Axelrad, 1998; Voogd and Glickstein, 1998; Schilling et al., 2008). The three-layer cortex receives information from three extracerebellar afferent inputs: the mossy fibers, the climbing fibers, and diffusely organized monoaminergic and cholinergic afferents (Voogd and Glickstein, 1998).

Dysfunction of the cerebellum can manifest itself in terms of a variety of clinical signs. Usually the main motor signs are cerebellar ataxia, i.e. lack of motor coordination, kinetic tremor, passivity, dysmetria and oculomotor deficit (e.g. nystagmus, macrosaccadic oscillation). Furthermore, cerebellar affection is also manifested with cognitive inefficiency, and psychiatric disturbances (Schmahmann and Sherman, 1997; Schmahmann, 2004; Manto, 2005; Massaquoi, 2012).

The classification of ataxias (wide spectrum of progressive cerebellar disorders with ataxia as the leading

symptom) distinguishes between hereditary and non-hereditary ataxias. Hereditary ataxias are related to a genetic deficit and can be divided into four groups: autosomal dominant ataxias, autosomal recessive ataxias, mitochondrial ataxias, and X-linked ataxias (Brusse et al., 2007). The non-hereditary ataxias are separated into sporadic degenerative ataxias, such as multiple system atrophy, and acquired ataxias, such as alcoholic cerebellar degeneration (Klockgether, 2007).

Although there is increasing insight into the genetic and pathophysiological mechanisms underlying hereditary ataxias, therapeutic options modifying neurodegenerative process are still very limited (Brusse et al., 2007). One of the potential approaches to therapy of cerebellar degenerative disorders is neurotransplantation. Although this therapy still represents more likely experimental possibilities, there are first attempts to introduce this approach into human medicine (e.g. Wu et al., 1991; Lee et al., 2008; Tian et al., 2009).

The broad spectrum of human cerebellar degenerative disorders is also reflected in animal models of cerebellar ataxias (see reviews Lalonde and Strazielle, 2007; Manto and Marmolino, 2009; Cendelin, 2014). Mouse models are widely used to study symptoms, pathogenesis, and cell death mechanisms, as well as to develop and test therapeutic approaches for these diseases (Cendelin, 2014). For the purpose of this thesis, three mouse models of hereditary cerebellar ataxia will be reviewed. *Lurcher* mice represent a spontaneous semi-dominant mutation, *Purkinje cell degeneration* (*pcd*) mice represent a spontaneous recessive mutation and the mouse model of spinocerebellar ataxia type 2 (SCA2) represents transgenic dominant mutation.

Lurcher mice

Lurcher (*Lc*; Phillips, 1960) mice constitute the mutation (*Grid2*^{Lc}) in the δ2 glutamate receptor (GluRδ2) gene that changes the receptor into a leaky membrane channel, which chronically depolarizes the cell membrane (Zuo et al., 1997). GluRδ2 is expressed predominantly by Purkinje cells (Araki et al., 1993) and therefore, cell-autonomous degeneration of Purkinje cells is a primary effect of the mutation (Wetts and Herrup, 1982b, a). Extensive degeneration of Purkinje cells also induces retrograde degeneration of their primary afferents, granule cells and inferior olivary neurons (Caddy and Biscoe, 1975; Caddy and Biscow, 1976; Wilson, 1976).

Lurchers are characterized by ataxia (Fortier et al., 1987), spatial orientation impairments (Lalonde et al., 1988; Cendelin et al., 2008), changes in classical conditioning of eyelid response (Porras-Garcia et al., 2005) and alterations of anxiety-related behaviors (Hilber et al., 2004).

Lurcher mice are fertile and mating capable cerebellar mutants, but their breeding capacity is limited due to litter size reduction (Phillips, 1960). These mutants were also used as a model for the cerebellar neurotransplantation therapy (Dumesnil-Bousez and Sotelo, 1993; Tomey and Heckroth, 1993; Cendelin et al., 2009).

