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REVIEW

Aging of cerebellar Purkinje cells

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Abstract Cerebellar Purkinje cells (PCs), the sole output neurons in the cerebellar cortex, play an important role in the cerebellar circuit. PCs appear to be rather sensitive to aging, exhibiting significant changes in both morphology and function during senescence. This article reviews such changes during the normal aging process, including a decrease in the quantity of cells, atrophy in the soma, retraction in the dendritic arborizations, degeneration in the subcellular organelles, a decline in synapse density, disorder in the neurotransmitter system, and alterations in electrophysiological properties. Although these deteriorative changes occur during aging, compensatory mechanisms exist to counteract the impairments in the aging PCs. The possible neural mechanisms underlying these changes and potential preventive treatments are discussed.

Keywords Cerebellum · Purkinje cells · Aging · Morphology · Function

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Introduction

Cerebellar Purkinje cells (PCs), the sole output neurons in the cerebellar cortex, undergo significant age-related morphological and functional alterations. These alterations may relate to age-related cerebellar disabilities, such as dysfunctions in postural control (Hogan 2004), deficits in motor activities (Hilber and Caston 2001; Mattay et al. 2002; Taniwaki et al. 2007), a decline in the intellect (Lee et al. 2005), and impairments in cognitive functions (Hogan 2004; Paul et al. 2009) in the elderly. Moreover, a multitude of age-related cerebellar diseases are accompanied by obvious alterations in the morphology and function of PCs, such as essential tremor (ET) (Louis et al. 2009), Alzheimer's disease (AD) (Sjöbeck and Englund 2001), and Lewy Body disease (LBD) (Tu et al. 1997). This review focuses on PC modifications that occur during the normal aging process, which have not been reviewed previously, and will increase our understanding of the mechanisms underlying aging in degenerative diseases.

Age-related PC loss

PCs are among the most vulnerable neurons in the brain (Patrick and Anderson 2000; Woodruff-Pak 2006; Servais et al. 2007; Dhar et al. 2007; Woodruff-Pak et al. 2010) and are prone to aging insult (Quackenbush et al. 1990; Hadj-Sahraoui et al. 2001; Andersen et al. 2003; Zhang et al. 2006). A complicated and disputed issue is whether the quantity of PCs decreases or remains constant during the normal aging process. Some evidence has shown that PCs exhibit significant age-related neuronal loss (Ogata et al. 1984; Rogers et al. 1984; Woodruff-Pak 2006; Pires et al.

2010; Woodruff-Pak et al. 2010). Hall and Millerakh Corsellis (1975) reported a ~2.5% PC loss per decade during aging, whereas other studies found no obvious age-related decline in PC number (Drüge et al. 1986; Bakalian et al. 1991). Another report demonstrated that PCs remained constant in most cerebellar parts, except in the anterior lobe, where a highly significant decline in the number of cells of 40.9% occurred during aging (Andersen et al. 2003). While it becomes more and more prevalent that many brain regions, such as striate cortex (Hua et al. 2008) and hippocampus (von Bohlen und Halbach and Unsicker 2002), undergo no significant neuron loss during the aging process, the cerebellar PCs might not comply with the same rule. Woodruff-Pak et al. (2010) used unbiased stereology to estimate the total number of PCs in cerebellum and pyramidal neurons in the hippocampus, the results revealed significant loss of PCs but stable pyramidal neurons during brain aging. We speculate that the discrepancies among these literatures might be due to variations in species, cerebellar regions and counting methods (for example, using the unbiased stereological technique or by visual examination), or depend on whether an undistinguishable aging disease (such as an early AD) or shrinking factors caused by tissue processing were considered or not (Andersen et al. 2003).

