Jan Evangelista Purkyně and the cerebellum then and now

Vožeh, F.[1,2]

[1] Department of Pathophysiology, Faculty of Medicine in Pilsen, Charles University, Pilsen, Czech Republic

[2] Laboratory of neurodegenerative disorders, Biomedical Centre, Faculty of Medicine in Pilsen, Charles University, Pilsen, Czech Republic

Author´s address:

Department of Pathophysiology, Faculty of Medicine in Pilsen, Charles University,
323 00 Plzeň, Alej Svobody 1655/76, Czech Republic

Summary

The name of Jan Evangelista Purkyně and the cerebellum belong inseparably together. He was the first who saw and described the largest nerve cells in the brain, de facto in the cerebellum. The most distinguished researchers of the nervous system then showed him the highest recognition by naming these neurons as Purkinje cells. Through experiments by J. E. Purkyně and his followers properly functionally was attributed to the cerebellum share in precision of motor skills. Despite ongoing and fruitful research, after a relatively long time, especially in the last two decades, scientists had to constantly replenish and re-evaluate the traditional conception of the cerebellum and formulate a new one. It started in the early 1990s, when it was found that cerebellar cortex contains more neurons than the cerebral cortex. Shortly thereafter it was gradually revealed that such enormous numbers of neural cells are not without an impact on brain functions and that the cerebellum, except its traditional role in the motor skills, also participates in higher nervous activity. These new findings were obtained thanks to the introduction of modern methods of examination into the clinical praxis, and experimental procedures using animal models of cerebellar disorders described below.

Key words

Animal models, Ataxia, Cerebellum, Neurodegenerations, Purkinje cells,

Jan Evangelista Purkyně was the most formidable figure in Czech physiology on the world who brought many scientific discoveries into the biological, physiological and biomedical sciences. Among the systems to which he paid attention it was mainly the nervous system and especially the cerebellum. J. E. Purkyně was the first scientist to see and describe the largest nerve cells in the brain, de facto in the cerebellum. He hand-illustrated them at his memorable lecture to the professional public in Prague in 1837. Moreover Purkyně depicted and precisely described the individual three layers of the cerebellar cortex when the largest neurons were named ganglial bodies (Druga 1986). Later, S. R. y Cajal (1911), one of the most distinguished researchers of the nervous system, recommended in his monumental monography to designate these large neurons according an author who described them for the first time. Since that time also other researchers used this eponyme and the Purkinje cells (in English-language texts) represent one of the most cited scientific terms in the neuroscientific literature and the name Purkyně is inseparably connected with the cerebellum. On the basis of experiments with animals of many species (sheep, rabbits, chickens, pigeons, ortolans, fish) and also by examination of human brains J. E. Purkyně (Valentin 1836, Druga 1986, Rokyta 2011) and later his followers (Friede 1963, Eccles et al. 1967, Szentagothai 1968, Ito 1970, 1972, 1984, Palay, Chan-Palay 1974) attributed to the function of the cerebellum a share in the control and precision of motor skills. Despite their enormous scientific discoveries the cerebellum resisted for some time further knowledge even though it prepared for another surprise. The first relevation came in the early 1990s, when it was found that cerebellar cortex contains more neurons than the cerebral cortex (Glickstein 1992) and that the cerebellum has bidirectional connections with almost all significant structures of the brain (Schmahmann 1996, Schmahmann and Pandya 1997, Middleton and Strick 2001, Ito 2006). Shortly thereafter it was revealed that such an enormous number of nerve cells as well as functionally highly potential cerebellar connections exert some impact on brain functions. Shortly thereafter it was confirmed that the cerebellum, except its traditional role in the precision of motor skills, also participates in the higher nervous functions (Buckner 2013).

Functional and morphological characteristics of the cerebellum

The cerebellum is a brain structure well known even to people not educated in biology or biomedical science. This is first of all thanks to its beautiful texture which resembles the Biblical tree of life or Arbor vitae (in Latin). And, of course, Purkinje cells with their shrubby dendrites belong to the most beautiful creations of living nature of all.

As a part of the hindbrain (rhombencephalon) the cerebellum is localized in the posterior part of the cranial cavity, behind the pons and medulla oblongata. The surface of the cerebellum is formed by vermis, paravermal zones and hemispheres. From a functionally-developmental point of view, the cerebellum consists of three lobes. Flocculonodular lobe (archicerebellum, vestibulocerebellum), smallest and phylogenetically oldest component of the cerebellum, situated at its bottom part. It receives afferentation from the vestibular nerve and nuclei, and is responsible for balance and posture.

The anterior lobe (paleocerebellum, spinocerebellum) is a phylogenetically younger part of the cerebellum and represents 1/3 of its hemispheres. Afferentation comes mainly from the spinal cord and enables the spinocerebellum to be responsible for muscular tonus.

The posterior lobe (neocerebellum, pontocerebellum), the largest and developmentally youngest part of the cerebellum with afferentation from the neocortex, is responsible for the coordination of movements, motor stereotypes and also participates in higher nervous activity.

The bidirectional communication of the cerebellum with the brainstem and other parts of the CNS provide the three pairs of the cerebellar peduncle: the inferior, which contain both afferent and efferent fibres; the middle, with afferent fibres coming from the nuclei pontis, and the superior which consist mainly from efferent fibres from the deep cerebellar nuclei (Kandel et al. 2000).

