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Selective changes in the contents of noradrenaline, dopamine and serotonin in rat brain areas during aging

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Summary. This study examines the age-associated changes in noradrenaline (NA), dopamine (DA), 3,4-dihydroxyphenyl-acetic acid (DOPAC), serotonin (5-HT) and 5-hydroxy-3-indoleacetic acid (5-HIAA) in different brain areas of rats. DA and DOPAC concentrations in striatum increased at third month of age, remaining without significant variations until 12th month of age, and decreasing in 24-month-old rats. DA concentration dropped in hippocampus, amygdala and brainstem of 24-month-old-rats, whereas DOPAC levels decreased only in hippocampus. These changes suggest an age-dependent deficit of the dopaminergic system, presumably related to a reduced number/activity of DA nigrostriatal and mesolimbic neurons. An age-induced decline in NA content was found in the pons-medulla, the area containing NA neuronal bodies. Concentrations of 5-HT were reduced with aging in frontal cortex, showing a tendency to decrease in all brain areas examined. The increased 5-HIAA/5-HT ratio found in frontal cortex, amygdala and striatum suggests an age-related decreased synthesis and an accelerated 5-HT metabolism. The 5-HIAA content decreased in brainstem of the oldest rats. These findings point to a selective impairment of nigrostriatal and mesolimbic DA in aging rats, whereas reductions in NA were restricted to cell bodies region and 5-HT showed changes of different extent in areas of terminals and neuronal cell bodies.

Keywords: Age, aging, serotonin, dopamine, noradrenaline, monoamines.

Introduction

The study of the age-dependent changes in the functional capacity of neurotransmission has been a matter of interest since alterations in monoamine

neurotransmitters might increase the vulnerability of older individuals to the development of physiological and psychiatric disorders (Burchinsky, 1985; Morgan and May, 1990).

So far, attempts to involve an impaired catecholaminergic activity in the neurochemical mechanisms of aging in rodents have been successful. Thus, several reports suggested that a decline in nigrostriatal dopaminergic transmission may occur during the aging process, since the levels and the turnover rate of dopamine (DA) decreased in the striatum of aged rodents (Finch et al., 1978; Demarest et al., 1980; Ponzio et al., 1982; Strong et al., 1982; Carfagna et al., 1985; Machado et al., 1986; Moretti et al., 1987; Venero et al., 1991). In addition, either age-dependent decreases or lack of changes in the levels of DA, 3,4-dihydroxyphenyl-acetic acid (DOPAC) and tyrosine hydroxylase activity were found in several limbic areas (i.e., hypothalamus, hippocampus and olfatory tracts) of rats (Estes and Simpkins, 1980; Algeri et al., 1983; Moretti et al., 1987; Santiago et al., 1988; David et al., 1989; Venero et al., 1993).

The data concerning the age-related changes in the noradrenergic system are controversial. Thus, whereas reductions in noradrenaline (NA) content were described in limbic area, spinal cord, medulla oblongata and pons of old animals (Ponzio et al., 1978, 1982), different results have been reported for other brain areas such as hypothalamus, striatum, mesolimbus and cerebral cortex (Carfagna et al., 1985; Harik and McCracken, 1986; Machado et al., 1986; Moretti et al., 1987).

Discordant data have been also reported on the role of the serotonergic system in aging. An age-related decrease in the content and turnover of serotonin (5-HT) has been described in the striatum (Strong et al., 1984; Machado et al., 1986; Venero et al., 1991) and other limbic areas of the rat (Meek et al., 1977; Roubein et al., 1986), while evidence for unchanged or enhanced 5-HT metabolism was observed in the rat hypothalamus, hippocampus and frontal cortex (Simpkins et al., 1977; Venero et al., 1993). Some authors found age-related reduction in 5-HT uptake in rat brain (Brunello et al., 1988), while others found no alterations (Pradhan, 1980).