It has been shown that a number of factors might account for age-related PC loss, such as excessive amino acids (Felici et al. 1989), a decrease in neuroglobin (a kind of neuroprotective protein) (Sun et al. 2005) and loss of reciprocal interaction with target neurons (Huang et al. 1999). Neuronal loss is usually viewed as one of the important causes of age-related deteriorations of neurological functions. Because PCs are responsible for cerebellar cortical-dependent forms of behavior (Woodruff-Pak 2006), age-related PC loss will lead to significant cerebellar dysfunctions, such as a delay in eyeblink conditioning (Woodruff-Pak 2006) and deficits in spontaneous motor activity (Larsen et al. 2000). Loss of PCs in the cerebellum also is considered to be a factor in cerebellar atrophy during normal aging (Woodruff-Pak et al. 2001).

Atrophy in the PC soma

While there is a dispute on age-related PC loss, it is evident that the aging process will result in a decisive shrinkage in the PC soma. Ogata et al. (1984) has reported that the PC volume from the rats aged 18, 24 and 30 months significantly decrease as compared with that of 3-month-old counterparts, and Andersen et al. (2003) estimated a significant decrease of 33% in the PC somatic volume in aged human cerebellum. A decrease in PC volume may be related to the decline of nuclear elements (Ogata et al. 1984) and the degeneration of other organelles or loss of the cytoplasmic matrix in the perikaryon (Monteiro 1991). These changes suggest a significant decline in substance synthesis as well as trophic deficiencies and possibly neuronal dysfunction in the aged PCs.

Retraction in PC dendritic arborizations

PC dendritic arborizations are profuse and approach the pial surface in young cerebellum, whereas old dendrites appear significantly atrophied (Quackenbush et al. 1990; Hadj-Sahraoui et al. 2001; Zhang et al. 2006). The height of PC dendrites (measured from the maximal point in the arbors perpendicularly to the PC layer) accounts for a large percentage of the molecular layer thickness in younger cerebellum, whereas that of the old PC dendrites occupies significantly less of the molecular layer thickness, despite a significant atrophy in the molecular layer during cerebellar aging (Hadj-Sahraoui et al. 2001). The width of PC dendrites (measured as the extent of the arbors along an axis parallel to the PC layer in the molecular layer) is also significantly smaller in the elderly compared to the young (Hadj-Sahraoui et al. 2001). In addition, the branches from young PCs are nearly homogeneous in each segment, whereas the aging dendrites exhibit abundant vacuolar profiles and membrane swirls (Chen and Hillman 1999). This phenomenon indicates cytoarchitecture aberrations in aging PC dendrites, which greatly affect the small distal dendrites and decrease substance transport to distal terminals, thereby accounting for the preferential loss of distal branchlets during PC dendritic aging (Rogers et al. 1984; Quackenbush et al. 1990).

Reduction in PC dendrites may attenuate the exchanges of neural information, because PCs receive synaptic inputs mainly through their dendritic networks. Age-related loss of PC arborizations could directly reduce the amount of information input, reduce afferent efficacy, and affect information integration and signal transmission in the aged cerebellum, consequently leading to a reduction in cerebellar function. In addition, loss of PC dendritic arborizations might also contribute to the decline in the thickness of the molecular layer in the aged cerebellum (Zhang et al. 2006).

The causes of age-related loss of PC dendrites remain unclear. An important aspect is the effect of age-related decrease of inputs from parallel fibers to PCs (Dlugos and Pentney 1994; Huang et al. 1999, 2006b). The parallel fibers arise from granule cells in the cerebellar cortex and form synapses onto the dendrites of Purkinje cells. Thus, loss of parallel fibers (Huang et al. 1999) or granule cells (Pentney et al. 2002; Zhang et al. 2006) may trigger the dendritic loss in aging PCs. In addition, since specific trophic factors, such as insulin-like growth factor-1 (IGF-1)

and brain-derived neurotrophic factor (BDNF), can promote dendritic growth (Niblock et al. 2000; Binder 2007), but exhibit age-related reduction in aging brain (Markowska et al. 1998; Erickson et al. 2010), it is reasonable to propose that age-related declines of PC dendrites might also be associated with such reduced trophic support during cerebellar aging.

