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BIOCHEMICAL AND ANATOMICAL CHANGES IN BASAL GANGLIA OF AGING ANIMALS

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I. Introduction

Along with memory loss, a cardinal feature of senescence is deteriorating motor function. Indeed, slow movements, tremor, stooped posture, and a shuffling gait - also symptoms of Parkinson's disease (PD) - are hallmarks of old age as well as parkinsonism in the elderly (Bennett et al., 1996; Mortimer & Webster, 1982; Teräväinen & Calne, 1983). When it was discovered that the brains of individuals who suffered from PD were deficient of the neurotransmitter dopamine (DA) (Ehringer & Hornykiewicz, 1960) and that these symptoms were successfully reversed by the dopamine precursor L-DOPA (Cotzias et al., 1969; Cotzias et al., 1967), researchers were provided with a neurochemical mechanism underlying these deficits. Consequently, the basal ganglia became the primary neuroanatomical loci for studies of not only PD, but also of non-pathological age-related declines in motor function. Although the majority of previous studies have focused upon age-related structural alterations in the basal ganglia, more recent studies have attempted to characterize changes in neuronal function. These functional decrements arguably account for much of the deterioration of motor capacities that are observed in senescence.

A. Definition of Basal Ganglia

The basal ganglia are a group of interconnected subcortical nuclei that interact with cortical and limbic regions to produce meaningful, goal-directed behavior (Gray, 1995). They are comprised of the striatal and pallidal portions of the basal telencephalon, the substantia nigra, ventral tegmental area, and the subthalamic nucleus (Marin et al., 1998; Wilson, 1998). The striatal and pallidal components of the basal ganglia are functionally segregated into dorsal and ventral portions. The dorsal component is comprised of the dorsal striatum, i.e., caudate nucleus and putamen (in primates and felines), or caudate-putamen (in other mammals), the internal and external segments of the globus pallidus segment (in primates), or globus pallidus and entopeduncular nucleus, respectively (in non-primates). The ventral component is comprised of the ventral striatum, i.e., the nucleus accumbens and portions of the olfactory tubercle and the ventral striatum (Marin et al., 1998).

B. Animal Models of Aging

While many laboratory animal species have been used in aging studies, the majority of non-human studies of age-related changes in the nigrostriatal DA system age have been conducted with rodents (Austad, 1997). The major species employed have been Fischer 344 (F344), Wistar or Sprague-Dawley rats, or C57BL mice.

One outstanding issue in aging research has been the lack of a standardized scheme of classifying an animal of a particular species as "aged". Ideally such a scheme would be based upon comparative data regarding the species' life-span and the extent to which the species' age-related alterations parallel those of aging humans. Although there is variation between rat strains regarding longevity (Masoro, 1990; Sprott & Austad, 1996), researchers have generally defined rats as aged at $\geq$ 22 months and C57BL mice are generally classified as aged at $\geq$ 21 months. Cats are typically labeled aged at $\geq$11 years and the aged group in studies using monkeys is typically $\geq$ 22 years of age. Subjects in human studies in which age-related effects have been reported are generally $\geq$ 70. Because, with few exceptions, these are the ages typically employed to classify subjects as "aged", studies that report no effects of aging in animals younger than the aforementioned values are not included in this review. Age-related changes in humans will be cited throughout the chapter for comparative purposes.

C. Functional Neurobiological Changes Associated with Aging

Because of its role in motor behavior, the nigrostriatal DA system has been the subject of the majority of studies examining age-related decrements in basal ganglia function. For this reason, the age-related changes in the basal ganglia that will be covered in this chapter will focus predominately upon the ascending nigrostriatal DA tract. The discussion will include alterations in the structural integrity of dopaminergic neurons and their connections in senescence, as well as the functional integrity of pre- and postsynaptic neuronal mechanisms. The chapter will conclude with a brief review of alterations of other neurotransmitter systems that interplay with dopaminergic neurons in the aged basal ganglia. In all cases we have tried to be comprehensive. However, undoubtedly we have failed to include some pertinent data and citations.