The cerebellar cortex is composed of gray matter, which is largely folding so that the cerebellar surface is formed by transverse folia (which in sagittal sections resemble above mentioned Arbor vitae). This is the reason that 85 % of the surface is hidden, despite the size of this area being fully comparable to the cortical area of the big brain. The cerebellar cortex consists of three layers viewed from the surface: the molecular layer, the Purkinje cell layer and the granule cell layer (deepest) (Kandel et al. 2000). The input to the cerebellum comes via the mossy fibers and via the climbing fibers. Both of these are glutamatergic (excitatory). Nevertheless synapses between cerebellar cortical interneurons and Purkinje and granule cells are GABAergic (inhibitory). Also the output from Purkinje cells to the deep cerebellar nuclei is GABAergic. Therefore the functional effect of the cerebellum on the other part of the CNS is inhibitory (Danbolt et al. 2004).

Under the gray matter the central part of the cerebellum is composed of white matter - medulla, which consists of nervous fibres. Inside of the cerebellar hemispheres there are four pairs of cerebellar nuclei embedded in the medullary center. From the midline to the lateral side there are: the fastigial nucleus, the globose nucleus, emboliform nucleus and the largest of them, the dentate nucleus. The input to the cerebellar nuclei comes from the Purkinje cells

(they represent the only output from the cerebellar cortex) and from sources outside the cerebellum (pontocerebellar, spinocerebellar, and olivocerebellar fibres, together with fibres from reticular nuclei). Most of these afferents are collaterals of fibers proceeding to the cerebellar cortex. A few rubrocerebellar fibers end in the globose and emboliform nucleus, and the fastigial nucleus receives afferents from the vestibular nerve and nuclei. The outputs from the cerebellar nuclei go to the brain stem (from fastigial nucleus through the inferior cerebellar peduncle descending through the reticular formation and the lateral vestibular nuclei to the spinal cord and ascending through ventrolateral nucleus of the thalamus to the primary motor cortex). Efferents from the other nuclei leave the cerebellum through the superior peduncle and terminate in the brain stem and neurons of the ventral lateral nucleus of the thalamus projecting to the limb areas of motor cortex (Barr and Kiernan 1988, Kandel et al. 2000).

Although the human cerebellum represents only 1/10 of the whole brain volume, recent research has shown, that number of neurons in this structure represents 80 % of all neurons in the brain. Except humans the same situation is valid for agouti and galago, whereas e.g. in the mouse the cerebellum holds 60 %, in rat, guinea pig and macaque it represents 70 % of all brain neurons (Herculano-Houzel 2010). Because such huge functional potential was not surprising, that except its traditional role in maintaining balance, posture control and motor function, the cerebellum participates in cognition, language, learning, memory and emotions which is a core of the new cerebellar conception (Buckner 2013, Dennis and Schutter 2013). Within the framework of this conception, it is possible to sum up that the cerebellum receives sensory and predictive stimuli, which include signals from receptors of muscles, tendons and joints (proprioceptors). These then integrates with motor commands so that it leads to precise control of movements and proper modulation of cognitive-emotional activities (Dennis and Schutter 2013).

The cerebellar disorders and methods of examination and research of the cerebellum

The cerebellar disorders include mainly motor deficits but also mental and behavioral abnormalities.

Inhibitory cerebellar syndrome as a consequence of the destruction of this structure (due to injuries, ischemia, hemorrhage, tumors, inflammation, intoxication and inherited neurodegenerative conditions) is characterized by:

- increased muscle passivity and weakness, intention tremor and ataxia

- asynergy and hypermetry of movements (lack of movements coordination and overreaching the intended object or goal)
- adiadochokinesia (inability to perform rapid alternating movements)
- speech disorders (slow, incoherent, slurred) (Kandel et al. 2000).

Mental and behavioral abnormalities in the cerebellar disorders are known in humans as cognitive-affective syndrome, which is typical with:

- deficit in the formation of words,
- diminished ability of planning and abstraction,
- disorder of working memory,
-altered personality with blunted emotions and inappropriate behavior (Schmahmann and Sherman 1997).

There are also evidence for a probable pathogenetic connection with schizophrenia (findings of small vermis and asymmetric hemispheres in these patients) and with autism (Andreasen and Ronald Pierson 2008, Fatemi et al. 2012).

Less frequent are the cerebellar disorders characterized by the so-called
irritative cerebellar syndrome, which represents abnormalities in the sense of hyperfunction due to pathologic irritation. It is characterized by:

- muscle hypertonia
- resting tremor
- flexion posture
- hypokinesia

These symptoms resemble the hypertonic-hypokinetic syndrome in parkinsonism (Záhlava 1994, Kishore et al. 2014). Here is useful to stress, that unilateral cerebellar lesions cause functional disorders on the ipsilateral side in contrast to cerebral defects when motor abnormalities are contralateral. The reason is crossing of both the cerebellar (decussation of the superior cerebellar peduncle) and cerebral (cross in the rubrospinal and corticospinal systems) pathways (Kandel et al. 2000).

It is obvious that the knowledge for formulation of the new conception of the cerebellum would not be obtained without incredible effort of clinical and experimental researchers, and of course, thanks to modern devices as well as the introduction of new special clinical and laboratory methods put into praxis.

