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REVIEW

Twenty Years of Cerebellar Degeneration Research at the Department of Pathological Physiology, Faculty of Medicine, Pilsen, Charles University

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Summary

Mutant Lurcher mice represent an animal model of naturally occurring cerebellar degeneration. A gene mutation causes the demise of all Purkinje cells, as along with certain other types, as well as the functional elimination of the cerebellar cortex. Involvement in the research using this model of the C3H strain began at the Department of Physiology, UCL in 1995/96. It continued in scientific cooperation with other European laboratories where we obtained Lurcher mice of the B6CBA strain. The aim of the effort was first to identify the extent to which the cerebellum is involved in the higher nervous activity, i.e. cognitive and other functions. In that research, use was made of an entire array of methodological procedures to examine learning, memory, motor functions and emotional behavior. It was completed with an electrophysiological examination of the brain and special microscopic procedures. The results demonstrated that the cerebellum (aside from its traditional tasks) does in fact play a significant role in cognitive function, emotions, etc. It was further found that the neurodegenerative processes also affected the immune and endocrine functions, confirming the concept of the unity of the psycho-neuroendocrine-immune system. Surprisingly, despite their neurological impairment, the affected animals were able to learn to some extent and, make progress with physical training, improving not only their motor skills but also learning and memory, including deferring of signs of aging. These particular findings may prove useful for human medicine.

Key words

Lurcher mice • Cerebellar degeneration • Spinocerebellar ataxias • Neurotransplantation

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Introduction

The year 2017 marked 20 years since the Institute of Pathological Physiology of the Faculty of Medicine, Charles University in Pilsen, Czech Republic, launched consistent research of cerebellar degeneration on animal models. The Lurcher (+/Lc) mutant mice with which the research began are one of the animal models of naturally occurring cerebellar degeneration. In essence, these are heterozygous individuals, in which the cause of the impairment is a disappearance of practically all Purkinje cells and a major portion of granular cells in the cerebellum cortex, as well as a significant portion of the neurons in the inferior olive due to a genetic mutation (Phillips 1960, Caddy and Biscoe 1979). This causes an entire functional elimination of the cerebellar cortex and thus also of the regulation of all neural processes that the cerebellum normally significantly affects. Upon crossing a heterozygous individual with a healthy one, approximately half of the offspring in the nest are again +/Lc and the other half are healthy individuals of the wild

type (+/+), presenting an ideal control group.

The involvement of the research facility in using this model initiated at the Department of Physiology, University College London (UCL) in 1995-1996. Lurcher mice were obtained here of the C3H type. Then subsequent further scientific collaboration with a number of European laboratories continued through involvement with the EU COST Program in the area of neurosciences. Lurcher mice of the B6CBA strain were also obtained from the University of Brussels within this collaboration. The goal of the research was to identify the degree to which the cerebellum is involved in the higher nervous activity (cognitive and subsequently other functions) as well as to further explore the pathogenetic mechanisms of genetically conditioned cerebellar degenerations, including possibilities to affect them. The primary drivers for this experimental research were findings indicating that the cerebellum contains more neurons than the cerebral cortex (Glickstein 1992) as well as the excellent animal models of Lurcher mice available at UCL. Further publications released at the time confirmed that this direction for the research was correct. These studies gradually proved that the cerebellar pathways represent two-way connections to practically all main structures of the brain (Schmahmann 1996, Schmahmann and Pandya 1997, Middleton and Strick 2001). Further, they also began to prove that, aside from the traditional role in the area of motor skills and balance, the cerebellum also participates in cognitive functions, the formation of language, learning, memory, emotions and another processes (Schmahmann and Sherman 1997, Buckner 2013, Dennis and Schutter 2013, Malinová-Ševčíková *et al.* 2014, Tüdös *et al.* 2018). Thus, it became apparent that in case of the cerebellum, much as in other parts of the body, nothing is purposeless. It is also clear that the enormous volume of neurons that, in the case of humans, is now known to represent 80 % of all nervous cells in the brain (Herculano-Houzel 2010) and the numerous connections of the cerebellum with other nervous structures are not autotelic but form a high-performance functional potential.

Experimental procedures

At first, the experimental subjects of the ontogenetically focused research of cerebellar degenerations in animal models were the above-mentioned +/Lc, derived from two strains (CH3, B6CBA). Later, PCD (Purkinje cell degeneration) mice from similarly naturally formed mutants were included. Of the precise models of human spinocerebellar ataxias (SCA) artificially formed through genetic engineering methods, further experiments were performed with transgenic mice of the SCA1 and SCA 2 type.

In these experiments an entire array of both traditional and continually updated methodology processes were used for examining learning, memory, motor skills and emotional behavior. Electrophysiological examinations of the brain also contributed to important findings, along with variously conceived microscopic examinations. From the beginning, animals were tested in learning and memory (practically from the earliest age to maturity), using two methods of passive avoidance. The ‘step through’ version was used for animals from birth (P0) to (P10), and the ‘step down’ method for older and adult animals.