One striking characteristic of the effects of aging on the central monoaminergic systems is that they are manifested at various levels of the functional organization of the brain, and probably involve changes of different extent on each neurotransmitter system. Indeed, most data accumulated so far have been obtained in a limited number of cerebral regions and based on the comparison of two age groups, usually in the middle and at the upper end of the lifespan. The present study shows in detail the time-course of the age-dependent changes in the contents of DA, NA, 5-HT and some of their main metabolites in several brain areas which might be representative of the structural organization of these neurotransmitter systems in the rat brain.

Material and methods

Male Sprague-Dawley rats from B&K Universal (Barcelona, Spain) were used. Animals were housed in a climate (21°C) and light-controlled room (12:12 LD cycle; lights on at

08.00h) and allowed food and water ad libitum. At either 1, 3, 6, 12 or 24 months of age, groups of five animals were killed by decapitation between 17.00h–19.00h. The brains were quickly removed and placed on a chilled glass plate on ice to be dissected in discrete brain areas according to Glowinski and Iversen (1966). Brain tissues were frozen at −80°C for later assays.

The content of DA, DOPAC, NA, 5-HT and 5-hydroxy-3-indoleacetic acid (5-HIAA) in the brain tissues was measured by HPLC in a single analysis per sample. Basically, the chromatographic system consisted of a Waters M501 solvent delivery pump, a Spherisorb ODS_2 reversed-phase analytical column (3 μm particle size, 150 × 4 mm), and a Coulochem M5010A detector that included an analytical cell set at +50 mV (first electrode) and +300 mV (second electrode). The mobile phase composed of a mixture of 0.1 M PO_4H_2K, 0.1 mM Na_2EDTA, 0.8 mM octanesulphonic acid and 18% methanol (final pH of 3.10 with phosphoric acid) was pumped isocratically at a rate flow of 0.8 ml/min at room temperature. Tissues were sonicated in the mobile phase, centrifuged 5 min at 12,000 × g, at 4°C and supernatants filtered through a 0.22 μm nylon filter. The concentration of monoamines and metabolites was estimated from data obtained from 20 μl sample aliquots injected into the chromatographic system by comparing peak heights to those of appropriate standards. To estimate procedural losses, an internal standard, 3,4-dihydroxybenzylamine, was added to each sample and data were corrected for recovery of the internal standard (95–100% recovery). Protein contents were measured from aliquots of the homogenate of tissue samples following the Bradford method (1976).

Data were expressed as mean ± standard error of mean (S.E.M). The groups of ages were statistically compared by one way ANOVA followed by Duncan's multiple-range test.

Results

Dopaminergic system

The concentrations of DA and the main dopaminergic metabolite, DOPAC, in the different brain areas studied are shown in Figs. 1 and 2. The DA and DOPAC concentrations showed a progressive increase from young (1 month-old) to adult rats (6 month-old) in the striatum but not in other brain regions with lower catecholamine content. In aged rats (24 months), a significant drop in the striatal contents of DA (−41% vs 3-month-old, −45% vs 6-month-old rats) and DOPAC (−27% vs 6-months-old, −29% vs 12-month-old rats) were observed. Decreased contents of DA and DOPAC were also found in the hippocampus from the 24 month-old rats (DA: −36% vs 3 months, −32% vs 6 months; DOPAC: −40% vs 3 months, −32% vs 12 months). In the amygdala, the concentration of DA was significantly lower (36–38%) in the older rats than in the middle-aged animals (3–6 month-old). The concentrations of DA also fell significantly in the brainstem of aged rats (24-month-old) as compared to animals of one (−30%) and six months (−28%) of age.

Noradrenergic system

The concentration of NA in hippocampus, amygdala and frontal cortex increased significantly from the first to the third month of age; in these areas, the levels of catecholamines were not affected by senescence (Fig. 3). Only the NA content in the pons-medulla decreased significantly in aged rats (24-