II. Morphological Changes

A. Cell Number

It has long been a biological doctrine that normal (i.e., non-pathological) aging is accompanied by widespread neuronal loss. This commonly accepted belief was based largely upon early studies in which extensive cell death was inferred from measurements of decreased neuronal densities in brain regions known to be affected in Alzheimer's disease - specifically, regions of the neocortex and hippocampus (Brody, 1955; Colon, 1972; Dayan, 1970). Likewise, the prevalence of parkinsonian-like symptoms that often accompany aging has led to the suggestion that normal aging occupies a "pre-parkinsonian" position on a continuum which includes PD as a manifestation of accelerated aging (Barbeau, 1973; Beck, 1978; Mann & Yates, 1982; McGeer et al., 1977; Mortimer & Webster, 1982). This hypothesis seems to be supported by reports of age-associated decreases in the number of substantia nigra pars compacta neurons on the order of 30 to 50% between 20 and 90 years of age in humans (Fearnley & Lees, 1991; Mann & Yates, 1983; McGeer et al., 1977; however, see references cited in McNeill & Koek, 1990, for evidence to the contrary). Likewise, a 50% decrease in the number of substantia nigra neurons of aged (25-27-year-old) Rhesus monkeys has also been reported (Emborg et al., 1998). DA cell loss in the aged rodent substantia nigra pars compacta, however, has not been observed (Emerich et al., 1993; Flood & Coleman, 1988; McNeill & Koek, 1990).

Several caveats regarding the interpretation of age-related DAergic cell death as it relates to functional deficits should be considered. While there have been reports of decreased numbers of DA neurons in aged primates, there are quantitative as well as qualitative differences between the physiological substrates of normal age-related motor deficits and the pathophysiological substrates of PD (e.g., Fearnley & Lees, 1991; Hubble, 1998; Kish et al., 1992). These differences have become recognized as a result of critical analyses of previous data, improvements in histopathological methodology, and analysis of the distinct etiologies of the motor deficits that accompany each of these conditions. Other considerations relate to the methods used to determine age-related loss of DA neurons. Recent studies using un-biased stereological cell-counting methods have cast doubt on the long-held belief that neuronal death is an inevitable consequence of aging (West, 1993; West et al., 1994; West & Gunderson, 1990; see also Morrison & Hoff, 1997). These methods have also challenged previous findings regarding the inevitability of nigral cell loss with age (Irwin et al., 1994; Pakkenberg et al., 1995; Strothjohann et al., 1993). Nevertheless, a recent study using stereological methods to determine age-related nigral cell-loss reported a 50% reduction of tyrosine hydroxylase (TH) immunoreactive neurons in the substantia nigra of aged monkeys (Emborg et al., 1998). However, caution should likewise be exercised when interpreting studies in which the number of DA-containing neurons were determined based on the immunoreactivity of cells to TH, as decreases in TH immunoreactivity may overestimate DA neuronal loss as a result of functional deficiencies in residual cells and staining methods (Emborg et al., 1998; McGeer et al., 1977).

Notwithstanding these methodological concerns, the decreases observed in these previous studies of age-related DA cell loss were generally less than 50%. Although age-related motor deficits coincide with modest DA neuronal loss, decreases in DA neuron numbers reported in the previous studies barely approach the magnitude of loss that is necessary to produce the $\geq$80% striatal DA depletion required for gross functional impairment in humans with PD or in animal models of PD (Hornykiewicz, 1963; Lloyd, 1977; Stricker & Zigmond, 1976). Indeed, if PD cell-loss criteria were employed, extrapolation of the regression lines reported in studies of age-related DA cell loss would not place individuals at risk of gross motor decline until they were 100 years old (Kish et al., 1992; McGeer et al., 1977; Mortimer & Webster, 1982). Clearly, DA cell-loss is an insufficient explanation for gross, age-related declines in motor function.