Clinical and neuro-imaging procedures

Clinical medical examination of the cerebellar function is made mostly in persons suspected of alcohol intake as a complement to the blood alcohol determination or/and as a preliminary neurological examination before further diagnostic procedures. It involves the assessment of posture and gait with eyes closed, coordination and accuracy of movements, quality of speech and handwriting. Further, common studies with psychologists on cerebellum-injured patients have reported e.g. deficits in generating words, performing tasks requiring anticipatory planning and the occurence of dysgraphia and agrammatism (Fiez et al. 1992; Silveri et al. 1994, Schmahmann 1996, Leggio et al. 2008). Very significant progress both in diagnostics and research was then done thanks to the introduction of modern imaging methods e.g. PET and MRI (positron emission tomography and magnetic resonance imaging). Using these methods, for example, the participation of the cerebellar dentate nucleus in tasks related to planning was proved in healthy subjects tested in procedural learning abilities (Kim et al. 1994; Van Mier et al. 1998, 2002, Sharma et al. 2015).

The experimental research on animals

Experiments on animals play irreplaceable role in neuroscience research. In particular the use of animal models of cerebellar disorders has brought valuable insights into the physiology and pathophysiology of the cerebellum (Akita et al. 2009, Manto and Marmolino 2009, Ebner et al. 2013). The first was the confirmed participation of the cerebellum in different types of learning and memory (Bickford 1993, Lalonde et al. 1993, 1996, Cendelín et al. 2008, Hilber and Caston 2001, Křížková and Vožeh 2004; Thullier et al. 1997; Vožeh et al. 1997, 1999, 2001). Also some pathogenetic mechanisms of cerebellar disorders were clarified including the possibilities of influencing them (e.g. by means of non-invasive procedures, forced motor activity, enriched environment, pharmacologically or by transplantation of embryonic cerebellar tissue as well as stem cells). It was possible thanks to a battery of sophisticated behavioral tests, electrophysiological investigation together with use not only classic neuro-histological procedures but also modern immunofluorescence methods (Cendelín and Vožeh 2013, Purkartová and Vožeh 2013).

There are two groups of these models of various cerebellar dysfunctions, known also in human beings, used in this research

1) mouse models derived from naturally arising mutations in genome of individuals that were then further bred and prepared for experimental research.

2) mouse models that were developed by means of genetical engeneering procedures as transgenic animals which have to be treated according to rules for the manipulation with genetically modified organisms (GMO).

1) Naturally arising animal models

Lurcher mutant mice

Lurcher mice represent the first described mutant animal of the 1st group (Phillips 1960 4 Fmtom), gradually derived from four strains (DBA, C57B6, C3H, CBA). The mice suffer from olivocerebellar degeneration due to semi-dominant spontaneous mutation *Grid2*^{Lc} in the gene for delta 2 glutamate receptor localized on chromosome 6 (Zuo et al. 1997, De Jager et al. 1997). Heterozygous animals (+/Lc) exhibit almost complete postnatal loss of Purkinje cells and significantly decreased the number of granule cells and inferior olive neurons (ION) during 3 postnatal months (PM). The death of Purkinje cells is a type of excitotoxic apoptosis (Norman et al. 1995, Zuo et al. 1997, Selimi et al. 2000, Purkartová and Vožeh 2013) due to an inborn mutation. Nevertheless, some features are present which indicate necrotic cell death (Dumesnil-Bousez and Sotelo 1992, Dusart 2006) and autophagy (Wang et al. 2006). It means that multiple Purkinje cell death pathways play role in Lurchers (Nishiyama and Yuzaki 2010, Zanjani et al. 2013). The degeneration of granule cells and ION is a consequence of the lost target of their axons (Purkinje cells) similarly, as described below, decrease of cerebellar interneurons (Golgi, stellate and basket cells) (Zanjani et al. 2006). Homozygous Lurcher mice die shortly after birth due to massive loss of brain-stem neurons during late embryogenesis. Homozygous wild type littermates of Lurcher mutants (+/+) represent about one half of newborns in the litter. They are completely healthy and serve as ideal controls. Degeneration of the deep cerebellar nuclei is relatively mild in Lurchers (Heckroth 1994, Sultan et al. 2002). Functionally, the Lurchers suffer from multiple neural problems. Except ataxia, which is more or-less a common symptom of all cerebellar ataxic mice, they exhibit higher excitability, impairment of learning and memory, higher stress response and worse maternal behaviour (Lalonde et al. 1988, Lalonde and Thifault 1994, Frederic et al. 1997, Tuma et al. 2013, Caston et al. 1998, Hilber et al. 2004). Further, the Lurcher mice exhibit a lower resistance of ION against neurotoxine 3-acetylpyridine already before the Purkinje cell degeneration starts (Caddy and Vožeh 1997). There were also described changes in classical

eylid conditioning in Lurchers (Porras-Garcia et al. 2005, 2010). Nevertheless, they are capable of learning to a certain degree both cognitive and motor tasks. This was proven in spatial memory using the Morris water maze but also with some motor tests whereby significant improvement was observed in trained animals (Lalonde et al. 1993, Lalonde et al. 1996, Hilber and Caston 2001, Křížková and Vožeh 2004). Also the positive effect of forced motor activity was evident in motor and cognitive functions in generam, and especially in the impact on age dependent decline of these abilities (Cendelín et al. 2008, Cendelín and Vožeh 2013).