Purkinje cell degeneration mice

Pcd mice carry a mutation (*Agtpbp1*^{pcd}) that affects the *Agtpbp1* gene located on chromosome 13 (Fernandez-Gonzalez et al., 2002). *Agtpbp1* gene encodes the cytosolic carboxypeptidase 1 (CCP1) that belongs to the metallocarboxypeptidase gene family. The predominant

pathology in *pcd* mutants is the loss of Purkinje cells. The pathogenic process may be summarized as abnormal inclusions and organelles within the soma of Purkinje cells (for review see Wang and Morgan, 2007). The degeneration of Purkinje cells triggers a secondary loss of cerebellar granule cells and inferior olivary neurons (Ghetti et al., 1987; Triarhou, 1998). *Pcd* mutants also showed a degeneration of thalamic neurons (O'Gorman, 1985; O'Gorman and Sidman, 1985), mitral cells of olfactory bulb (Greer and Shepherd, 1982) and retinal photoreceptors (Blanks et al., 1982; LaVail et al., 1982).

The major neurological symptom of *pcd* mice is cerebellar ataxia (Mullen et al., 1976). Besides motor disabilities, *pcd* mice were impaired in spatial navigation task in the Morris water maze (Goodlett et al., 1992) and eyeblink conditioning (Chen et al., 1996).

The adult *pcd* females are fertile, but have difficulties in rearing the few litters they produce (Mullen et al., 1976). Male *pcd* mice are sterile, because they have reduced numbers of sperm that are abnormally shaped and non-motile (Mullen et al., 1976; Handel et al., 1988). A number of studies have shown that transplantation of wild type cerebellar primordia into the *pcd* mice either as cell suspensions (Sotelo and Alvarado-Mallart, 1986; Chang and Ghetti, 1993; Triarhou et al., 1995; Zhang et al., 1996) or as solid graft (Sotelo and Alvarado-Mallart, 1987a, b) can mitigate some aspects of the *pcd* phenotype.

Mouse model of spinocerebellar ataxia type 2 (SCA2)

Transgenic SCA2 mice carrying human ataxin-2 gene (*ATXN2*), with an enlarged CAG repeat sequence (Huynh et al., 2000). In SCA2, expansion of CAG triplets in the *ATXN2* gene causes expansion of polyQ domain in

ATXN2 protein (Dansithong et al., 2015). It is thought that the toxic gain-of-function protein aggregation affects RNA processing, resulting in degenerative processes affecting preferentially cerebellar neurons (Damrath et al., 2012).

The loss of the cerebellar Purkinje cells in SCA2 mice is accompanied by a progressive functional deficit. The rotarod test revealed significant differences in motor performance compared to the healthy littermates (Huynh et al., 2000; Aguiar et al., 2006; Dansithong et al., 2015). It seems that the morphological changes as well as motor decline in SCA2 transgenic mice was more severe in lines with longer CAG repeats (for review see Cendelin, 2014).

Although, SCA2 transgenic mice constitute an animal model of human pathology, there are only a few studies with a therapeutic approach (Liu et al., 2009; Chang et al., 2011).

2 AIMS

The general aim of this thesis was to contribute to the understanding of the cerebellar involvement in behavioral processes, particularly spatial behavior and the impact of cerebellar degeneration. For this purpose, mouse models of olivocerebellar degeneration were used. Most of this work was focused on the analysis of spatial and emotional behavior in *Lurcher* and *pcd* mutant mice. The second part of this thesis was to elaborate on the breeding capacity of *Lurcher* mice and the therapeutic potential of cerebellar mutants as models for experimental therapy of cerebellar degeneration.

