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Effect of Age and Monosodium-L-Glutamate (MSG) Treatment on Neurotransmitter Content in Brain Regions from Male Fischer-344 Rats

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Peripheral administration of monosodium-L-glutamate (MSG) has been found to be neurotoxic in neonatal rats. When administered in an acute, subconvulsive dose (500 mg/kg i.p.), MSG altered neurotransmitter content in discrete brain regions of adult (6 month old) and aged (24 month old) male Fischer-344 rats. Norepinephrine (NE) content was reduced in both the hypothalamus (16%) and cerebellum (11%) of adult rats, but was increased in both the hypothalamus (7%) and cerebellum (14%) of aged rats after MSG treatment. MSG also altered the dopamine content in adult rats in both the posterior cortex and the striatum, causing a reduction (23%) and an increase (12%), respectively. Glycine content in the midbrain of aged rats increased (21%) after MSG injection. Of particular interest is the widespread monoamine and amino acid deficits found in the aged rats in many of the brain regions examined. NE content was decreased (11%) in the cerebellum of aged rats. Dopamine content was reduced in both the posterior cortex (35%) and striatum (10%) of aged rats compared to adult animals. Cortical serotonergic deficits were present in aged rats with reductions in both the frontal (13%) and posterior cortex (21%). Aged rats also displayed deficits in amino acids, particularly the excitatory amino acids. There were glutamate deficits (9–18% reductions) in the cortical regions (posterior and frontal) as well as midbrain and brain stem. Aspartate, the other excitatory amino acid transmitter, was reduced 10% in the brainstem of aged rats. These data indicate that an acute, subconvulsive, dose of MSG may elicit neurochemical changes in both adult and aged male Fisher-344 rats, and that there are inherent age-related deficits in particular neurotransmitters in aged male Fisher-344 rats as indicated by the reductions in both monoamines and amino acids.

KEY WORDS: Monosodium-L-glutamate; aging; neurotransmitters; Fischer 344.

INTRODUCTION

The effect of aging on central monoamine and amino acid neurotransmitters is of great interest in regards to the specificity of age-related neuronal loss and decline in cognitive function. Recent studies on the functional role of the cholinergic neurons of the basal forebrain in aging and memory have generated interesting hypotheses and animal models for age-related neuropathology (1–5). In contrast, the data on age-related changes in monoamine transmitters are conflicting and few studies have addressed the significance of age-related changes in the endogenous excitatory amino acids. This is despite the fact that excitotoxins are thought to play a role in several neurodegenerative diseases and are known to be important mediators of neuronal death (6,7).

Glutamate (GLU) is known to evoke the release of norepinephrine (NE) and dopamine (DA) from a number

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of different brain regions (8,9). Thus, there appears to be significant functional interactions between glutamatergic and monoaminergic neurotransmitter systems. Previous studies in our laboratory have shown that acute injections of GLU can evoke increases in the metabolism of both NE and DA in the hypothalami of adult mice (10). Excitatory amino acid analogs can, when administered intracerebrally or systemically, produce seizures and substantial increases in NE release (9,11). There also appears to be a functional antagonism of excitatory amino acid-induced seizures by α_2-adrenergic receptors in the limbic system (12–15). Thus, age-related changes in NE could alter the excitotoxic potential of endogenous excitatory amino acids.

Previous studies examining monoamine content in the brains of aged rats have not given a consistently clear assessment of the degree or nature of deficits in regional distribution of monoamines, and no studies have examined both amino acid and monoamine content from the same brain regions. The primary aim of the present study was to provide data on the regional content of monoamines and amino acids in the brains of adult (6 month) and aged (24 month) Fischer-344 rats. This information would form the basis for examining specific brain regions for functional deficits in behaviors mediated by transmitters found to show significant age-related alterations.

The second aim of the present study was to assess the neurochemical consequences of the parental administration of a subconvulsive dose of monosodium-L-glutamate (MSG, 500 mg/kg i.p.). MSG can cause degeneration of the ganglion layer of the retina (16), and also cause lesions of the arcuate nucleus and other circumventricular organs in mammals (17,18). When administered to neonatal rats, MSG produces widespread neurochemical and hormonal deficits (19–26). Extremely high doses of MSG have been shown to result in convulsions in adult rats (27). This experiment has the two-fold purpose of assessing the functional integrity of the blood-brain-barrier with regards to plasma GLU in aged rats and also determining the pharmacological action of GLU in the aged brain. In summary, neurochemical indices of monoamine-amino acid neurotransmitter interactions were examined to determine if significant age-related changes could be detected in specific brain regions.