Purkinje cell degeneration mice

Purkinje cell degeneration (pcd) mutants mice are similar to Lurchers, characterized by autosomal recessive Agtpbp1pcd/J mutation in the gene encoding cytosolic ATP/GTP binding protein 1(cytosolic carboxypeptidase-like protein, CCP1) on chromosome 13 (resulting in lack of this protein) (Mulen et al. 1976, Fernandez-Gonzalez et al. 2002). Therefore the pcd mice are homozygous. They exhibit almost a complete loss of Purkinje cells at the end of 1st postnatal month (PM) (Mullen 1976) and their death is of apoptotic origin together with autophagy (Kyuhou et al. 2006, Chakrabarti et al. 2009, Berezniuk and Fricker 2010). The animals suffer also from progressive extinction of 90 % of the granule cells (between PM 3 – 20 %) because of the loss of their target – Purkinje cells (Ghetti et al. 1987, Triarhou 2010). Probably due to the missing input from Purkinje cells there is also about a 20% reduction of the deep cerebellar nuclei (in PM 10) (Triarhou et al. 1987). At PM 10 is also present a significant decrease (almost 50 %) of ION as a cosequence of the lost Purkinje cells, their target. Except for these defects, these mice are affected by degeneration of retinal photoreceptors (Blanks et al. 1982, 1992, LaVail et al. 1982), bulb mitral olfactory neurons and selected thalamic neurons (O'Gorman and Sidman 1985). In addition, there is also defective spermatogenesis, which results in the pcd males being sterile (Kim et al. 2011). Except the cerebellar ataxia, pcd mice exhibit subtle habitus and poor health. Functionally they show worse performance in the rotarod, coat-hanger tests but also in stationary beam (Le Marec and Lalonde 1997). In the Morris water maze they are unable to successfully navigate to the hidden platform compared to reaching a visible goal where they are better (Goodlett et al. 1992). The pcd mice are impaired in the delay eye-blink classical conditioning when compared with wild type controls (Chen et al. 1996), while in trace eye-blink conditioning there were no differences between them (Brown et al. 2009). The results indicate that the

essential neural circuitry for trace conditioning bypasses the cerebellar cortex and differs from the one for classical eye blink conditioning.

Staggerer mice

The Staggerers, simillarly like the pcd mice suffer from an autosomal recessive mutation (Rora^{sg}) in the gene encoding the retinoid-related orphan receptor alpha on chromosome 9 (Hamilton et al. 1996). They are characterized by a staggering gait, hypotony tremor, smaller body size and except for Purkinje cells also granule cells and ION degeneration is present. At the end of PM 1, 60-90 % of Purkinje cells are missing (in dependence on region), likewise more than 90 % of granule cells and about 60 % of ION (Landis and Sidman 1978, Herrup and Mullen 1979, Blatt and Eisenman 1985). Despite a 30% reduction in the volume of the deep cerebellar nuclei, the number of neurons remains unchanged (Roffler-Tarlov and Sidman 1978, Roffler-Tarlov and Herrup 1981). The development of Purkinje cells in Staggerer mice is characterized by a delayed growth of their spines and surviving Purkinje cells exhibit smaller somata and dendritic trees (Landis and Sidman 1978, Herrup and Mullen 1979).

Hot-foot mutant mice

Hot foot mice are characterized by autosomally recessive mutation in the gen for delta 2 glutamate receptor (Grid 2ho) localized on chromosome 6 which is identical with the one in Lurcher mutants (Lalouette et al. 1998). They display defective presynaptic inervation of Purkinje cells due to ectopic spine and partial necrotic loss of granule cells. They suffer from ataxia with typically irregular movements of hind limbs (as walking on a hot plate) (Guastavino et al. 1990). Hot-foot mutants further exhibit poor performance in the rotating grid, wooden beam, coat-hanger, rotarod tests and also in Morris water maze (Lalonde et al. 1996). Neverheless, they are capable of partial learning in the rotating grid and coat hanger tests (Lalonde et al. 1995, 1996, 2003).

Nervous mice

Nervous mice represent autosomal recesive mutants who suffer from severe degeneration of Purkinje cells and ION. The nervous mutation (nr) is located on chromosome 8 (Campbell and Hess 1996, De Jager et al. 1998). Purkinje cells exhibit abnormally rounded mitochondria (Landis 1973) and 90 % of them undergo to necrotic degeneration. About 10 % of Purkinje cells survive. Nevertheless 1/3 of ION die by retrograde degeneration because of the lost of their target. Nervous mutants are typical with ataxia and hyperactivity (Lalonde and Strazielle

2003) and they display bad performance in the beam, coat-hanger and rotarod tests. In the Morris water maze, they fail in experiments with the hidden platform but not in those with a visible goal (Lalonde and Strazielle 2003). Nervous mice also suffer from retinal regeneration which is in early postnatal period prompt but then slows down with an almost complete loss of photoreceptors in PM 17 (Mullen and LaVail 1975, LaVail et al. 1993).