The specific aims of this thesis were the following:

1) **Cognitive and emotional processing in *Lurcher* mice**

   To assess exploratory behavior of *Lurcher* mice
   To assess visual guidance and spatial learning of *Lurcher* mice
   To assess anxiety and depressive-like behavior of *Lurcher* mice

2) **Comparison of cognitive and emotional processing in *Lurcher* and *pcd* mice**

   To compare exploratory behavior of the mutants
   To compare visual guidance and spatial learning of the mutants
   To compare anxiety and depressive-like behavior of the mutants

3) Fertility and maternal behavior in *Lurcher* mice

To test fertility of *Lurcher* females
To test maternal behavior of *Lurcher* females

4) Experimental therapy in mouse models of cerebellar degeneration

To test applicability of mouse models of cerebellar degeneration in experimental therapy

3 RESULTS

3.1 List of original articles

1. Maternal infanticide and low maternal ability in cerebellar mutants *Lurcher*

Jan Tuma, Jan Cendelin and Frantisek Vozeh

Neuroendocrinology Letters 2013; 34(7): 618-623
[IF 0.799]

2. Mutation-related differences in exploratory, spatial, and depressive-like behavior in *pcd* and *Lurcher* cerebellar mutant mice

Jan Tuma, Yaroslav Kolinko, Frantisek Vozeh and Jan Cendelin

Frontiers in Behavioral Neuroscience 2015; 9: 116
[IF 3.270]

3. Morphological analysis of embryonic cerebellar grafts in SCA2 mice

Zdenka Purkartova, Jan Tuma, Martin Pesta, Vlastimil Kulda, Lucie Hajkova, Ondrej Sebesta, Frantisek Vozeh and Jan Cendelin

Neuroscience Letters 2014; 558: 154-158
[IF 2.030]

4. The effect of genetic background on behavioral manifestation of *Grid2*^{Lc} mutation

Jan Cendelin, Jan Tuma, Ivana Korelusova and Frantisek Vozeh

Behavioural Brain Research 2014; 271: 218-227
[IF 3.028]

5. Transplantation of embryonic cerebellar grafts improves gait parameters in ataxic *Lurcher* mice

Vaclav Babuska, Zbynek Houdek, Jan Tuma, Zdenka Purkartova, Jana Tumova, Milena Kralickova, Frantisek Vozeh and Jan Cendelin

Cerebellum 2015; 14(6): 632-641
[IF 2.717]

3.2 Abstracts

ARTICLE 1:

Tuma, J., Cendelin, J. and Vozeh, F. 2013: Maternal infanticide and low maternal ability in cerebellar mutants *Lurcher*. *Neuroendocrinology Letters* 34(7): 618-623.

ABSTRACT:

Objective: One of the common, but less studied deficiencies in mouse models of cerebellar disorders is impaired breeding capacity. Nevertheless, there is no extensive study in *Lurcher* (*Grid2*^{Lc}) mice, a model of olivocerebellar degeneration. The aim of this work was to analyze a breeding capacity of these mutants.

Methods: *Lurcher* females mated with healthy wild type males were compared with two control groups: wild type females mated with wild type males and wild type females mated with *Lurcher* males. The breeding capacity of *Lurcher* mice was analyzed using a fertility rate, mating capability and pups survival rate through three consecutive litters.

Results: *Lurcher* dams did not show significantly reduced fertility and mating capability. Nevertheless, their breeding capacity was affected by reduced litter size, maternal infanticide and higher pup mortality during the maternal care period.

Conclusion: *Lurcher* mice are fertile and mating capable cerebellar mutants, but their breeding capacity is reduced due to the postpartum behavioral abnormalities. With regard to hyper-reactivity of the hypothalamo-pituitary-adrenal axis followed by behavioral disinhibition during stressful events in *Lurcher* mutants, we hypothesize that the lower breeding capacity is associated with these endocrine and behavioral abnormalities.

ARTICLE 2

Tuma, J., Kolinko, Y., Vozeh, F. and Cendelin, J. 2015: Mutation-related differences in exploratory, spatial, and depressive-like behavior in *pcd* and *Lurcher* cerebellar mutant mice. *Frontiers in Behavioral Neuroscience* 9: 116.