B. Pathological Accumulations

The escalating presence of lipofuscin in nerve cells is considered to be a sign of neuronal aging, as the amount of the pigment has been shown to gradually increase with age in a variety of tissues in several species (Peters et al., 1991; Sohal & Wolfe, 1986). Age-related accumulation of lipofuscin in DA neurons of the substantia nigra pars compacta have been reported in C57BL/6J (Ingram et al., 1993) and C57BL/6NNia (McNeill et al., 1984) mice. While the observations of McNeill and colleagues (1984) were not quantitative, they reported increases in lipofuscin beginning at 10 months of age, with a preponderance of accumulation at 30 months. Ingram and colleagues (1993) quantified the increase, reporting that lipofuscin accumulation was approximately 20% higher in 18 month old as compared to 3-month-old mice. Although the presence of lipofuscin at low levels does not necessarily support pathology, with increasing accumulation it may be associated with progressively lower levels of ribonucleic acid in the cytoplasm (Peters et al., 1991). This may indicate an increasing decrement of the cell's exocitotic capacity (Sohal & Wolfe, 1986) or an alteration in the cell's metabolic or neuronal activity (McNeill et al., 1984).

While the pathological significance of lipofuscin is debatable, Lewy bodies, which are a histological signature of PD (Kopin, 1993), are readily associated with basal ganglia pathology. Lewy bodies have been observed in the substantia nigra of a small percentage of non-parkinsonian human controls over the age of 50 (e.g., 6% reported by Fearnley & Lees, 1991). Although Fearnley and Lees (1991) reported increases in the prevalence of incidental Lewy bodies with age, they argued that the presence of Lewy bodies are not an aspect of normal aging, but are indicative of presymptomatic PD. This suggestion is supported by a lack of reports of Lewy bodies in aged animals.

C. Connections

In studies that have reported age-related changes in morphological features of neurons in the basal ganglia, most have focused on the dendrites of striatal neurons. Levine (1988) reported decreases of 40-49% in spinal densities of medium spiny GABAergic neurons in the caudate nucleus of old (15-18 years) cats compared to mature (1-3 years) cats. Furthermore, total dendritic length, average dendrite length, average branch length, and the radius of the dendritic field were also decreased by 40%, 30%, 35%, and 30%, respectively, in the medium spiny neurons in the caudate nucleus of the aged cats. These decreases began in 13-year-old cats and may have been the basis for altered striatal electrophysiological responses to cortical and nigral stimulation.

In a study utilizing C57BL/6N mice, McNeill and colleagues (1990) found that medium spiny neurons in the caudal striata of aged mice exhibited significant elongation (138%) between 25 and 30 months. This elongation was partially attributed to compensatory responses to degeneration of neighboring neurons. The caudal striatal medium spiny neurons of young (3 month), motor-unimpaired aged (30 months), and motor-impaired aged (30 month) mice were compared. Although each group had total dendritic lengths that were comparable, when frequency distributions based upon ranges of dendritic lengths (0-600, 601-1200, 1201-1800, >1800 μm) were compared, the neurons of the motor-impaired aged mice differed from the other two groups. Specifically, the number of neurons containing "compact dendritic arbors" (i.e., neurons with total dendritic lengths of <600 μm) in the motor-impaired aged mice was 244% higher than the young mice and 684% higher than the motor-unimpaired aged mice (recall that the dendrites were elongated in the non-impaired aged group, accounting for a lower frequency of neurons with compact dendritic arbors). The authors also reported such qualitative observations as an increased prevalence of cells exhibiting small shrunken dendrites, and atypical dendrites with terminal swellings (instead of the growth cones observed in the non-impaired aged mice) indicative of cellular degeneration in the motor-impaired aged mice.

Although the majority of studies examining age-related morphological changes in the basal ganglia have been limited to the striatum, a few have examined DA neurons in the substantia nigra. Emborg and colleagues (1998) recently reported qualitative observations of degeneration (i.e., decreased neuropil, abnormally-shaped perikarya, stunted neurites) of nigrostriatal DA neurons in aged (25-27 years) Rhesus monkeys. Like McNeill and colleagues (1988, 1990) reported in rats, Emborg and colleagues (1998) reported a significant correlation between behavioral and morphological measures (i.e., nigral DA cell count, see section II-A) in Rhesus monkeys. The altered morphological structure of nigral DA neurons is consistent with similar findings in the pars compacta of the substantia nigra in aged humans (Cruz-Sánchez et al., 1995).