Weaver mice

Weaver mice are affected by autosomal semidominant Grikwv mutation in the gene (encoding a G-protein) located on chromosome 2 (Patil et al. 1995). The consequences of the mutation result in an impairment of the cerebellar and some extracerebellar structures. In contrast to other mutants described, there mainly cerebellar granule cells suffer from apoptotic degeneration, while Purkinje cells are relatively unimpaired (Migheli et al. 1995, Wullner et al. 1995). Weaver homozygous have 72 % and heterozygous up to 86 % of the normal number of Purkinje cells when ION in both of them are actually intact (Blatt and Eisenman 1985). On the other hand, homozygous Weaver mutants exhibit 23 – 25% decrease in the number of deep cerebellar nuclei neurons (Maricich et al. 1997). Except the cerebellum there were still further described: the degeneration of dopaminergic neurons in the substantia nigra together with a decreased concentration of dopamine in the nucleus caudatus and in the striatum (Roffler-Tarlov and Graybiel 1984). Morphological changes (thickening of the pyramidal cell layer) were observed in the hippocampus of Weaver mice. From the functional point of view the Weaver failed in the spatial learning in the Morris water maze, and they also had lower exploratory activity as well as worse performance on the wooden beam and grid tests. Just like some other cerebellar mutant mice (e.g. pcd mice) the Weaver homozygous males are sterile due to the death of germ cells in their testes.

Reeler mice

Reeler mice are typical for autosomal recessive mutation in the gene encoding extracellular matrix protein reelin, which is important for neural cell migration (D´Arcangelo et al. 1995). This mutation located on chromosome 5 leads to abnormal migration of neurons during brain development (Beckers et al. 1994). There are therefore ectopic cell localizations not only in the cerebellum (Hamburgh 1963, Terashima et al. 1983), but also in some other brain structures (hippocampus, neocortex, inferior olive, olfactory bulb, superior colliculus, substantia nigra) (Mikoshiba et al. 1980, Wyss et al. 1980, Kang et al. 2010). In homozygous Reeler mice, the cerebellum is reduced in size (Mariani et al. 1977) with Purkinje cells

reduced to less than half the normal amount, but only about 5 % of them are localized normally. About 10 % of Purkinje cells are placed within the granular layer while, some granule cells are located in the molecular layer (Terashima et al. 1985, Heckroth et al. 1989). Also the inferior olivary complex is reduced in size by 22.6 %. Despite all these abnormalities, the specificity of the cerebellar connections is mostly preserved (Mariani et al. 1977). Functionally the Reeler mice exhibit poor performance in the active avoidance task, water maze, wooden beam, coat-hanger and rotarod tests (Lalonde et al. 2004). The lower neurogenesis rates together with a higher inclination to ischemic brain injury and epilepsy were described in Reeler mice (Patrylo et al. 2006, Won et al. 2006). Because of special behavioral abnormalities in heterozygous Reeler mice, some authors suggest considering them as a model of schizophrenia (Costa et al. 2002, Schmitt et al. 2013).

Scrambler mice

Scrambler mice are characterized by the spontaneous autosomal recessive scrambler mutation (Dab1scm-3J) in the gene on chromosome 4 (Sweet et al. 1996). The cerebellum is reduced in size already in 1M old homozygous mice. The number of Purkinje cells is decreased and only 5 % of them are normally located. The number of granule cells is reduced by 80 %. Despite these abnormalities, the cerebellar afferent systems are preserved (Goldowitz et al. 1997). Homozygous Scrambler mice display ataxia and whole body tremor as early as the 2nd postnatal week. From the functional point of view, they exhibit poor performance in the rotarod, wooden beam and coat-hanger tests. In the Morris water maze test of spatial navigation, they failed in both variants with the submerged or visible platform (Jacquelin et al. 2012, 2013).

Toppler mutant mice

Toppler mice suffer from autosomal recessive mutation in a gene on chromosome 8. The dramatic loss of Purkinje cells with typical abnormalities of their dendritic trees is evident already from 2nd postnatal week. Besides Purkinje cells there is present also degeneration of Bergmann glia and these both processes are evidently in a functional relationship. The Toppler mutants exhibit serious ataxia, which worsen with age and leads to a shorter lifespan (8-12 months). They represent a useful model for investigation of the developmental interaction of Purkinje cells and Bergmann glia (Duchala et al. 2004).

Pogo mutant mice

Pogo mice are naturally occuring mutants derived from an inbred strain of the Korean wild mouse. The autosomal recessive mutation affects a gene, which is located on chromosome 8. The mice show ataxia and difficulty in maintaining their posture. It is further characterized by a wobbly gait and a tendency to fall over, which appear at about 2 postnatal weeks and continue throughout life without progression. Morphologically in Pogo mice is the extent loss of Purkinje cells with ectopic spines, emanating from their primary dendrites (Lee and Jeong 2009). In addition, parallel fiber varicosities were larger than in the control mice and a single fiber often established synaptic contacts with up to four dendritic spines of a Purkinje cell. These multiple synapses were observed in both the cerebellar vermis and the hemispheres. Moreover, condensed and vacuolated granule cells nuclei were observed in the granular layer of the ataxic Pogo but not in the control cerebella. These morphological defects suggest that there could be massive synaptic abnormalities between Purkinje cells and the cerebellar afferent pathways in the Pogo cerebellum (Lee et al. 2011).