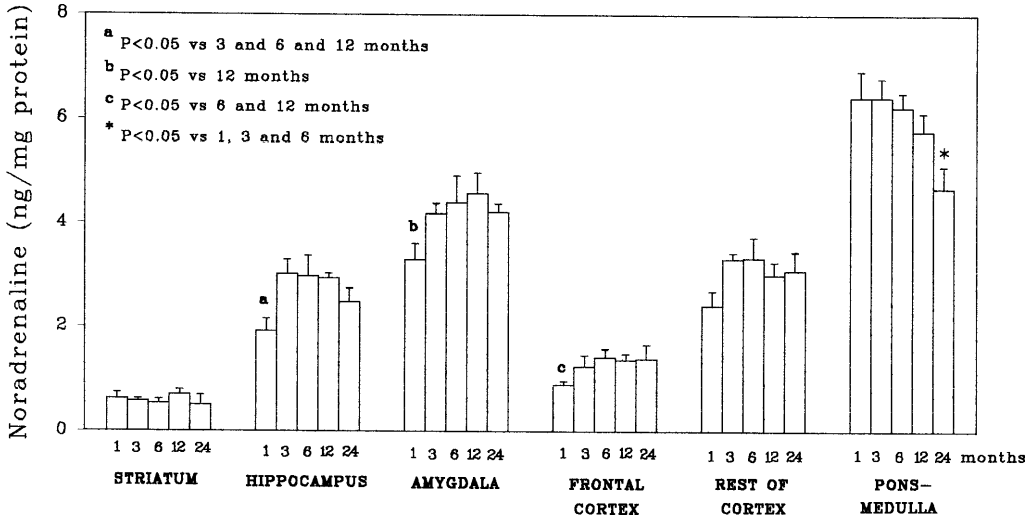

Fig. 1. Changes with age in the levels of noradrenaline in several brain areas of the male rat. Values are the means ± SEM of five animals from each group of age (1, 3, 6, 12 or 24-months-old, axis-X). The statistical significance of differences was calculated by one-way ANOVA followed by Duncan's test

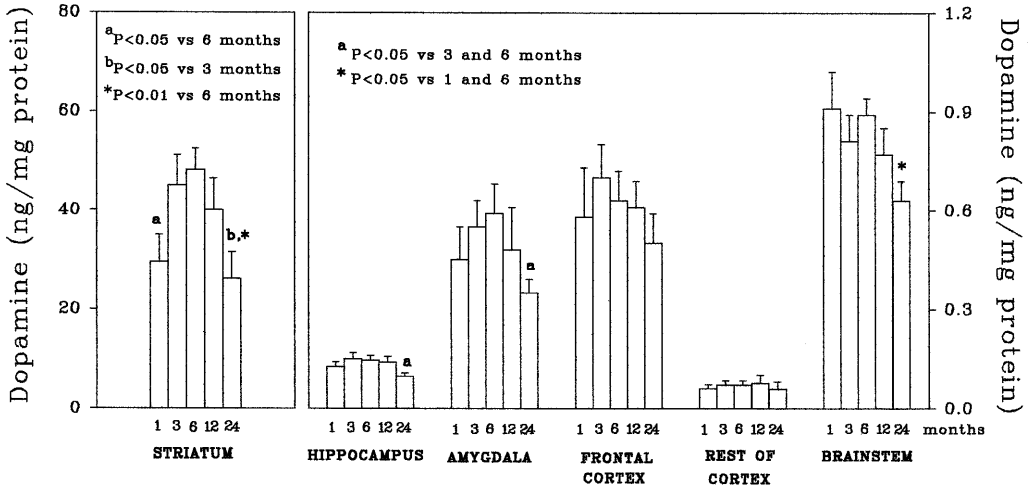

Fig. 2. Changes with age in the levels of dopamine in several brain areas of the male rat. Values are the means ± SEM of five animals from each group of age (1, 3, 6, 12 or 24-months-old, axis-X). The statistical significance of differences was calculated by one-way ANOVA followed by the Duncan's test

month-old), showing concentrations 25–27% lower than in animals of 1, 3 or 6 months of age.