EXPERIMENTAL PROCEDURE

Adult (6 month) and aged (24 month) male Fischer-344 rats (Harlan Sprague Dawley, Indianapolis, IN) were used for all studies. Animals were individually housed and maintained on a 12 hour photoperiod. Food and water were available ad libitum. Animals were randomly assigned to either saline control (isosmotic saline, i.p.) group, or MSG (500 mg/kg, i.p.) group (Sigma, St. Louis, MO). Thirty minutes post-injection, when plasma GLU is at its peak (28,29), animals were sacrificed by decapitation. Trunk blood was collected, and the brains were rapidly removed and dissected on an ice cold glass plate by a modification of the method of Glowinski and Iverson (30). The brain regions isolated consisted of the striatum (STR), hypothalamus (HYP), hippocampus (HIPP), cerebellum (CER), posterior cortex (PCX), frontal cortex (FCX), midbrain (MB), and brain stem (BS, including both the pons and medulla). Tissues were quickly frozen on dry ice and stored at −80°C until analysis. Trunk blood was centrifuged at 3,000 *g* for 10 minutes, plasma was removed and stored at −20°C until amino acid analysis.

Tissues were analyzed for both amino acids and biogenic amines by high performance liquid chromatography with electrochemical detection (HPLC-EC). Briefly, tissues were weighed and homogenized in approximately 20 volumes of 0.1M perchloric acid (PCA) and centrifuged at 10,000 *g* for 10 minutes. The resulting supernatant was injected for monoamine analysis (31) using an isocratic system from Bioanalytical Systems (West Lafayette, IN) consisting of a PM-30 pump, LC4B amperometric detector, LC22A temperature controller, model 7125 Rheodyne injector, and a Zorbax C18, 4.6 mm × 25 cm column (Dupont, Wilmington, DE). Mobile phase was filtered by vacuum through a 0.45 micron filter then purged with helium and consisted of 0.02M monobasic sodium phosphate, 0.02M citrate, 2.5% acetonitrile, 80 mg/l octadecyl sulfate (OSS), and was pH adjusted to 3.5 with 1.8 ml of phosphoric acid. Flow rate and temperature were maintained at 1.5 ml/min, and 35°C, respectively. Data were integrated using a Model 3390A Hewlett Packard integrator. Amino acids were analyzed by diluting the PCA extract with amino acid mobile phase. The resulting final dilution ranged from 1:2 up to 1:10 depending on the tissue. Plasma (300 μl) was deproteinated by the addition of methanol (700 μl) and was then analyzed without further dilutions. The samples were centrifuged for 3 minutes in a Beckman microfuge prior to injection. Amino acids were quantitated using an isocratic system from Bioanalytical Systems consisting of a PM-11 pump, LC4B amperometric detector, "Short-One" C18, 4.6 mm × 10 cm, 3 micron column (Rainin, Woburn, MA), and a Model 7125 Rheodyne injector. Flow rate was 0.97 ml/min at room temperature (25°C). Mobile phase was filtered through a 0.45 micron filter, purged with helium, and consisted of 0.05 M monobasic sodium phosphate, 5% acetonitrile, and 5% tetrahydrofuran at a pH of 5.0. Data were integrated using a model 3390A Hewlett Packard integrator. Amino acid analysis was accomplished by precolumn derivitization with *o*-pthalaldehyde (OPA) using a modification of a method used by others (32,33). Briefly, OPA reagent was prepared by dissolving 81 mg of *o*-pthalaldehyde with 1.5 ml of 100% methanol followed by the addition of 15 ml of 0.1 M Borate (pH = 10.0). To activate the reagent, 60 μl of mercaptoethanol was added, and the activated reagent was allowed to stand for 24 hours at room temperature. OPA-amino acid derivitization was accomplished by the addition of 175 μl of OPA to 200 μl of sample. The reaction was allowed to proceed for 2 minutes at room temperature at which time 25 μl of iodoacetamide (IAA), a thiol scavenger, was added to remove unreacted OPA and reduce the solvent front (34). The mixture was then vortexed and injected. All compounds and reagents were HPLC grade or the highest analytical grade available from Sigma (St. Louis, MO) or from Fisher Scientific (Springfield, NJ).