The standard Morris water maze method was used for testing spatial learning and memory. Various experiment protocols were used because, unlike in the case of previous avoidance methods, a motor skill impairment that gradually develops in impaired individuals does not play a role while swimming. A classic rotarod method (a test mouse sustaining being turned around a rod) served to examine motor function. The CatWalk (capable of evaluating up to 14 parameters at once) and DigiGait (forced motion on a treadmill belt) systems were used for the more detailed evaluation of walking skills.

In studying emotional behaviors, the ‘elevated plus maze’ method was used to establish anxiety levels. A special device system was used for the examination of excitability, capable of measuring degrees of startle response and evaluating prepulse inhibition. As mentioned, a number of valuable results were obtained using electrophysiological processes, including recordings of EMG, EEG, LTP (long-term potentiation of the hippocampus) and eye blink conditioning. Influencing of cerebral degeneration by neurotransplantation (embryonic cerebellar tissue or stem cells) or topical administrations of precisely defined substances were performed stereotactically. A number of experiments were then supplemented by microscopic examinations using a regular light microscope, as well as a fluorescent microscope and laser confocal fluorescent microscope.

Overview of knowledge obtained

Among the first results it is worth mentioning findings obtained back at the Department of Physiology

UCL, that, in the case of +/Lc, the neuron sensitivity of the inferior olive to neurotoxin 3-acetylpyridine is already notable in the early post-natal period, prior to their secondary degeneration (after the extinction of the Purkinje cells) (Caddy and Vožeh 1997). Later, in the first experiments already conducted in the pilsener laboratory, using both the methods of passive avoidance and, in particular, the Morris water maze, it was possible to initially prove and gradually confirm that the cerebellum, in fact, significantly contributes to cognitive functions (Vožeh *et al.* 1997, Vožeh *et al.* 1998, Vožeh *et al.* 1999, Vožeh *et al.* 2001, Cendelín and Vožeh 2002, Cendelín *et al.* 2003).

Interesting findings also regarded the development of motor functions. Here, it became clearly evident that, despite their neurological impairment, mutant mice are capable of learning to a notable degree and significantly improving their motor skill through gradual training, compared with untrained individuals (Křížková and Vožeh 2004). A further finding achieved which we considered very significant, is the fact that both in the case of +/Lc and +/+, forced motor activity had an additional positive effect on cognitive skills. Additionally, in trained animals of both groups, the negative effects of aging were delayed (Cendelín *et al.* 2007, Cendelín *et al.* 2008, Markvartová *et al.* 2010).

Among other interesting findings regarding Lurcher mice we must mention that, despite the exact same impairment, identical phenotype symptomatology as well as cerebellar histology (Purkartová and Vožeh 2013, Kolinko *et al.* 2016), strain differences appeared in a number of experiments. These were apparent not only in the +/Lc strains C3H and B6CBA, but also in +/+. This was particularly the case in spatial orientation and learning, but also partly in the development of motor skills. While in the Morris maze, individuals from the B6CBA strain were clearly the best; these differences were not as apparent in most motor-skill tests and, in some, the C3H mice performed better (Vožeh *et al.* 2002, Cendelín *et al.* 2014).

The differences given by the strain were also further proven in the monitoring of excitability and pain perception. Here, the excitability in both +/Lc strains was higher than in +/+, but both healthy and impaired animals of the C3H strain showed higher excitability compared with B6CBA individuals. The situation was slightly different in pain response where, in the 'tail flick' test, animals of the B6CBA strain had a significantly lower threshold compared with C3H mice. Even so, differences between healthy and impaired animals of both strains were not statistically significant. To the contrary, in the 'plantar' test, no significant strain differences were found. However, within the C3H strain, +/Lc individuals had a significantly lower pain threshold than the +/+ subjects (Vožeh *et al.* 2001).

Subsequently, strain differences were also identified when monitoring the pharmacological effects on mediator systems where, for example, SCH 23390 a D1 dopamine receptor antagonist negatively affected the ability of spatial learning in both types of mice (+/Lc and +/+) of the B6CBA strain, while the same effect only appeared in the +/+ group of the C3H animals (Cendelín and Vožeh 2001, Vožeh *et al.* 2002). Regarding the dopaminergic system, differences between +Lc and +/+ in both strains in the area of distribution of the D1 and D2 receptors were further identified. Here, the +/Lc strain of B6CBA showed a significantly higher density of both these receptors in the hippocampus. In the case of C3H animals, only the number of D1 receptors was increased. In the case of the +/Lc strain of B6CBA, D1 receptors had a lower density in the cerebellum, while D2 receptors were not impaired. In the striatum, the density of both receptors in the +/Lc mice was comparable to results of both strains of +/+ (Mysliveček *et al.* 2007).