D. Receptors and Transporters

Numerous studies have reported decreases in DA receptor (DAR) densities - especially the D_2-type - with age in mammals. In humans (>70 years) and Rhesus monkeys (22 years), age-related decreases of 30-42% of D_2 binding sites in caudate nucleus have been reported (Lai et al., 1987; Morgan et al., 1987; Severson et al., 1982; Wong et al., 1984). Age-related decreases in D_2 receptor concentrations have been reported to range from 30-60% in rats and mice (>22 months), (Han et al., 1989; Lai et al., 1987; Morgan & Finch, 1988; Severson & Randall, 1985). Decreases in DAR densities have been attributed to decreased production of the receptor protein, as both steady-state levels and synthesis of the D_2 receptor mRNA has been reported to be diminished by 50% in the striata of aged (>22 month) Wistar rats (Mesco et al., 1991; Mesco et al., 1993).

Several groups have reported reductions in DA-stimulated striatal adenylate cyclase in aging. Govoni and colleagues (1977) reported that the activity of adenylate cyclase in 20-24-month-old Sprague-Dawley rats was 64% lower than that of 2-3-month old rats following DA stimulation. Likewise, Makman and colleagues (1979,1980) reported that DA-stimulated adenylate cyclase activity was 50% lower in 5+-year-old rabbits than it was in rabbits < 1-year-old. These reported alterations may be the result of age-related decreases in D_1 DAR densities

(Giorgi et al., 1987) since this receptor has been demonstrated to be positively coupled with adenylate cyclase (Kebabian & Calne, 1979). There is also evidence for regional-specificity of this alteration, as age-related changes in cAMP and adenylate cyclase activity within the striatum but not the nucleus accumbens have been reported (Sugawa & May, 1993).

Age-related decreases in transmembrane proteins are not limited to DARs. There is also evidence for age-related alterations in DA transporters (DATs), which provide the primary mechanism for terminating synaptic DA signals (Giros et al., 1996). Volkow and colleagues (1998) have suggested that the expression of DARs and DATs is regulated by a common mechanism which functions independently of age. Age-related decreases of approximately 70% in the number of DATs between 19 and 90 years have been reported in humans (Allard & Marcusson, 1989; De Keyser et al., 1990). Reported decreases in DATs are lower in rats and monkeys than in humans. Emborg and colleagues (1998) reported decreases in DAT number of 33% and DAT density of 24% in the substantia nigra of 25-27-year old Rhesus monkeys. Araki and colleagues (1997) reported decreases in DATs of 20% in striatum and 50% in substantia nigra of aged 24-month-old F344 rats. Age-related decreases in DAT mRNA in 24-month-old rats (~ 22%; Himi et al., 1995) and 65-72-year-old humans (up to 75%; Bannon & Whitty, 1997) have also been reported. Since age-related decreases in DAT mRNA exceed the rate of DA neuron loss, the observed reductions in DATs have been attributed primarily to decreased DAT mRNA rather than decreased numbers of DA terminals (De Keyser et al., 1990).

E. Summary

In this section, evidence regarding age-associated structural changes in the basal ganglia was reviewed. While the notion of widespread neuronal death in the aging basal ganglia is not supported by the literature, there is evidence for morphological alterations in DA neurons such as decreased dendritic complexity and density of receptor and uptake sites in the striatum. Reports of these alterations are corroborated by functional changes which will be discussed below.

III. Functional Changes

Many factors intrinsic to principal DA neuronal elements are essential for optimal functioning. These factors include such presynaptic processes as neurotransmitter synthesis, storage, metabolism, release, and reuptake/uptake, as well as such postsynaptic processes as receptor functioning, metabolism, and interactions with other concurrent neuromodulators. Compromises in these processes potentially account for the majority of age-related changes in the basal ganglia.