Statistical analysis was accomplished by using a two-way analysis of variance (age × treatment) with planned multiple comparisons performed using the least significant difference test (LSD test).

RESULTS

I) Biogenic Amine Neurochemistry. Norepinephrine (NE) content (Figure 1) in the cerebellum of aged Fischer-344 male rats was significantly reduced ($P<0.05$) with respect to age. MSG treatment resulted in a significant ($P<0.05$) increase in the NE content of aged rats, whereas adult rats showed a 11% reduction. MSG treatment significantly ($P<0.05$) reduced NE content in the hypothalamus of adult rats by 16%. In contrast, the content in aged rats was increased by 7%, producing a significant ($P<0.05$) difference between treatment groups. Dopamine (DA) stores (Figure 2a & 2b) exhibited age-related reductions in both the posterior cortex and in the striatum of 35% and 10% respectively. MSG treatment exacerbated these differences in the striatum, and also caused a reduction of DA content in the posterior cortex of adult rats. The DA metabolite, dihydroxyphenylacetic acid (DOPAC), was reduced in the frontal cortex of aged animals by 17% (Table I). MSG exacerbated the age effects in the striatum by reducing DOPAC content by 24% in aged rats relative to adult rats. In the midbrain of adult rats, MSG treatment resulted in a significant ($P<0.05$) reduction of DOPAC (23%). There was an age-related 24% reduction in midbrain DOPAC content of aged rats. The other DA metabolite, homovanillic acid (HVA), was significantly ($P<0.05$) reduced in the STR of aged rats by 28%. The indole, 5-hydroxytryptamine (serotonin, 5-HT) (Figure 3). and its metabolite, 5-hydroxyindoleacetic acid (5-HIAA) (Table I) were not altered by MSG, but did display age related decreases in the posterior cortex and frontal cortex (21% and 13% respectively) for 5-HT and a 13% increase in 5-HIAA content in the striatum. There was no change in the 5-HT precursor, trytophan, with respect to either age or treatment in either age groups (data not shown).

II) Amino Acid Neurochemistry. Glutamate content (Figure 4) in the frontal cortex and posterior cortex exhibited age-related deficits of 17% and 16% respectively. A small (9%), yet significant age-related glutamate decline was present in both the midbrain and brainstem of aged rats. A small, non-significant, reduction of GLU stores in the hypothalamus of aged rats was exacerbated by MSG treatment. The treatment with MSG resulted in a significant ($P<0.05$) 26% increase in glutamate levels in the posterior cortex of aged rats. Aspartate content (Table II) was reduced by 10%–16% in the brain stem of both saline and MSG treatment group of aged rats.