2) Transgenic animal models

Animals of this group represent mainly transgenic mice arising from the same type of hereditary determined neurodegeneration in humans resulting from repeating CAG triplets in the genetic information. Besides Huntington disease also dentatorubral-pallidoluysian atrophy, spinal and bulbar muscular atrophy, Niemann-Pick disease, Friedreich ataxia and also 7 types of spinocerebellar ataxias (SCA 1, 2, 3, 6, 7, 17, 23) from more than many scores of those in humans belong to this group (Yamada et al. 2008, Cendelín 2014). The aforementioned triplet codes for polyglutamine (polyQ) in each respective gene, resulting in mutants to the expansion of these sections mutated proteins.The severity of disability depends on the number of CAG triplet repeats (Yamada et al. 2008). In any case, these transgenic animals represent more precise models of the above-mentioned diseases.

Mouse models of human hereditary cerebellar ataxias

SCA1

Spinocerebellar ataxia type 1 (SCA1) represents one of the autosomal dominant hereditary ataxias. SCA1 causes about 3 to 16 percent of autosomal dominant cerebellar ataxias. In addition to ataxia, SCA1 is associated with the difficulty of speaking, swallowing, impaired cognition and increased reflexes are also common. SCA1 usually starts in the mid-30s and

progresses more rapidly than other SCA subtypes (Manto 2005) It is caused by an enlarged region of CAG repeat in the gene for ataxin-1 which results in the expansion of the polyQ tract in the ataxin-1 protein. Normally the length is between 6 – 35 repeats, while in affected people it is 39-83 (Taroni et al. 2013). To understand the pathophysiology of this disease, the transgenic mice expressing the human SCA1 gene were generated with either a normal or an expanded CAG tract. Both transgenes were stable in parents to offspring transmission and therefore six transgenic lines of mice for both normal or an expanded CAG tract were obtained. While all six transgenic lines expressing the unexpanded human allele had normal Purkinje cells, in transgenic animals from five of six lines with the expanded SCA1 allele (carrying 82 CAG repeats), ataxia and Purkinje cell degeneration developed (Burright et al. 1995). There is a marked loss of Purkinje cells, and those surviving have abnormal dendritic trees. Bergmann glia proliferation, a shrunk molecular layer with gliosis and ectopic Purkinje cells in it and also in the granular layer are further typical findings in the SCA1 mice cerebellar cortex. Ataxia with shorter strides start at PM 3, with worse performance on the rotarod test observed during PM 2 and serious gait abnormalities subsequently at PM 12 (Clark et al. 1997). The data obtained contributed to the clarification of some important pathogenetic mechanisms of SCA1 as a role of nuclear localization of the pathological ataxin-1 (Klement et al. 1998), its proteasomal degradation (Cummings 1999) as well as the effect of expanded ataxin-1 in the downregulation of genes acting in signal transduction and calcium homeostasis prior to manifestation of the pathology (Lin et al. 2000).

SCA2

SCA2 type of the autosomal dominant spinocerebellar ataxia causes about 6 to 18 % of all types of this disease. Besides progressive ataxia SCA2 is characterized by progressive ataxia, dysarthria, posture tremor, slow saccades, hyporeflexia of the upper limbs, autonomic dysfunction, sleep disturbances, ophthalmoparesis, dementia, and parkinsonism (Huynh et al. 2000). The onset age varies from 2 to 65 years, and onset before the age of 20 years correlates with a more aggressive disease course. SCA2 is caused by another CAG trinucleotide repeat, this time encoding a protein called ataxin 2. Normal ataxin-2 usually contains 22 or 23 glutamines, while SCA2 patients have 32–77 repeats. SCA2 transgenic mice generated in several lines differ in lengths of the CAG repeat segment and vary in severity of symptoms of this disease. Those with 58 CAG repeats are characterized by about 50% reduction of Purkinje cell numbers in PM 6. In animals from all three generated lines, SCA2 mice exhibited a reduced stride length to the end of PM 4. Some interesting findings in animals of

two lines were observed in the rotarod test when 6 weeks old transgenic animals did not differ in their performance from wild type controls, while SCA2 homozygotes and heterozygotes failed by PM 4 or PM 6 respectively (Huynh et al. 2000). From the above mentioned phenomena it is evident that a more severe manifestation is in mouse-lines with prolonged polyQ tracts. It is in agreement with the facts obtained in humans when prolonged CAG repeats characterized an earlier onset of symptoms and vice versa. Research performed on transgenic SCA2 animals has brought important knowledge about the pathogenetic mechanisms of this disease. It was shown, that nuclear localization and inclusion body formation of ataxin-2 was not necessary for disease development. (Huynh et al. 2000). Further glutamate induced death of Purkinje cells and its partial prevention by dantrolene was proved. This a calcium-ion stabilizer used in long-term treatment of SCA2 mice also alleviated motor deficits and Purkinje cell loss. These observations confirmed calcium signaling role in the pathogenesis of SCA2 (Liu et al. 2009).