A. Presynaptic

1) Neurotransmitter Synthesis

The synthesis of DA has been reported to be decreased by 26-28% in the striatum of aged (≥25 months) rats (Marshall & Rosenstein, 1990; Ponzio et al., 1978; Watanabe, 1987). This decrease in DA synthesis may be related to reported age-related decreases of approximately 40% in the level of tyrosine hydroxylase (TH) mRNA in substantia nigra of aged (24 month) rats (Himi et al., 1995), and consequential decreased TH activity in striatum (93% decrease reported by Algeri et al., 1977; 32% decrease reported by Ponzio et al., 1982) and substantia nigra (31% decrease reported by Ponzio et al., 1982) of aged (18-30 month) rats. Likewise, decreases of 24-28% in levels of DOPA accumulation following the administration of the aromatic acid decarboxylase inhibitor NSD-1015 have been reported in aged (24-27 month) rats (Marshall & Rosenstein, 1990; Venero et al., 1991; Watanabe, 1987). Some researchers, however, have reported no changes in striatal DA synthesis in aged rats as evidenced by levels of DA and DA metabolites in postmortem tissues (Demarest et al., 1980; Friedemann & Gerhardt, 1992; Hebert & Gerhardt, 1998).

2) Neurotransmitter Storage

Studies examining age-related differences in DA storage (or content) have produced conflicting results. For example, decreases of 20-60% in DA whole tissue content have been reported in the striata of rodents (24-29 month rats; 24-28 month mice) and in the caudate nucleus and putamen of humans (>72.5 years) (Carlsson & Winblad, 1976; Demarest et al., 1980; Finch, 1973; Joseph et al., 1978; Kish et al, 1992; Osterburg et al., 1981; Yurek et al., 1998). However, in other studies, no significant differences in DA levels between young and aged rats and humans were found (Adolfsson et al., 1979; Friedemann & Gerhardt, 1992; Hebert & Gerhardt, 1998; Rose et al., 1986). Likewise, one study reported significant age-related decreases of 34% in striatal DA levels of Rhesus monkeys by 18 years of age (Goldman-Rakic & Brown, 1981), while another reported no significant age effect (Wenk et al., 1989). Finally, Irwin and colleagues (1994) reported a 30% decrease in DA levels in putamen, but not caudate nucleus, of aged (20 years) squirrel monkeys. Although there is a lack of consensus regarding age-related alterations in dopamine content, the point may be functionally moot. These reported decreases in DA levels are not large enough to produce PD-like effects in animals and humans (Hornykiewicz, 1963; Lloyd, 1977; Stricker & Zigmond, 1976). In addition, it has been demonstrated that the amount of DA stored within neurons does not necessarily relate to the release capacity of DA neurons (Dobrev et al., 1995; Friedemann & Gerhardt, 1992; Hebert & Gerhardt, 1998; Rose et al., 1986).

3) Neurotransmitter Release

Numerous studies have reported decreases in stimulus-evoked DA release in the aged striatum (e.g., Friedemann & Gerhardt, 1996; Gordon et al., 1995; Kametani et al., 1995; Rose et al., 1986; Yurek et al., 1998). Diminished potassium-evoked DA release of 22-50% has been demonstrated in the striata of aged (12-24 month) rats (Dobrev et al., 1995; Gregerson & Selmanoff, 1990; however, see Gerhardt & Maloney, 1999 and Kametani et al., 1995 for exceptions) and monkeys (Gerhardt et al., 1995). Likewise, age-related decreases of 30-60% in amphetamine-evoked DA overflow has been reported in the rat (Dluzen et al., 1991; Gerhardt & Maloney, 1999; Kametani et al., 1995; Yurek et al., 1998). Since the neuronal release of DA has been demonstrated to be mediated through primarily either Ca^{2+}-dependent or Ca^{2+}-independent mechanisms, both of these mechanisms may be susceptible to age-related decrements. Besides decreased calcium regulation (Reimann et al., 1993), other mechanisms thought to be responsible for diminished DA release include alterations in the efficacy of neuromodulators and other neurotransmitters that modulate DA release (Buck et al., 1981; Chesselet, 1984; Friedemann & Gerhardt, 1996; Joseph & Roth, 1988a, Joseph & Roth, 1988b) and decreases in DA synthesis (Nakano & Mizuno, 1996).