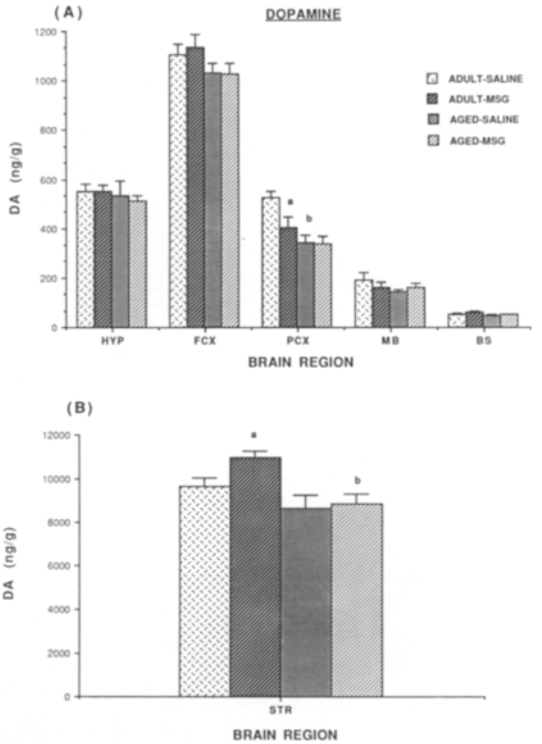

Fig. 2. Dopamine content in (A) hypothalamus, frontal cortex, posterior cortex, midbrain, brain stem, and (B) striatum from adult (6 month) and aged (24 month) F-344 rats (n = 7–8/group). Saline groups received isosmotic saline i.p. while glutamate groups received 500 mg/kg MSG i.p. 30 minutes prior to sacrifice. Analysis was done according to outline in Methods. Data are expressed as mean (ng/g wet weight) ± SEM.
[a] $P<0.05$, treatment effect; saline vs. MSG
[b] $P<0.05$, age effect; 24 month old vs. 6 month old F-344 rats.

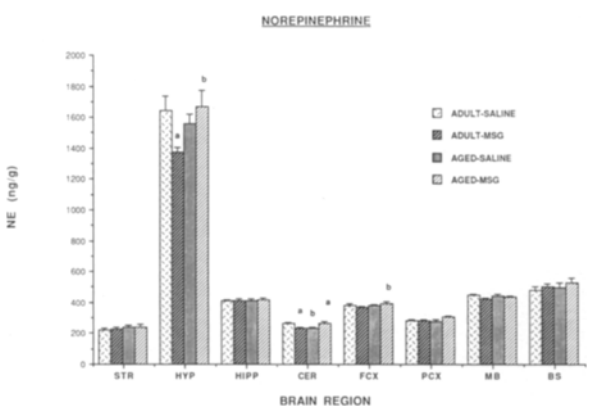

Fig. 1. Norepinephrine content in brain regions from adult (6 month) and aged (24 month) F-344 rats (n = 7–8/group). Saline groups received isosmotic saline i.p. while glutamate groups received 500 mg/kg MSG i.p. 30 minutes prior to sacrifice. Analysis was done according to outline in Methods. Data are expressed as mean (ng/g wet weight) ± SEM.
[a] $P<0.05$, treatment effect; saline vs. MSG
[b] $P<0.05$, age effect; 24 month old vs. 6 month old F-344 rats.

Table I. Regional Metabolite Content from 6 Month Old and 23 Month Old Male F-344 Rats.

	DOPAC (mean ng/g ± SEM)							
	STR	HYP	HIPP	CER	FCX	PCX	MB	BS
Adult-saline (n=8)	1271 ±35	151 ±12	n.d.	n.d.	270 ±16	71 ±4	61 ±5	39 ±2
Adult-MSG (n=8)	1406 ±64	137 ±12	n.d.	n.d.	251 ±9	62 ±4	47[a] ±4	39 ±5
Aged-saline (n=7)	1126 ±76	124 ±19	n.d.	n.d.	223[b] ±9	67 ±9	45[b] ±4	30 ±3
Aged-MSG (n=8)	1066[b] ±78	109 ±10	n.d.	n.d.	208[b] ±10	53 ±4	46 ±5	29 ±1

	5-HYDROXYINDOLEACETIC ACID (mean ng/g ± SEM)							
	STR	HYP	HIPP	CER	FCX	PCX	MB	BS
Adult-saline (n=8)	551 ±24	571 ±29	419 ±22	72 ±5	392 ±27	319 ±10	687 ±20	397 ±11
Adult-MSG (n=8)	605 ±22	524 ±13	426 ±14	77 ±4	363 ±16	351 ±20	682 ±19	381 ±16
Aged-saline (n=7)	625[b] ±24	591 ±17	432 ±22	74 ±5	353 ±22	322 ±19	721 ±24	404 ±17
Aged-MSG (n=8)	690 ±41	597[b] ±20	472 ±28	79 ±4	411 ±17	335 ±17	721 ±25	417 ±19

Data expressed as mean ng/g wet weight ± SEM
MSG (500mg/kg) was administered i.p.
[a]$p<0.05$ MSG vs Saline
[b]$P<0.05$ AGED vs Adult