In electrophysiologically focused experiments, were subsequently monitored the hippocampal LTP by affecting the availability of the gaseous mediator – nitric oxide (NO). Here interesting results were also achieved, including strain differences. Additionally, the effect of administration of L-arginine (L-Arg), a substrate for NO synthesis, and nitro-L-arginine (nL-Arg), an inhibitor of NO synthase (NOS), and their subsequent effects were monitored in adult animals of both types and both strains (+/Lc, +/+; C3H, B6CBA). In the case of animals of the +/+ strain of C3H, the administration of the NOS inhibitor significantly decreased the amplitude of LTP potentials, while the higher availability of NO (upon administering L-Arg) caused their significant increase. In the case of the +/Lc of the same strain, the identical effect was only notable upon the administration of NOS inhibitor, while the increase of NO availability (after L-Arg) remained without a response. The results in animals of the B6CBA strains were generally similar as in C3H individuals, however with the difference that administration of L-Arg paradoxically caused a decrease of LTP potentials in +/+ animals (Barcal *et al.* 2001).

Among other experiments with various

functional and morphological consequences of cerebellar degeneration in +/Lc mice, the findings obtained through a collaboration with histologists stand out. In this case, that this neurodegenerative process was also found to affect the immune and endocrine functions, which confirmed the concept of interconnection of the psycho-neuro-endocrine-immune system. Here, significant changes were observed in both immunocompetent (thymus, spleen, lymphatic nodes) and endocrine (both adrenal cortex and medulla) organs. Generally, these were changes in the sense of regression with signs of weakening function, here also with minor strain differences (Beranová *et al.* 2002, Vožeh *et al.* 2002, Vožeh *et al.* 2014). As was subsequently confirmed by more recent works, abnormal stress reactions were proven in +/Lc, undoubtedly related to the impairment of regulation on the HPA axis (hypothalamus – pituitary gland – adrenal glands) (Hilber *et al.* 2004, Tůma *et al.* 2017).

As mentioned above, our research on cerebellum degeneration began in a foreign laboratory and the international collaboration focusing on this subject then continued, as it does today. Results of the last two areas of the research, the overview of which is the main goal of this work, may serve as examples. The first are results achieved through collaboration with colleagues from the Pablo de Olavide University, Seville, Spain, regarding the contribution of the cerebellum to excitability and, particularly the participation of cerebellar nuclei in eye blink conditioning. This study also identified certain differences between +/Lc and +/+, particularly regarding the reflex response to electric stimulation, as an unconditioned stimulus. However, the effect of the lesion of the cerebellar interpositus nucleus, the participation of which on the conditioning of this reflex is without a doubt, was comparable in both types of animals. Nonetheless, some electrophysiologically registered signs of compensation of the missing neurons in the cerebellar cortex were found in the case of +/Lc (Porras-Garcia *et al.* 2005, Porras-Garcia *et al.* 2010).

The last significant activity, on which the research was focused over ten years, was the effort to affect various types of cerebellar degenerations through neuro-transplantations. The activity in this field was launched at the Department of Neuroscience and Rita Levi Montalcini Centre for Brain Repair, University of Turin, Italy, in the laboratory of Professor Rossi. The processes of the embryonic cerebellar tissue transplantations were then transferred from Turin to the laboratory of the Department of Pathophysiology in Pilsen.

A transplant was introduced to the impaired as well as healthy individuals, either as a solid particle of an embryonic tissue or as a suspension of embryonic, stem and other cells. So, thus both mice of the B6CBA and C3H strains were affected, as well as the PCD and SCA2 mice (Cendelín *et al.* 2009, Houdek *et al.* 2011, Houdek *et al.* 2012, Cendelín 2014). The period of survival of the transplant was monitored, along with its morphology, in different periods after the transplantation and functional effects (Cendelín *et al.* 2012, Purkartová *et al.* 2014, Babuška *et al.* 2015, Cendelín 2016).

Conclusions

Despite certain difficulty in transposing the experimental finding into human medicine, it must be stated that some experimental findings can be applied to humans. First, it should be stressed that in case of existing neurological impairment, its impacts could be positively affected. An example is the above mentioned (forced) physical activity that significantly improved not only motor skills but also cognitive functions. It is no less important that this effect was equally apparent in both impaired individuals and control groups. It also proved to significantly defer negative effects of aging in both the area of motor skills and cognition, both in impaired and control healthy mice.

Transposed to humans, these experimental findings confirm the enormous significance of rehabilitation in case of most neurological defects, whether congenital or acquired. The positive effect of physical activity on the improvement of motor skills, as well as cognitive functions and overall psychological condition, is particularly encouraging.

The remaining problem is the prevention of the development of congenital, in our case cerebellar, degenerations. Pharmacotherapy certainly represents some options, but without hope on a success, also are not above mentioned neurotransplantation.

Nevertheless, despite certain evident improvements, these cannot currently be recommended as a treatment method, because the effect was not always convincing and was often likely caused by the effect of stimulation of formation of endogenic or transplant-supplied substances, such as growth factors (Vožeh 2015, Cendelín *et al.* 2018).

An additional problem also remains in the fact that cerebral tissue affected by neurodegeneration

(although not in all models used) is not very favorable for graft transplantation, unlike the environment that is more receptive in healthy tissues. However, neurotransplantation that produces more promising results in other neurodegenerations (e.g. Parkinson's disease) remains a significant therapeutic hope for human spinocerebellar ataxias as well.

Conflict of Interest

There is no conflict of interest.

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