Serotonergic system

The concentrations of 5-HT in the rat hippocampus rose significantly from the first to the third month of age, and a progressive age-related increase in the

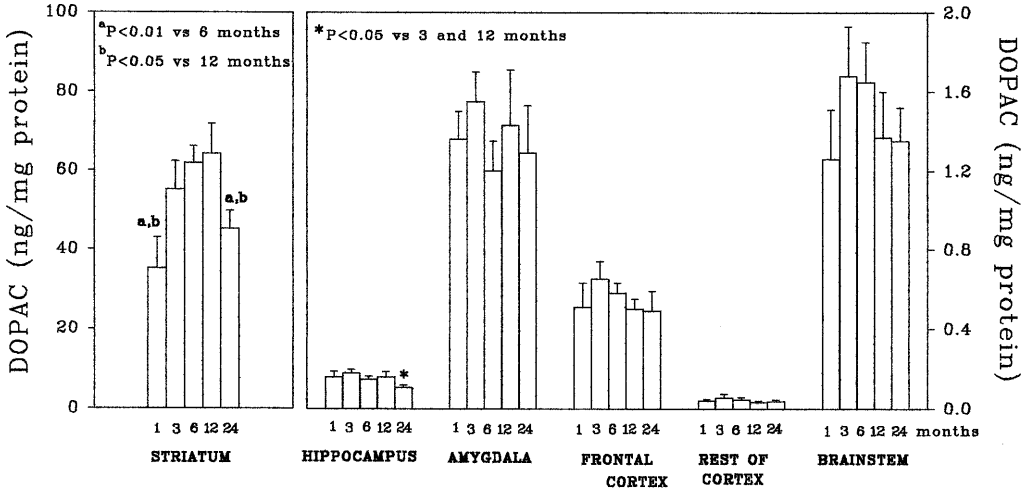

Fig. 3. Changes with age in the levels of DOPAC in several brain areas of the male rat. Values are the means ± SEM of five animals from each group of age (1, 3, 6, 12 or 24-months-old, axis-X). The statistical significance of differences was calculated by one-way ANOVA followed by the Duncan's test

Table 1. Variations with age in the concentration (ng/mg protein) of 5-HT in several brain regions of the Sprague-Dawley rat

Brain region	1 month	3 months	6 months	12 months	24 months
Striatum	1.19 ± 0.21	1.66 ± 0.28	1.94 ± 0.31	1.80 ± 0.29	1.34 ± 0.19
Hippocampus	1.16 ± 0.07	1.64 ± 0.16[a]	1.59 ± 0.17	1.71 ± 0.12[a]	1.37 ± 0.19
Amygdala	2.02 ± 0.22	2.49 ± 0.42	2.59 ± 0.13	2.71 ± 0.21	2.07 ± 0.23
Frontal cortex	0.92 ± 0.20	1.56 ± 0.21	1.48 ± 0.16	1.33 ± 0.17	0.90 ± 0.18*
Rest of cortex	0.58 ± 0.10	0.79 ± 0.13	0.68 ± 0.13	0.65 ± 0.15	0.52 ± 0.09
Brainstem	4.84 ± 0.65	5.59 ± 0.57	5.55 ± 0.80	5.49 ± 0.64	5.06 ± 0.82
Pons-medulla	4.14 ± 0.45	4.77 ± 0.52	4.35 ± 0.50	4.34 ± 0.39	3.79 ± 0.36

Values are mean ± SEM of five animals. [a] $P < 0.05$ vs animals of one month of age; * $P < 0.05$ vs animals of three and six months of age

concentration of 5-HT from the youngest (1 month-old) to the adult (12 month-old) rats was observed in all the brain regions studied (Table 1). From middle age to 24 months of age, the 5-HT content showed a tendency to decline in all brain regions, although this reduction was significant only in frontal cortex (−42% vs 3-month-old; −39% vs 6-month-old rats). These changes in 5-HT levels were not accompanied by alterations in the content of the 5-HIAA in the 5-HT terminal regions (Table 2), and a significant increase in the 5-HIAA/5-HT contents ratio was found in the amygdala (4.46 ± 0.38 ng/mg protein in 24-month-old rats vs 3.18 ± 0.28 ng/mg protein in 6-month-old rats; $P < 0.05$), the striatum (4.33 ± 0.28 ng/mg protein in 24-month-old rats vs 3.09 ± 0.29 ng/mg protein in 6-months-old rats; $P < 0.05$) and the frontal cortex (3.12 ± 0.35 ng/mg protein