ABSTRACT:

The cerebellum is not only essential for motor coordination but is also involved in cognitive and affective processes. These functions of the cerebellum and mechanisms of their disorders in cerebellar injury are not completely understood. There is a wide spectrum of cerebellar mutant mice which are used as models of hereditary cerebellar degenerations. Nevertheless, they differ in pathogenesis of manifestation of the particular mutation and also in the strain background. The aim of this work was to compare spatial navigation, learning, and memory in *pcd* and *Lurcher* mice, two of the most frequently used cerebellar mutants. The mice were tested in the open field for exploration behavior, in the Morris water maze with visible as well as reversal hidden platform tasks and in the forced swimming test for motivation assessment. *Lurcher* mice showed different space exploration activity in the open field and a lower tendency to depressive-like behavior in the forced swimming test compared with *pcd* mice. Severe deficit of spatial navigation was shown in both cerebellar mutants. However, the overall performance of *Lurcher* mice was better than that of *pcd* mutants. *Lurcher* mice showed the ability of visual guidance despite difficulties with the direct swim toward a goal. In the probe trial test, *Lurcher* mice preferred the visible platform rather than the more recent localization of the hidden goal.

ARTICLE 3

Purkartova, Z., Tuma, J., Pesta, M., Kulda, V., Hajkova, L., Sebesta, O., Vozeh, F. and Cendelin, J. 2014: Morphological analysis of embryonic cerebellar grafts in SCA2 mice. *Neuroscience Letters* 558: 154-158.

ABSTRACT:

SCA2 transgenic mice are thought to be a useful model of human spinocerebellar ataxia type 2. There is no effective therapy for cerebellar degenerative disorders, therefore neurotransplantation could offer hope. The aim of this work was to assess the survival and morphology of embryonic cerebellar grafts transplanted into the cerebellum of adult SCA2 mice. Four month-old homozygous SCA2 and negative control mice were treated with bilateral intracerebellar injections of an enhanced green fluorescent protein-positive embryonic cerebellar cell suspension. Graft survival and morphology were examined three months later. Graft-derived Purkinje cells and the presence of astrocytes in the graft were detected immunohistochemically. Nissl and hematoxylin–eosin techniques were used to visualize the histological structure of the graft and surrounding host tissue. Grafts survived in all experimental mice; no differences in graft structure, between SCA2 homozygous and negative mice, were found. The grafts contained numerous Purkinje cells but long distance graft-to-host axonal connections to the deep cerebellar nuclei were rarely seen. Relatively few astrocytes were found in the center of the graft. No signs of inflammation or tissue destruction were seen in the area around the grafts. Despite good graft survival and the presence of graft-derived Purkinje cells, the structure of the graft did not seem to promise any significant specific functional effects. We have shown that the graft is available for long-term experiments. Nevertheless, it would be beneficial to search for ways of enhancement of connections between the graft and host.

ARTICLE 4

Cendelin, J., Tuma, J., Korelusova, I. and Vozeh, F. 2014: The effect of genetic background on behavioral manifestation of *Grid2*^{Lc} mutation. *Behavioural Brain Research* 271: 218-227.

ABSTRACT:

Mutant mice are commonly used models of hereditary diseases. Nevertheless, these mice have phenotypic traits of the original strain, which could interfere with the manifestation of the mutation of interest. *Lurcher* mice represent a model of olivocerebellar degeneration, which is caused by the *Grid2*^{Lc} mutation. *Lurchers* show ataxia and various cognitive and behavioral abnormalities. The most commonly used strains of *Lurcher* mice are B6CBA and C3H, but there is no information about the role of genetic background on the *Grid2*^{Lc} manifestation. The aim of this work was to compare spatial navigation in the Morris water maze, spontaneous activity in the open field and motor skills on the horizontal wire, slanted ladder and rotarod in B6CBA and C3H *Lurcher* mutant and wild type mice. The study showed impaired motor skills and water maze performance in both strains of *Lurcher* mice. Both C3H *Lurcher* and C3H wild type mice had poorer performances in the water maze task than their B6CBA counterparts. In the open field test, C3H mice showed higher activity and lower thigmotaxis. The study showed that genetic backgrounds can modify manifestations of the *Lurcher* mutation. In this case, B6CBA *Lurcher* mice models probably have more validity when studying the behavioral aspects of cerebellar degeneration than C3H *Lurcher* mice, since they do not combine abnormalities related to the *Grid2*^{Lc} mutation with strain-specific problems.