SCA3

SCA3 type of spinocerebellar ataxia is better known as Machado-Joseph disease. SCA3 is characterized by progressive cerebellar ataxia, areflexia, peripheral amyotrophy, muscle atrophy, parkinsonian features, dystonia, and spasticity (Bettencourt et al. 2008). However, some minor presentations, such as external progressive ophthalmoplegia are also present. Its onset varies from 5 to 75 years of age and it represents around 1 % from all SCA cases. In normal alleles, CAG trinucleotides repeat length varies between 12 and 44, in SCA3 patients, the length is 52–86 (Taroni et al. 2013). SCA3 transgenic mice were generated with polyQ tracts of 64, 67, 72 76 and 84 repeats (Cemal et al. 2002). The severity of symptoms depends on the number of CAG repeats. Therefore in the mice expressing ataxin-3 with an expanded polyglutamine tract with 79 repeats suffer except from a wide gait, tremor and lower activity also from progressive ataxia starting at PM 5-6 despite the fact that the loss of cerebellar neurons is mild (Chou et al. 2008, 2011). These findings suggest that the decline in cerebellar function is more dependent on down-regulation of cerebellar expressions of proteins and neuronal dysfunction than on Purkinje cell loss (Chou et al. 2011). Research results obtained from experiments on SCA3 mice contributed to the understanding of more pathogenetic mechanisms of this disease mainly by pointing out the role of altered voltage-activated potassium channels (Shakkottai et al. 2011), calcium dependent calpain-type proteases (Hubener et al. 2013) and the disruption of dendritic development as well as metabotropic glutamate receptor signaling in Purkinje cells by mutant ataxin-3 protein (Konno et al. 2014).

SCA6

The spinocerebellar ataxia type 6 (SCA6) is characterized by CAG polyQ repeat expansion in the CACNA1A gene encoding the alpha 1A-voltage-dependent calcium channel (CaV2.1) (Zhuchenko et al. 1997) and it represents the most frequent type of all SCAs (from 5 to 18 %). SCA6 is characterized by a slowly progressive ataxia, dysarthria, intention tremor, gaze-evoked and/or downbeat nystagmus, dysphagia, positional vertigo, and sensory, pyramidal, and extrapyramidal motor deficits (Stevanin et al. 1997). Normal alleles have 4 – 18 repeats, while alleles in diseased people contain 20 – 33 polyQ repeats. SCA6 generated transgenic mice which have the 84 polyQ repeats tract are characterized by progressive motor abnormalities and the aggregation of the pathological protein CACNA1A. Homozygous animals have shown hypoactivity and worse performance on the accelerating rotarod (Watase et al. 2008). Heterozygotes did not differ from wild type mice according to visual assessment up to PM 20 despite performing worse than controls on the rotarod test at PM 19. Regardless of motor disturbances no neuronal loss and morphological changes on Purkinje cells were observed in these mice at PM 20. From the point of view of pathophysiological mechanisms, the observations in SCA6 mice with 28 or 84 polyQ repeats suggest that alteration of CaV2.1 channel properties does not play any role in the SCA6 pathology which may be linked to the accumulation of mutant channels (Saegusa et al. 2007, Watase et al. 2008).

SCA7

Spinocerebellar ataxia type 7 (SCA7) is a neurodegenerative disease caused by the expansion of a CAG repeat within the gene encoding ataxin-7. The normal range is 7–19 repeats. Pathological alleles contain from 37 to more than 400 CAG triplets. SCA7, with the onset in childhood, is characterized by progressive ataxia, macular or retinal degeneration with visual loss, slow saccades, ophthalmoplegia, dysphagia, somatosensory and neuropsychiatric impairment (David et al. 1998). Among SCAs, it is the only one characterized by severe ataxia, and at the same time by blindness. (Taroni et al. 2013). Generated transgenic mice with 90 polyQ repeats have nuclear inclusions of mutant protein ataxin-7 in Purkinje cells and photoreceptors, and exhibit both abnormal motor coordination together with vision impairment. Nevertheless, there are big differences in the spectrum of findings in dependence on the polyQ tract length. For instance the mice with 266 CAG repeats suffer from an infantile form of SCA7 characterized by ataxia, visual impairment, abnormal short-term synaptic potentiation and untimely death (Yoo et al. 2003). On the other hand, the mice with 92 polyQ repeats and ataxin-7 expression in all CNS neurons, except Purkinje cells, display

severe degeneration just of these cells, ataxic gait disorder and typical ataxin-7 nuclear aggregates which correlate with visible symptoms including anearlier death (Garden et al. 2002). Conversely, transgenic mice with 52 CAG repeats suffer from ataxia, without a significant loss of Purkinje cells. All these findings suggest that the Purkinje cell degeneration in SCA7 is not cell-autonomous and that in the patogenesis of this disease yet other factors play a role, for instance changes in gene expression with an impact on glutamatergic transmission, signal transduction, myelin formation, axonal transport neuronal differentation and glial function (Chou et al. 2010). This hypothesis was confirmed by observation when the suppression of the mutant gene (to 50 %), one month after the ataxia started, was effective in delaying motor disorders, reducing ataxin-7 pathological protein aggregation in Purkinje cells and preventing the synaptic loss between Purkinje cells and the climbing fibers (Furrer et al. 2013).