Decreased DA release may be responsible for decreased locomotor activity observed in aged rats. Although some studies have failed to reveal age-related decreases in spontaneous locomotor activity in rats, when rats are habituated to the activity monitor, age-related decreases are robust and stable over time (Hebert & Gerhardt, 1998). The finding that potassium-stimulated DA release was lower in aged rats than in young rats, along with the demonstration that nomifensine, a DA-uptake inhibitor, increased locomotor activity in aged rats (Hebert & Gerhardt, 1998), suggests that prolonging the postsynaptic DA signal may reverse the age-related decline in spontaneous locomotor activity.

4) Autoreceptor Feedback

As previously mentioned, age-related decreases in the number of D_2 DARs have been reported for a number of species. The fact that presynaptic DA autoreceptors are classified as the D_2 type (Morelli et al., 1988) leads to the question of whether DA autoreceptors are likewise affected by age. In a behavioral assay that is thought to reflect DA autoreceptor function in rats, Stoessl and colleagues (1989) reported that old (23-26 months) Sprague-Dawley rats exhibit diminished yawning following low-dose apomorphine administration when compared to mature (6-8 months) rats. Since DA autoreceptors provide the neuron with feedback regarding the synaptic DA signal, this decreased feedback may provide a compensatory mechanism with which to counter age-related decreases in DA release. Furthermore, the decrease in DA autoreceptor density may also have functional consequences for DA uptake, as the latter process has been reported to be linked in part to D_2 DA autoreceptors (Cass & Gerhardt, 1994).

5) Reuptake/Uptake

As stated earlier, the number of DATs decrease with age in rats and humans. Declines of up to 70% in the number of DATs (De Keyser et al., 1990), as well as the amount of DAT mRNA in rats (~22% decrease) and humans (~75% decrease) have been reported (Bannon & Whitty, 1997; Himi et al., 1995). These decreases have generally not been accompanied by alterations in binding affinities (Allard & Marcusson, 1989; Shimizu & Prasad, 1991). Functional consequences of these changes have been measured through *in vivo* stimulus-evoked DA release and DA clearance (Friedemann, 1992; Friedemann & Gerhardt, 1992; Hebert & Gerhardt, 1999). For example, DA uptake capacity can be measured by examining the amplitude and decay of exogenously applied DA. Hebert and Gerhardt (1999) demonstrated that when 20 pmol of DA was locally applied in the dorsal striatum of 24-month-old F344 rats, the amplitude of the DA signal was almost 3 times greater than the signal recorded in a 6-month-old rat given the same dose. Furthermore, the uptake rate was slower in the aged rats than in the young rats. When uptake rate/μM DA signal amplitude was measured, this value was 39% slower in aged rats than in young rats. Likewise, the maximal uptake rates for aged rats were 72% slower than those for young rats. In studies which have utilized the DA uptake inhibitor nomifensine to measure DAT function, the effectiveness of the drug in blocking the clearance of DA in aged (24-30 month) rats was diminished by almost 50% when compared to young (6 month) rats (Friedemann, 1992; Friedemann & Gerhardt, 1992; Hebert & Gerhardt, 1999). These age-related changes in dopamine clearance may be regionally specific, as Hebert and Gerhardt (1999) reported a slowing of dopamine clearance in the dorsal striatum but not in the nucleus accumbens.

Whereas there is a decrease in striatal DA release with age, the decline in number of uptake sites may be a compensatory mechanism through which the DA neuron adapts to decreased DA signal. This compensation would be consistent with the remarkable adaptive capacity of the nigrostriatal dopamine system (Cass et al., 1995; Hornykiewicz & Kish, 1987; Zigmond et al., 1990). For example, the density of DATs has been reported to decrease in individuals with PD (Uhl et al., 1994), suggesting that a down-regulation of DATs may be an adaptive mechanism through which to increase the amount of extracellular DA. Likewise, there may be a down-regulation of DATs to adapt to the decreased DA signal that has been demonstrated to occur in normal aging.