ARTICLE 5

Babuska, V., Houdek, Z., Tuma, J., Purkartova, Z., Tumova, J., Kralickova, M., Vozeh, F., and Cendelin, J. 2015: Transplantation of embryonic cerebellar grafts improves gait parameters in ataxic *Lurcher* mice. *Cerebellum* 14(6): 632-641.

ABSTRACT:

Hereditary cerebellar ataxias are severe diseases for which therapy is currently not sufficiently effective. One of the possible therapeutic approaches could be neurotransplantation. *Lurcher* mutant mice are a natural model of olivocerebellar degeneration representing a tool to investigate its pathogenesis as well as experimental therapies for hereditary cerebellar ataxias. The effect of intracerebellar transplantation of embryonic cerebellar solid tissue or cell suspension on motor performance in adult *Lurcher* mutant and healthy wild-type mice was studied. Brain-derived neurotrophic factor level was measured in the graft and adult cerebellar tissue. Gait analysis and rotarod, horizontal wire, and wooden beam tests were carried out 2 or 6 months after the transplantation. Higher level of the brain-derived neurotrophic factor was found in the *Lurcher* cerebellum than in the embryonic and adult wild-type tissue. A mild improvement of gait parameters was found in graft-treated *Lurcher* mice. The effect was more marked in cell suspension grafts than in solid transplants and after the longer period than after the short one. *Lurcher* mice treated with cell suspension and examined 6 months later had a longer hind paw stride (4.11 *vs*. 3.73 mm, $P < 0.05$) and higher swing speed for both forepaws (52.46 *vs*. 32.79 cm/s, $P < 0.01$) and hind paws (63.46 *vs*. 43.67 cm/s, $P < 0.001$) than controls. On the other hand, classical motor tests were not capable of detecting clearly the change in the motor performance. No strong long-lasting negative effect of the transplantation was seen in wild-type mice, suggesting that the treatment has no harmful impact on the healthy cerebellum.

4 DISCUSSION

4.1 Spatial behavior

The main topic of this thesis was to assess a behavior deficit in two mouse models of olivocerebellar degeneration, *Lurcher* and *pcd* mice, with particular attention paid to their cognitive and emotional disturbances. Based on current knowledge, both mutants constitute a distinct type of mutation affecting the olivocerebellar system either exclusively (*Lurcher*) or inclusively (*pcd*) and determining a noticeable pathological phenotype.

Spatial behavior in *Lurcher* and *pcd* mice was tested using a Morris water maze (Morris et al., 1982; Morris, 1984; for reviews see D'Hooge and De Deyn, 2001; Wahlsten, 2011). Nevertheless, we also tested exploration and anxiety in the open field (Hall and Ballachey, 1932; Hall, 1934; for reviews see Walsh and Cummins, 1976; Wahlsten, 2011), as well as depressive-like behavior in the Porsolt's forced swimming test (Porsolt et al., 1977; Porsolt et al., 1978; Porsolt et al., 1979; for reviews see Wahlsten, 2011; Slattery and Cryan, 2012) to describe a complex behavioral profile and to avoid a misleading interpretation of results obtained from the Morris water task.

We have confirmed severe impairments in cognitive and behavioral tests in both *Lurcher* and *pcd* mutant mice (**Article 2**: Tuma et al., 2015). Contrary to previous studies (Goodlett et al., 1992; Lalonde and Thifault, 1994), we have shown that overall performance in the Morris water maze test was better in *Lurcher* than in *pcd* mutants (**Article 2**: Tuma et al., 2015). We have found that

navigation to the visible platform is only partially disabled in *Lurcher* mutants, but *pcd* mice failed in both visual and hidden goal tests (**Article 2**: Tuma et al., 2015). On the basis of these behavioral findings and the extent of cerebellar and non-cerebellar affections, we proposed that the poor performance of cerebellar mutants in the water maze task could be caused by at least four types of factors, alone or in combination: 1) cognitive disturbances, 2) sensory disorders, 3) motor deficits, and 4) motivation and behavioral abnormalities (**Article 2**: Tuma et al., 2015). The intensity of employment of these basic mechanisms in the individual mouse is determined by various factors, such as mutations, genetic background (strain), and sex (**Article 2**: Tuma et al., 2015; **Article 4**: Cendelin et al., 2014).