SCA17

SCA17 type of spinocerebellar ataxia late-onset degenerative disorder is caused by an expanded polyQ repeat in the TATA-box-binding protein (TBP). The disease is characterized by progressive gait and limb ataxia, seizure, cognitive dysfunction, neuropsychiatric impairment, and pyramidal and extrapyramidal features such as spasticity, dystonia, chorea, and Parkinson's disease. While healthy people have 23 – 43 CAG polyQ repeats, patients suffering from this pathology have 45 – 63 repeats polyQ tract. The disease is very rare, i.e. below 1 % of all SCAs (Lasek et al. 2006). Despite that, two mouse models of this disease were generated (Friedman et al. 2007, Chang et al. 2011), it is only type of SCA when a rat TBPQ64 model SCA17 has shown to be more advantageous. Similarly as in mouse models for SCA17, TBPQ64 rats show a severe neurological symptomatology including ataxia, impairment of postural reflexes and hyperactivity in the early stages followed by a reduced activity, loss of body weight, and early death. Neuropathological findings showed neuronal loss, particularly in the cerebellum, degeneration of Purkinje, basket, and stellate cells as well as, changes in the morphology of the dendrites. In addition, nuclear TBP-positive immunoreactivity and axonal torpedos were found by light and electron microscopy. It was also shown that some crucial characteristics of SCA17 are better mirrored in TBP rats than in existing mouse models. The use of this model for the first time by means of PET and diffusion tensor imaging (DTI) were also replicated recent PET studies in human SCA17 patients. These results further confirmed that DTI are potentially useful correlates of

neuropathological changes in TBPQ64 rats and raise the hope that DTI imaging could provide a biomarker for SCA17 patients (Kelp et al. 2013).

SCA23

Spinocerebellar ataxia type 23 (SCA23) is an adult-onset extremely rare neurodegenerative disorder characterized by slow progressive gait and limb ataxia, with variable additional features, including peripheral neuropathy and dysarthria (Bakalkin et al. 2010). In the literature a Dutch family was reported with autosomal dominant late-onset spinocerebellar ataxia affecting at least 13 members spanning 3 generations. Only 1 patient, with a disease duration of 23 years, was wheelchair-bound. The MRI of that patient showed severe cerebellar atrophy with memory deficits beginning around age 50. Postmortem examination of 1 patient displayed frontotemporal atrophy, atrophy of the cerebellar vermis, pons, and spinal cord. There was also neuronal loss in the cerebellar vermis, dentate nuclei, and inferior olives, but not in the pons. Moreover there was thinning of the cerebellopontine tracts and demyelination of the posterior and lateral columns of the spinal cord. SCA23 maps to chromosome region 20p12.3-p13 and missense mutations in the prodynorphin PDYN gene appear to cause the disease. (Verbeek 2004). Prodynorphin knock-out mice are more sensitive to noxious stimuli but have normal responses to non-noxious stimuli (Wang et al 2001); additionally, mutant dynorphin proteins have enhanced non-opioid excitatory activities which may undermine the development of SCA23 (Wang et al. 2013). Nevertheless, these mice have not yet been tested for phenotypic similarity to human SCA23 (Cendelín 2014).

Conclusions

As mentioned above a new conception of the cerebellum including a more detailed knowledge about physiology and pathophysiology of the cerebellum as well as about the cerebellar disorders would not be possible without the above-surveyed clinical and research methods including sophisticated procedures on experimental animals. First of all, both naturally arising and also artificially by genetic engineering prepared animal models created the basis for such enormous progress in cerebellar research. Because of these advances it is idisputable that studies mainly on cerebellar mutants provided a lot of valuable information about cerebellar function, manifestation of cerebellar disorders as well as pathogenesis and therapy, though there are also some limitations that prevent a direct translation of findings to humans.

Though the basic manifestation of cerebellar dysfunction is similar in most of the mouse models of cerebellar degenerations, some particular signs differ. Moreover, some of the mutations have extra-cerebellar impacts, which are integral components of the phenotype (e.g. olfactory bulb, retina and thalamus degeneration in pcd mice etc.). There are, of course, species differences in anatomy, metabolism, behavior, etc. between mice and men. Spontaneous mouse mutations are usually not identical to human ones and therefore mouse diseases can only be similar to human diseases. On the other hand, transgenic mice carry human pathological alleles and thus can be used as models for specific human diseases.

Nevertheless, even in transgenic mice the action of the mutation could significantly differ from the natural human mutation. The transgene could possibly be under the control of different promoters and its expression could differ from that seen in humans regarding intensity and cell type. The transgene usually does not replace the mouse wild type allele, if it is not knocked-out. In these cases the mouse has both pathological as well as fully expressed normal gene products. Autosomal dominant ataxias appear in humans mostly in the form of heterozygotes. However, mice can also be studied as homozygous individuals. These experiments have shown that homozygous mice often display more severe pathological phenotype than heterozygous mice suggesting that the diseases might be more accurately described as having a semi-dominant nature. Despite the limitations, cerebellar mutant mice are invaluable tools for research, when the goal is a better understanding the pathogenesis of cerebellar degenerative disorders and, hopefully, finding effective therapies for humans. Cerebellar mutant mice will continue to serve as valuable tools in preclinical studies investigating the therapeutic methods for treating human cerebellar degenerations.

Nevertheless, deep phenotypic characterizations, especially those of the new transgenic mouse models, and the elucidation of the pathogenesis and relationship of the functional disorders to the cerebellum will remain important. Verification of the conformity of the mouse models with human diseases on the morphological, functional and molecular level is also crucial for translation of experimental research to human medicine and thereby aid in its progress.

Finally, it is possible to wish our neuroscience research that it succeed, at least partially, as in the period of the J. E. Purkyně.

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