6) Monoamine Oxidase

The relationship between the catabolic enzyme monoamine oxidase (MAO) and age is controversial (Irwin et al., 1997; Shih, 1975). Studies that have examined MAO levels in rodents during aging have generally reported a positive relationship between age and the level of the "B"-type of MAO isoform (MAO-B) in the basal ganglia. By contrast, either no change or a decrease in the "A"-type of MAO isoform (MAO-A) has been reported. Increases in MAO-B have been demonstrated to be from 124-170% higher in basal ganglia of aged rats (24-25 month) and mice (10-25 month) when compared to young controls (Arai & Kinemuchi, 1988; Benedetti & Keane, 1980; Irwin et al., 1997; Saura et al., 1994; Venero et al., 1991). Conversely, no effect of age was seen in the levels of MAO types A and B as a function of age in squirrel monkeys (Irwin et al., 1997). Irwin and colleagues (1997) argued that their failure to find age-related increases was a true species difference and not related to methodology, since they did find an age-related increase in mice. They further suggest that their results may be a more accurate reflection of age-related changes in MAO, since the results of human studies are potentially confounded by uncontrolled disease states as well as by postmortem interval.

B. Postsynaptic and Extracellular Changes

1) Cellular Electrophysiology

There is considerable evidence for altered electrophysiological properties of aged nigrostriatal neurons. Most studies have reported an increased threshold for elicited responses with age (Cepeda et al., 1996; Gould et al., 1996; Levine, 1988). The increased thresholds have been demonstrated under several conditions. Cepeda and colleagues (1996) reported that the average iontophoretic current intensities necessary to elicit a response to excitatory amino acid (glutamate, NMDA) ejections in *in vitro* striatal cells of aged (24-26 month) rats were 147-161% higher than in young rats. Likewise, Levine (1988) stimulated corticostriatal and nigrostriatal cells electrically while recording responses of cells in the caudate nucleus of aged (11-14-year-old) cats *in vivo*. In this preparation, the electrical current necessary to elicit responses from caudate nucleus cells in aged cats increased 44% for cortical stimulation and 41% for nigral stimulation (however, the current necessary to produce corticostriatal responses in the 6-7-year-old cats was 79% higher than young cats). Finally, using pressure ejections of selective D_1 and D_2 DAR agonists (SKF 38393 and quinpirole, respectively), Gould and colleagues (1996) measured the doses required to produce *in vivo* changes of 50% in striatal neuronal firing rate. They reported that the ED_{50}s (measured in psi X s) required were 315% and 289% higher for SKF 38393 and quinpirole, respectively, in 26-27-month-old versus 3-month-old rats. Somewhat unexpectedly, Levine (1988) found that the average latencies of orthodromically evoked action potentials decreased with age in the caudate nucleus of cats. Upon further examination, however, this decrease was not attributed to increased speed of conduction, but to a loss of long-latency responses in the aged cats. Also reported in some studies were age-related diminishments in paired-pulse facilitation (Levine, 1988; Walsh & Ou, 1994), a deficit that may underlie the relatively diminished capacity for aged rats to habituate to a familiar environment or repeated stimulus (Hebert and Gerhardt, 1998).

In addition to increased response thresholds following either pharmacological or orthodromic stimulation, there are a variety of other altered response characteristics of aged striatal neurons. These include the following: general lack of response, decreased proportion of neurons responding in a distinctive manner, "unusual" responses, reduction in the components of a response, significant changes in the proportion of occurrence of different types of responses, increased durations of response inhibitions and decreased average spontaneous firing rates of caudate nucleus neurons (Cepeda et al., 1996; Levine, 1988).