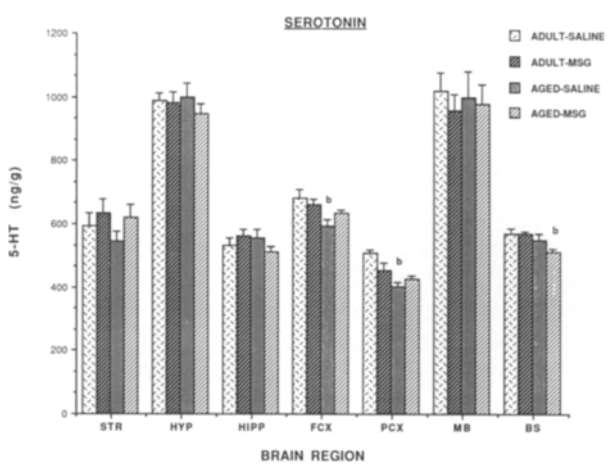

Fig. 3. Serotonin content from adult (6 month) and aged (24 month) F-344 rats (N=7–8/group). Saline groups received isosmotic saline i.p. while glutamate groups received 500 mg/kg MSG i.p. 30 minutes prior to sacrifice. Analysis was done according to outline in Methods. Data are expressed as mean (ng/g wet weight) ± SEM.
[b] $P<0.05$, age effect; 24 month old vs. 6 month old F-344

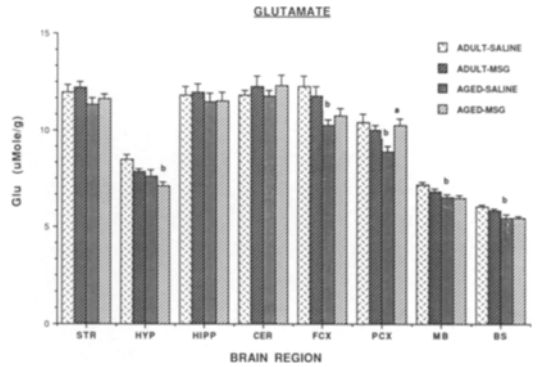

Fig. 4. Glutamate content from adult (6 month) and aged (24 month) F-344 rats (N=7–8/group). Saline groups received isosmotic saline i.p. while glutamate groups received 500 mg/kg MSG i.p. 30 minutes prior to sacrifice. Analysis was done according to outline in Methods. Data are expressed as mean (μMole/g wet weight) ± SEM.
[a] $P<0.05$, treatment effect; saline vs. MSG
[b] $P<0.05$, age effect; 24 month old vs. 6 month old F-344 rats.

Table II. Content of Putative Amino Acid Neurotransmitters in Discrete Brain Regions from Adult and Aged Fischer-344 Rats

	Aspartate							
	STR	HYP	HIPP	CER	FCX	PCX	MB	BS
Adult-saline (n=8)	1.82 ±.21	2.29 ±.05	1.79 ±.09	2.00 ±.05	2.11 ±.07	1.87 ±.08	1.95 ±.05	2.15 ±.05
Adult-MSG (n=8)	2.41 ±.20	2.25 ±.06	1.84 ±.07	1.89 ±.05	2.11 ±.08	1.85 ±.07	1.91 ±.05	2.16 ±.06
Aged-saline (n=7)	1.99 ±.18	2.12 ±.07	1.76 ±.08	1.85 ±.03	2.03 ±.06	1.74 ±.05	1.85 ±.04	1.94[b] ±.06
Aged-MSG (n=8)	1.94 ±.17	2.09 ±.09	1.75 ±.07	1.87 ±.09	2.10 ±.08	1.89 ±.05	1.81 ±.03	1.81[a] ±.08

	Glycine							
	STR	HYP	HIPP	CER	FCX	PCX	MB	BS
Adult-saline (n=8)	0.92 ±.08	1.11 ±.07	0.64 ±.09	n.d.	n.d.	0.67 ±.02	0.69 ±.06	3.28 ±.36
Adult-MSG (n=8)	0.95 ±.02	1.06 ±.05	0.54 ±.05	n.d.	n.d.	n.d.	0.72 ±.06	3.38 ±.43
Aged-saline (n=7)	0.93 ±.04	1.15 ±.08	0.62 ±.03	n.d.	n.d.	n.d.	0.75 ±.06	3.33 ±.40
Aged-MSG (n=8)	0.93 ±.04	0.98 ±.04	0.54 ±.03	n.d.	n.d.	0.57 ±.06	0.91[a,b] ±.05	2.83 ±.31

Data expressed as mean μMole/g wet weight ± SEM
MSG (500mg/kg) administered i.p.
[a]$p<0.05$ MSG vs Saline
[b]$p<0.05$ aged vs adult

MSG treatment resulted in a 21% increase in glycine content (Table II) of the midbrain of aged animals. The other amino acids analyzed; asparagine, alanine, gluta-

mine, and trytophan showed no age-related, or treatment-induced change (data not shown).