Degeneration of PC organelles

The ultrastructures of PCs reportedly undergo significant age-related alterations (Ogata et al. 1984; Monteiro 1991; Monteiro et al. 1994; Fattoretti et al. 1996). Mitochondria in the aging PCs showed significant morphological degeneration, such as a decrease in mitochondrial volume, numerical density and volume density (Fattoretti et al. 1996, 1998). This degeneration might affect mitochondrial respiratory chain activity (Ojaimi et al. 1999) and lead to a reduced energy metabolism in the aging PCs (Atamna 2004). The smooth endoplasmic reticulum, an important calcium storage organelle (Monteiro et al. 2000), exhibits dilation in aged PCs (Dlugos 2005), which is a threat to PC calcium homeostasis. The lipofuscin in the cytoplasm markedly increased in aging PCs (Ogata et al. 1984; Monteiro et al. 1994), which might interfere with the intraneuronal configuration and might speed up the death of PCs (Monteiro et al. 1994). In addition, it has been shown that the aging nuclei become pyknotic and undergo regression (Ogata et al. 1984; Monteiro et al. 1994). The nucleolar volume decreases with age (Ogata et al. 1984) and the "nucleus-ribosome system" becomes impaired (Nosal 1979), including changes in the nucleolar texture, repartition in the the nucleolus, variations in interchromatin/perichromatin granules and redistribution of free ribosomes with age, which could possibly reflect the molecular dysfunction related to the production of various types of RNA and neuronal proteins in the old (Nosal 1979). Other PC organelles, such as the degeneration in Golgi apparatus and ground substance, emergence of dense bodies and vacuolations, have also been reported to occur during aging (Monteiro 1991; Nosal 1979). In summary, these age-related degenerations in PC organelles might affect neuronal functions of energy metabolism, substance synthesis and intraneuronal homeostasis. These vital alterations might lead to PC apoptosis and subsequently cause cerebellar dysfunctions in senile individuals.

Changes in PC synapses

Synapses are not immutable and static structures in the nervous system but are prone to be remodeled on both the morphology and function as a consequence of environmental stimulations during aging (Bertoni-Freddari et al. 1996; Poe et al. 2001) and behavior experience (Gruart et al. 2006; Lee et al. 2007). In the cerebellum, PC synapses are mostly formed with the parallel fibers (Dlugos and Pentney 1994; Huang et al. 1999, 2006a). A high correlation has been reported between synaptic density and PC density (Rogers et al. 1984); therefore, if the number of PCs declines and/or their dendritic arborizations is lost during aging, the synapses might also be lost. These synaptic losses may trigger other age-related cell losses in the aged cerebellum (Huang et al. 1999). Other studies reported significant loss of approximately 33% of synapses in PC dendritic spines (counted per tissue square area of electron micrograph) during aging, which might result from the impairment with advanced age of specific afferent neurons and/or a selective age-related vulnerability of dendritic spines (Glick and Bondareff 1979). In addition, the fluidity of the lipid bilayers of synaptosomal membranes degenerates in the aged (Ohyama et al. 1995), which suggests that the synapse is prone to collapse and could lead to synapse loss in senile PC. In summary, in addition to a reduced number of synapses and the degenerating junctional zones, any alterations at synaptic terminal regions may affect synaptic dynamic morphology and impair energy or information receiving in aged PCs (Bertoni-Freddari et al. 1986, 1996).

Altered response ability to neurotransmitters of aged PCs

It has been shown that both the concentration of the most neurotransmitters and the neuronal response ability to the neurotransmitters change with brain aging (Bickford 1993; Bickford et al. 1985; Bickford-Wimer et al. 1988), which greatly affect neuromodulatory actions. A widely studied neurotransmitter that affects the response of aging PCs is norepinephrine (NE), which preferentially inhibits the spontaneous activity in the young PCs rather than in the senescent (Bickford-Wimer et al. 1988). Electrophysiological and electrochemical techniques showed an age-related loss of noradrenergic function in postsynaptic compartments (Bickford-Wimer et al. 1988), which may relate to behavioral deficits in senescence (Bickford et al. 1985, 1999; Bickford-Wimer et al. 1988). NE is also an important neuromodulator in the cerebellar cortex that amplifies the action of gamma-aminobutyric acid (GABA) (Bickford 1993). Therefore, an age-related decrease in NE content will attenuate the GABAergic inhibitions to aging PCs and subsequently affect cerebellar functions. Alterations of neurotransmitters in aging PCs might be related to the changes of neurotransmitter enzymatic abilities, for example,