2) Neurotransmitter Interactions

Despite this chapter's deliberately exclusive concentration on age-related DA function, DA does not exist and function in isolation in the basal ganglia. Potential changes in other neuronal systems that impact on DA neurons may indirectly alter the function of DA neuronal systems in aging. The principal output neuron of the striatum is the medium spiny GABAergic neuron which is modulated not only by nigrostriatal DA neurons, but also by corticostriatal glutamatergic (Glu) neurons and striatal acetylcholinergic (ACh) interneurons (Di Chiara et al., 1994; Parent & Hazrati, 1995; Wilson, 1998). There have been very few studies to date reporting age-related changes in the interactions between different neurotransmitter systems in the basal ganglia. When examined in isolation, reports of age-related changes in corticostriatal Glu function are equivocal. Some studies have found stability of corticostriatal Glu function (e.g., Donzanti et al., 1993; Porras et al., 1993; Sanchez-Prieto et al., 1994), while others have found age-related diminutions or alterations (Castorina et al., 1994; Cepeda & Levine, 1991; Cepeda et al., 1996). Striatal GABA function has been reported to remain steady with age (Govoni et al., 1980; McGeer & McGeer, 1975; Strong et al., 1982). Studies of age-related ACh function have reported declines in synthesis (Gibson et al., 1981), loss of striatal muscarinic cholinergic receptors (Briggs et al., 1989; Norman et al., 1986) and diminished cholinergic receptor binding (Freund, 1980).

Although age-related changes in these non-DAergic striatal neurotransmitter systems appear to vary considerably, when age-related deficits occur in the nigrostriatal DA system, the balance between these modulators of basal ganglia motor output may be compromised (Cepeda et al., 1996; Porras & Mora, 1995; Randall, 1980). For example, in striatal brain slices from aged rats and cats the ability of DA to modulate excitatory amino acid receptor-mediated responses was reduced when compared to slices from young rats and cats (Cepeda et al., 1996). Specifically, depending upon the type of receptor, the response to DA was either lost or the threshold for the response was increased by 232%. Likewise, in the young rat striatum it has been demonstrated that the mixed D_1-D_2 DA receptor agonist apomorphine produces concentration-dependent increases in Glu and GABA release. This modulation was altered in older rats. As the Glu response to apomorphine was decreased the threshold for apomorphine-induced GABA release was increased (Porras & Mora, 1995). Finally, the importance of DA input to ACh function is evidenced by previous studies which have demonstrated that ACh neurons become hyperactive following loss of DA input (Stoof et al., 1992). Likewise, it has been demonstrated that the co-localization of DA autoreceptors and muscarinic and/or nicotinic cholinergic receptors provides a means for cholinergic agonists to enhance striatal DA release by inhibiting DA autoreceptors (Chesselet, 1984). Previous studies have demonstrated that the capacity for cholinergic agonists to enhance potassium-evoked DA release is decreased in aged rats (Joseph et al., 1988; Kametani et al., 1995).

IV. Conclusions

In conclusion, the evidence for age-related decrements in basal ganglia function is considerable and the nigrostriatal DA system seems to incur the majority of age-related deterioration. However, additional studies are needed to investigate potential changes in DA systems in mesolimbic DA pathways and in other areas of the basal ganglia that contain DA fibers. Although there is evidence for loss of DA neurons with age, the degree of loss is not of sufficient magnitude to account for the decrements in movement that accompany senescence that are often termed parkinsonism (Bennett et al., 1996). Of the age-related alterations in the nigrostriatal pathways that correlate with these decrements, most involve functional decrements of neuronal machinery. These include decreases in DA receptors, transporters, as well as DA release and reuptake. Further work, however, needs to be carried out in the areas of DA synthesis, storage, and release, as previous studies examining these processes have produced equivocal results.

With the increasing use of techniques that can study the dynamics of neuronal function, we have only begun to quantify the capacities of neural systems and how these capacities are affected by age. The fact that the weight of evidence indicates a primary role for alterations in the functional processes of existing neurons in age-related movement disturbances is encouraging. Research into these processes may facilitate the development of treatments that can alter the mechanisms of neurons to enhance movement functions in senescence.

V. References

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