The plasma amino acid profile of adult and aged rats given MSG is shown in Figure 5. The systemic administration of MSG increased plasma GLU (19.6 fold) in adult rats and (5.4 fold) in aged rats (Figure 5). MSG treatment also significantly elevated ALA in both adult and aged rats (Figure 5). ASP and GLN was elevated by MSG treatment in adults but not aged rats. Plasma TAU was significantly lower in aged rats than adults independent of MSG treatment (Figure 5). Plasma ASN, HIS, SER, GLY and THR were not altered by either age or MSG treatment (data not shown).

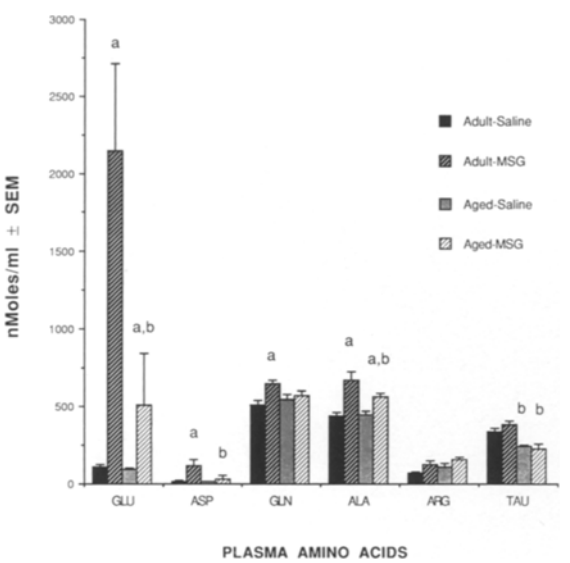

Fig. 5. Plasma amino acid profile in adult and aged F-344 rats. Saline or MSG (500mg/kg,i.p.) was administered 30 minutes prior to sacrifice. MSG treatment produced a significant rise in plasma GLU and ALA in both adult and aged rats.
[a] $P<0.05$, treatment effect; saline vs. MSG
[b] $P<0.05$, age effect; 24 month old vs. 6 month old F-344 rats.

Table III. Summary of Age-Related Changes in Amino Acid and Monoamine Content from Male Fischer-344 Rats

	NE	DA	DOPAC	5HT	5HIAA	GLU	ASP	GLY
Striatum	110	90	89	92	113*	95	109	101
Cerebellum	89*	n.d.	n.d.	n.d.	103	97	84	n.d.
Frontal Cortex	100	94	83*	87	90	82*	94	n.d.
Posterior Cortex	99	65*	94	79*	101	84*	93	n.d.
Midbrain	99	74	74*	98	105	91*	95	109
Brainstem	103	89	78	96	102	91*	90*	102
Hypothalamus	95	97	82	101	104	90	93	104
Hippocampus	100	n.d.	n.d.	104	103	97	98	97

Data are expressed as percent of the mean from age-matched controls
* $p<0.05$
n = 6-8/group
n-d-:not determined

DISCUSSION

Monosodium-L-glutamate (MSG) is commonly used as a flavor enhancer for food, and its neurotoxic characteristics have been well established. MSG, when administered peripherally does not cross the blood brain barrier (BBB) to a great degree. To date, much of the toxicological properties of MSG have been established utilizing neonatal animals due to their increased sensitivity to MSG. In the rat, the protective "tight" junctions of the BBB are functional by the second week of fetal life (35); therefore the major neurotoxic actions of MSG are due to an increased sensitivity of the circumventricular organs (CVOs) that are outside the BBB and to neurons that are adjacent to the CVOs.