age-related decline of glutamate dehydrogenase activity might result in overproduction of amino acids and contribute to cell loss, whereas age-related increase in monoaminooxidase function can reduce the neuron energetic production (Felici et al. 1989; Tranquilli Leali et al. 2003).

Alteration of the electrophysiological features in aged PCs

Age-related changes in the electrophysiological features of PCs have been widely reported (Rogers et al. 1981; Chung et al. 2003), for example, aging leads to deficits in the PC activation threshold and increases the inhibitory threshold (Rogers et al. 1981). Many factors might cause these changes, such as a declined receptor response (Parfitt 1988), decreased postsynaptic sensitivity to neurotransmitters (Marwaha et al. 1980), and functional alterations in many ion channels (Chung et al. 2001a, b, 2003).

Ion channels have been extensively studied for investigation of electrophysiological alterations in the aged PCs. The sodium channels are involved in the integration of synaptic input in cerebellar PCs (Schaller and Caldwell 2003). Modification of sodium channel availability is a candidate for age-related alteration of the action potential (Chung et al. 2003). In aged PCs, Na 1.1 immunoreactivity is greatly increased, which likely contributes to the mechanisms underlying the age-related alteration in action potential (Chung et al. 2003). In addition, immunoreactivities for Kv1.1 and Kv1.2 are increased specifically in aged PCs, which might also affect PC functions and cause age-related disorders (Chung et al. 2001a). Many neuronal processes are regulated by calcium influx through voltage-gated calcium channels (VGCCs), including firing patterns of action potentials (Chung et al. 2000). In aged PCs, immunoreactivity of the VGCC alpha (1C) subunits is increased whereas that of the alpha (1D) subunits is decreased, which might reflect a gradual loss of regulation of Ca^{2+} channels in the senescent period (Chung et al. 2001b). Takahashi et al. (2009) reported that age-dependent alterations in Cav2.1 channel function might result in aberrant synaptic signaling, leading to motor dysfunction, because Cav2.1 channels control neurotransmitter release and impair synaptic transmission (Kodama et al. 2006). These alterations on ion channels indicate a complex feature on the electrophysiological response during PC aging.

Behavior deficits as PC aging

Impairments of PCs will directly generate cerebellar dysfunctions under various situations, which were widely reported in Lurcher or Staggerer mutant mice (Hilber and Caston 2001; Caston et al. 2003; Porras-García et al. 2005, 2010; Chintala et al. 2009). These mutant animals are characterized by premature and aberrant apoptosis in the cerebellum, such as great loss of Purkinje cells and granule cells, which appears to be a good model of progressive neurodegeneration in aging cerebellum (Hilber and Caston 2001). As Lurcher mutant mice showed a decrease in both motor skills and motor learning (Hilber and Caston 2001), which was mainly caused by loss of PCs, we speculate that age-related loss in PCs could also result in motor skill and motor learning dysfunctions in the elderly. Lurcher mice also deficit in spatial orientation (water maze) and associative learning (eyelid classical conditioning) tasks (Porras-García et al. 2005), suggesting a similar age-related degeneration of orientation ability and associative learning activities in the old. However, not all the cerebellar dysfunctions in these mutants are related to PC loss. Stagger mice showed weaker motor behavior and working memory than those of the wild mice at the age when PC number was quite normal and similar to that of wild mice, indicating a fine structural and/or biochemical changes might precede PC death (Caston et al. 2003, 2004).