Table 2. Variations with age in the concentration (ng/mg protein) of 5-HIAA in several brain regions of the Sprague-Dawley rat

Brain region	1 month	3 months	6 months	12 months	24 months
Striatum	5.35 ± 0.91	5.18 ± 0.76	5.71 ± 0.44	5.93 ± 0.67	5.58 ± 0.46
Hippocampus	4.21 ± 0.32	4.06 ± 0.43	4.14 ± 0.73	4.00 ± 0.32	3.84 ± 0.09
Amygdala	8.04 ± 0.68	8.65 ± 0.44	8.15 ± 0.53	9.20 ± 0.56	8.97 ± 0.67
Frontal cortex	2.98 ± 0.60	3.07 ± 0.38	2.74 ± 0.34	2.39 ± 0.40	3.30 ± 0.23
Rest of cortex	2.36 ± 0.38	2.52 ± 0.33	1.96 ± 0.23	2.18 ± 0.26	2.17 ± 0.57
Brainstem	19.82 ± 1.30	24.40 ± 3.43	26.15 ± 2.00	27.89 ± 2.31	18.83 ± 2.12*
Pons-medulla	6.01 ± 0.84	5.74 ± 0.38	5.45 ± 0.50	5.55 ± 0.61	4.92 ± 0.48

Values are means ± SEM of five animals per group of age. *$P < 0.05$ vs 6-month-old and 12-month-old rats

in 24-month-old rats vs 2.14 ± 0.14 ng/mg protein in 6-month-old rats; $P < 0.05$). In addition, the levels of 5-HIAA decreased by 28–32% in the brainstem of aged rats as compared to middle-aged ones, but no change was observed in the ratio of the contents of 5-HIAA to 5-HT in the mesencephalic area.

Discussion

The present results indicate the existence of a depression in the functional status of brain biogenic amines during aging, which is characterized by a regional selectivity and a differential susceptibility according to the neurotransmitter system considered. We observed a reduction in DA and/or DOPAC levels in DA terminal regions (striatum, amygdala, hippocampus) which agrees with previous studies in the striatum and mesolimbic areas of rats (Demarest et al., 1980; Estes and Simpkins, 1980; Ponzio et al., 1980; Strong et al., 1982; Machado et al., 1986; Moretti et al., 1987; Venero et al., 1991) and humans (McGeer, 1981; Arranz et al., 1996). In addition, a decrease in the striatal DA turnover (Ponzio et al., 1978; Carfagna, 1985; Venero et al., 1991) and high affinity DA uptake (Strong et al., 1984) was found in aged rats, which seems to be related to the well-known loss of dopaminergic neurons projecting to the striatum (Brizee et al., 1981; Kish et al., 1992). The decreased content of DA in the old rat brainstem may reflect either the degeneration of the catecholaminergic neurons with age or, alternatively, the existence of a lower synthesis of DA, since a decrease in tyrosine hydroxylase activity was in fact reported in aging rats (Reiss et al., 1977; Algeri et al., 1983).

The DA striatal neurons come predominantly from the substantia nigra and, to a lesser extent, from the retrorubral and ventrotegmental areas of the brainstem (Ungerstedt, 1971), whereas the amygdala and the hippocampus receive innervation mainly through the mesolimbic tract which originates in the ventrotegmental group of cells (McGeer et al., 1987). It is noteworthy that age affects hippocampal and amydaloid DA content in a similar way to that in the striatum, this suggesting that both the nigrostriatal and the mesolimbic

dopaminergic systems might be simultaneously changed by aging. This result adds to that reported by Demarest et al. (1980) by indicating parallel age-dependent changes in both: the nigrostriatal and the tuberoinfundibular DA systems. However, the metabolism of DA was unchanged in other brain areas, such as the frontal or the remaning cortex, which also receive mesolimbic fibers, thus suggesting a selective age-dependent decline in DA content among the mesotelencephalic dopaminergic neurons.