Nevertheless, based on our findings, we suggest that an inability to solve the Morris water task arises in both *Lurcher* as well as *pcd* mice from a disturbed and aimless behavior, though different in nature (**Article 2**: Tuma et al., 2015). We have shown that *Lurcher* mutants are able to reach the visible platform and remember its position for several days (**Article 2**: Tuma et al., 2015). Therefore, we suppose that motor disability and cognitive deficit play only partial roles in spatial disturbance in these animals. On the other hand, *pcd* mice suffer from wide spectrum of extracerebellar brain damage (see above) and therefore, their spatial behavior could reflect more functional disturbances.

4.2 Other behavioral abnormalities

We have shown that abnormal emotional processing and/or motor deficit could also lead to a higher incidence of maternal infanticide in *Lurcher* dams (**Article 1**: Tuma et al., 2013). Although some cerebellar mutants display

poor maternal behavior or a complete inability to rear offspring, e.g. *pcd* (Mullen et al., 1976), *staggerer* (Guastavino, 1984), *reeler* (Guastavino et al., 1993), and *nervous* mice (Sidman and Green, 1970), maternal aggression towards own offspring in *Mus musculus* has been described as rare (McCarthy and vom Saal, 1985; for review see Weber and Olsson, 2008). Nevertheless, it has been reported that maternal cannibalism in mouse dams is related to emotionality and higher susceptibility to stress (Poley, 1974; Reeb-Whitaker et al., 2001). Therefore, we have suggested that in *Lurcher* females, maternal infanticide could be potentiated by the inability to inhibit impulsive actions (**Article 1**: Tuma et al., 2013) due to their behavioral disinhibition (Hilber et al., 2004). These findings are also supported by our results from open field and forced swimming tests (**Article 2**: Tuma et al., 2015). Moreover, regarding similar studies in other cerebellar mutants, we have confirmed that cerebellar degeneration could affect a distinct type of behavior, such as maternal behavior (**Article 1**: Tuma et al., 2013).

We can also hypothesize that *Lurcher* mice show impaired social communication. It was found that Purkinje cell loss in *Lurcher* mice modulates dopamine release in the prefrontal cortex and affects higher level cognitive processes, which are commonly deficient in autism spectrum disorders (Dickson et al., 2010; Rogers et al., 2013). Therefore, it could be speculated that impaired social cognition and communication could induce inappropriate maternal behavior in *Lurcher* females and in this way, reduce their breeding capability.

4.3 Applicability for experimental therapy

We have shown that embryonic cerebellar cells have the potential to survive in SCA2 mice (**Article 3:**

Purkartova et al., 2014) as well as in *Lurcher* mice (**Article 5:** Babuska et al., 2015). Moreover, the transplantation of embryonic cell suspension into the *Lurcher's* cerebellum led to mild improvement in ataxic gait (**Article 5**: Babuska et al., 2015). However, the behavioral benefit that is observed in treated animals could be attributed to the trophic effect of grafted immature tissue, rather than rewiring of disrupted circuits (Mattsson et al., 1997; Rossi and Cattaneo, 2002).

In spite of the fact that partial functional motor recovery brought about by cerebellar transplants has been reported in *pcd* (Triarhou et al., 1995; for review see Triarhou, 1996, 1996; Zhang et al., 1996) and *Lurcher* mice (**Article 5**: Babuska et al., 2015), the effect of intracerebellar transplantation on complex behavioral functions (e.g. cognitive and emotional processing) has not yet been studied. From this point of view, neurotransplantation holds no promise to become a sufficient and primary therapy for cerebellar neurodegenerative diseases, but only an alternative or complementary strategy, which might include neuroprotective therapy, neurosurgical approaches, and physical rehabilitation (Rossi and Cattaneo, 2002).