Compensatory mechanisms for age-related PC dysfunctions

Although PCs undergo significant age-related morphological and functional degeneration, a compensatory mechanism exists to counteract the degeneration. Age-related hyperplasia and hypertrophy of astrocytes (Sabbatini et al. 1999; Zhang et al. 2006) have been reported to provide neuroprotective effects on aging neurons, and might also exert protection for the aging PCs. Some compensatory mechanisms might be invoked by the aging brain. For example, despite the terminal dendritic segments of aging PCs were preferentially lost, the proximal regions of the network exhibited regrowth and reorganization, which might serve as a kind of compensation for age-related dendritic loss (Quackenbush et al. 1990). Although the number and total surface area of synapses decrease significantly with age, the average synaptic size exhibits a closely negative correlation to the synapse number during aging (Bertoni-Freddari et al. 1986, 1996; Chen and Hillman 1999), which helps maintain synaptic transmission between aging neurons. Such a correlation indicates a compensatory mechanism of dendritic deafferentation (Monteiro et al. 1992). In addition, the upregulation of the IGF-I receptor in the aged cerebellum suggests promotion of the survival of a degenerated population of PCs during aging (Chung et al. 2002).

Current strategies for preventing degeneration of PC aging

Aging is a progressive physiological syndrome that is unavoidable. However, proper treatments can slow down the aging process. Suppression of oxidative stress is considered to be an important mechanism for suspending neuronal vulnerability to aging effects (Joseph et al. 1998). 5-lipoxygenase (5-LOX), the concentration of which is increased in elderly brains, may participate in neurodegeneration during aging. Thus, decreasing the level of 5-LOX (such as by regulating hormonal level of melatonin or hyperglucocorticoidemia), might be a way to delay age-related neurodegeneration (Manev et al. 2000). In addition, administration of certain hormones, (e.g., steroid hormones; Schumacher et al. 2003; George et al. 2006), antioxidant-rich foods (Joseph et al. 1998; Bickford et al. 1999; Ho et al. 2009; Seo et al. 2009), neurotrophic factors (Lärkfors et al. 1994; Tolbert and Clark 2003), active exercise (Larsen et al. 2000; Martinez Gagliardo et al. 2008; Chae and Kim 2009), transplantation of endogenous stem/progenitor cells (Rao and Mattson 2001; Jin and Galvan 2007), and medications (Binstock et al. 2006) can also benefit aging neurons in different brain regions. Similarly, these manipulations might have similar effects in preventing degeneration of cerebellar PCs during senescence. Probably, with the development of the therapeutic techniques, transplantation of neural stem/progenitor cells to the aging cerebellum (Alcock et al. 2007) might be an optional treatment for age-related cerebellar dysfunctions in the future. The postnatal cerebellar cortex has been reported to have at least two distinct types of progenitor cells (Jankovski et al. 1996). These stem/progenitor cells are able to acquire the position and mature electrophysiological properties after transplantation (Klein et al. 2005). Therefore, it is reasonable to speculate that prevention of aging PC degeneration could be achieved by increasing the generation of endogenous stem/progenitor cells and/or transplantation of stem/progenitor cells. Recent evidence has shown that aging leads to deterioration of DNA repair mechanisms, such as lowering the efficiency of mismatch repair, base excision repair, nucleotide excision repair and double-strand break (Gorbunova et al. 2007), which will increase cell apoptosis, mutation or death in many tissues. These age-related changes could similarly occur in cerebellar PCs and lead to their degenerative changes during aging. As treating DNA oligonucleotide might correct age-associated decline of DNA repair capacity (Goukassian et al. 2002), such treatment can potentially improve DNA repair and delay PC aging.

In summary, normal aging does lead to a significant functional deficit of cerebellar PCs. However, the underlying neural mechanisms remain poorly understood. Some changes of morphology at cellular–subcellular level as well as modifications of neural transmitters and its corresponding receptors may contribute to functional decline of PCs that accompany senescence, whereas compensatory mechanisms expected to counteract PCs function degeneration are also proven to exist. Subsequent studies with integrative techniques of behavior assessment, electrophysiology, morphology and molecular tools are needed to clarify these issues so as to uncover potential strategies to prevent PC aging and related motor ability reduction in aged individuals.

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