The most consistent changes in NA were observed from the first to the third month of life. In this period, the concentration of NA increased significantly in hippocampus, amygdala and frontal cortex. A similar increase in neurotransmitter concentration during the first months of life were observed for 5-HT in most of the terminal regions of the serotonergic system, and for DA specifically in the striatum. These results suggest that development of NA, 5-HT and possibly DA in the striatum might be predominantly a postnatal event, as previously reported in other structures of the rat brain (Santiago et al., 1988).

In contrast to DA, the NA concentration in brain regions containing NA projections was scarcely affected by aging, whereas it was severely reduced in the pons-medullary area, a region which includes the locus coeruleus, with most of the NA cell bodies projecting to the diencephalic and telecencephalic structures (Ungersted, 1971). Our results confirm those of authors whose findings showed a reduction in NA activity in the rat locus coeruleus (Olpe and Steinmann, 1982) as well as absence of changes in the NA projection regions, with the exception of the hypothalamus where controversial data were reported (Estes and Simpkins, 1980; Bhaskaran and Radha, 1983; Carfagna et al., 1985). The decrease of NA content was not associated with a similar tendency in DA content in the pons-medulla, suggesting that the mechanism involved in the drop of NA specifically affects the synthesis or the storage of this neurotransmitter.

The content and the turnover of 5-HT in brain areas containing serotonergic nerve terminals have been reported as unchanged (Prahdan, 1980; Ponzio et al., 1982; Moretti, 1987), decreased (Machado et al., 1986; Venero et al., 1991), or increased (Santiago et al., 1988; Venero et al., 1993) with aging. Our results show a decreased 5-HT content in the frontal cortex of 24-month-old rats, although a tendency to decrease was also observed in all 5-HT terminal areas examined. This decline in amine content in brain areas of old rats could be explained because of a lower 5-HT synthesis rate in serotonergic terminal regions (Meek et al., 1977; Venero et al., 1991).

The levels of 5-HIAA, the main 5-HT oxidative metabolite, were found to be decreased in the brainstem of 24-month-old rats. This area contains the raphe nuclei, where most neuronal bodies of the ascending serotonergic system are found (McGeer et al., 1987). Since the levels of 5-HT observed in the brainstem did not change with aging, the deficiency of this amine in the serotonergic terminals of the aged rats could be related to the decrease in the catabolism of 5-HT to 5-HIAA because of the decline in the MAO-A activity (Strolin-Benedetti and Keane, 1980). These results are indicative of a different behavior for 5-HT in senescence, between the regions containing the

5-HT cell bodies and those containing the 5-HT terminals. In support of this hypothesis is the fact that the 5-HIAA/5-HT ratio (considered an index of the metabolic utilization of 5-HT) increased with age in the amygdala, striatum and frontal cortex, whereas it was unchanged in the brainstem. These data reflect that an age-dependent increased oxidative deamination occurs in the 5-HT terminal areas in spite of a lower synthesis of the amine and agree with previous results showing either increases in 5-HIAA content or in 5-HIAA/5-HT ratio in the striatum and mesolimbic areas of the old rats (Moretti et al., 1987; Venero, 1993).

The present results illustrate well that aging has complex effects on the neurotransmitter systems, and that a drop in the biochemistry of DA, NE and 5-HT was manifested at various levels of their functional organization. The hippocampus, amygdala, cortex and striatum are brain areas actively involved in age-related neurodegenerative processes, including motor malfunction, emotive and cognitive disorders, or learning deficiencies associated with dementia, Parkinson's or Alzheimer diseases (McGeer, 1981; Burchinsky, 1985; Kish et al., 1992). These areas show an important deficit of DA and 5-HT, while NA and also 5-HT appeared to be reduced in the lower brainstem, an area that has been related with sleep disturbances and depression in the elderly (Olpe and Steinmann, 1982; Burchinsky et al., 1985). Therefore, changes in the function of single neurotransmitters in specific brain areas or the imbalance between various neurotransmitter systems must be considered in order to understand the mechanisms of aging and to explain some of the age-related impairment of neurophysiological functions.

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