5 CONCLUSION

We have confirmed several behavioral impairments in both *Lurcher* and *pcd* mutant mice. Nevertheless, contrary to previous studies (Goodlett et al., 1992; Lalonde and Thifault, 1994), we have found that the manifestation of spatial behavior deficit is distinct in these two cerebellar mutants. The spatial task in the Morris water maze is solved by different behavioral components (Whishaw, 1985; Whishaw and Mittleman, 1986; Whishaw, 1991), including general procedures, such as inhibiting nonadaptive behavior, procedural learning, processing of self-movement idiothetic cues, and spatial procedures based on allothetic cues (Whishaw et al., 1997). With regard to the role of the cerebellum in each of these processes (see above), we have shown that the distinct pathogenesis of cerebellar degeneration in *Lurcher* and *pcd* mice could lead to differential solving of spatial tasks. Based on our findings, we proposed that the deficit of spatial performance in cerebellar mutants may potentially arise from a combination of 1) cognitive disturbances, 2) sensory deficits, 3) motor impairments, and finally, 4) affective disorder (**Article 2**: Tuma et al., 2015). Moreover, the resulting spatial behavior could be also modified by the specific effect of mutation, genetic background, and sex (**Article 2**: Tuma et al., 2015; **Article 4**: Cendelin et al., 2014). All of these four partial processes are integrated in the cerebellum and therefore, it is very hard to distinguish between them in the all-embracing Morris water maze task during the analysis of spatial behavior in cerebellar mutants.

We have also shown that cerebellar degeneration in *Lurcher* mice could affect other distinct behavioral

attributes, such as maternal behavior, and could lead to decreased breeding capability in *Lurcher* females. We have hypothesized that increased maternal infanticide and a low pup survival rate in *Lurcher* mice could arise not only from their motor disabilities or lower body weight of dams but also from their affective disturbances (**Article 1**: Tuma et al., 2013).

Although we have shown that an embryonic cerebellar graft survives well in both *Lurcher* (**Article 5**: Babuska et al., 2015) and SCA2 mice (**Article 3**: Purkartova et al., 2014), the morphology of the graft did not promise any strong specific behavioral effects. Furthermore, intracerebellar transplantation had only mild positive effects on gait parameters in *Lurcher* mice (**Article 5**: Babuska et al., 2015). From this point of view, intracerebellar transplantation does not seem to be a very effective therapy for degenerative diseases, but may serve only as an alternative or complementary strategy.

6 ANNEXES

6.1 List of articles not included in the thesis

Barcal, J., Cendelin, J., Korelusova, I., Tuma, J. and Vozeh, F. 2010: Glutamate receptor block in Lurcher mutant mice during ontogeny and its effect on hippocampal long-term potentiation. *Prague Medical Report*; 111(2): 127-134.

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Farar, V., Mohr, F., Legrand, M., d'Incamps, B.L., Cendelin, J., Leroy, J., Abitbol, M., Bernard, V., Baud, F., Fournet, V., Houze, P., Klein, J., Plaud, B., Tuma, J., Zimmermann, M., Ascher, P., Hrabovska, A., Myslivecek, J. and Krejci E. 2012: Near-complete adaptation of the PRiMA knockout to the lack of central acetylcholinesterase. *Journal of Neurochemistry* 122: 1065-1080. [IF 4.281]

Jindrova, A., Tuma, J. and Sladek, V. 2012: Intra-observer error of mouse long bone cross section digitalization. *Folia Zoologica* 61(3-4): 340-349. [IF 0.724]

6.2 List of abstracts

Tuma, J., Patkova, J., Vojtisek, M. and Vozeh, F. 2010: Sub-chronic lead exposure does not impair spontaneous behaviour and spatial learning in adult wild type and Lurcher mutant mice (CIANS Abstracts – Prague 2009). *Activitas Nervosa Superior Rediviva* 51: 96-97.

Tuma, J., Kolinko, Y., Jelinkova, D., Soukup, P., Vozeh, F. and Cendelin, J. 2015: Role of stress in spatial task acquisition in mouse model of olivocerebellar degeneration (The 7th International Symposium of SRC – Brussels 2015). *Cerebellum* (DOI 10.1007/s12311-015-0723-3; in press). [IF 2.717]

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