One of the goals of this study was to examine possible age differences in the ability to handle an acute, subconvulsive dose of MSG. Adult rodents appear to be relatively insensitive to the effects of MSG. Other studies have suggested that the aged brain may exhibit alterations in BBB function (36–38) as indicated by increased CSF/serum ratios for IgG and albumin; thus we wished to investigate the possible increased sensitivity of aged rats to MSG. Administration of MSG using an acute, subconvulsive dose (500 mg/kg i.p.) resulted in few neurochemical changes 30 minutes after injection. Although plasma levels of glutamate increased (5–19 fold), brain content was not significantly altered in any of the regions examined with the exception of the PCX. This is due to the ability of the BBB to regulate net GLU flux across of the BBB. Glutamate is transported into the brain by an acidic amino acid carrier. The Km for this carrier has been reported to be on the order of 40 μM (39). Under these conditions, the transporter is fully saturated at normal physiological plasma concentrations of glutamate, thereby not allowing accumulation of MSG in the brain. It appears from these data that although age-related differences in MSG absorption, distribution or metabolism exists in the periphery, the functional integrity of the BBB and GLU transporter function are intact in aged rats.

To date, there have been few comprehensive studies examining neurochemical differences as a result of the normal aging process. Most investigators have looked at a few select areas, or subnuclei within a region, but extensive investigations are lacking. Within the last year, Banay-Schwartz et. al. (40,41) published a very elegant

Table IV. Summary of MSG-treatment on Central Amino Acid and Monoamine Content from Adult and Aged Fischer-344 Rats.

	NE		DA		DOPAC		5HT		5HIAA		GLU		ASP		GLY	
	Y	O	Y	O	Y	O	Y	O	Y	O	Y	O	Y	O	Y	O
Striatum	104	100	114*	102	111	95	107	114	110	110	102	103	132	97	103	100
Cerebellum	89*	114*	n.d.		n.d.		n.d.		n.d.		104	104	94	101	n.d.	
FCX	94	104	103	99	93	94	97	97	93	116	96	105	100	103	n.d.	
PCX	100	109	77*	99	87	79	89	106	110	104	96	115	99	109	n.d.	
Midbrain	95	99	85	115	77*	102	94	98	99	100	95	100	98	98	104	121*
Brainstem	96	106	116	111	103	100	100	93	96	103	97	99	100	93*	103	85
Hypothalamas	84*	107*	100	96	91	88	99	95	92	101	93	93	98	99	95	85
Hippocampus	100	102	n.d.		n.d.		102	92	102	109	101	100	103	99	84	87

data are expressed as a percent of the mean from saline-controls
*$p < 0.05$
n = 6-8/group (Y: 6 month old, O: 24 month old F344 rats)
n.d.: not determined

study using Fischer 344 rats and the micropunch technique to examine a series of amino acids in fifty-three different regions of the brain. Many other studies have also been done utilizing differing strains, sex, age, or different species. Although conflicting, there is in general, either a decrease or no change in CNS neurotransmitters in different brain regions with respect to age. Other studies have suggested that the cholinergic system seems particularly vulnerable to the aging process in the basal forebrain, and the hippocampus (42–46). In our study, we examined the monoamines as well as putative amino acid transmitters.

Norepinephrine may be involved in protecting the brain from GLU toxicity through α_2-adrenergic receptors (12–15). Therefore, we chose to examine NE with regard to age and MSG treatment. The decreased cerebellar NE content reported in our study is in conflict with others who found no change in the cerebellum of aged rats (47). In the cerebellum, there is reportedly an age-related decrease in post-synaptic sensitivity to NE when applied to purkinje cells (48). This may be due to a decrease in β_2-adrenoceptor binding found in the cerebellum of aged animals (49–51). We found no age-related change in NE stores in the other brain regions studied. These data support the work by others who found no change in the NE stores of the midbrain, and cortex (42,53,54). There have been reports of decreased NE stores in the brainstem (47,54), midbrain (47,54), hypothalamus (47,53–57), and cortex (58) as well as increased NE content (58) in the striatum which were not substantiated by our findings. Simpkins and co-workers showed a decreased NE content and turnover in discrete nuclei of the hypothalamus, including; median eminence, preoptic area, medial forebrain bundle, and the suprachiasmatic nucleus (56,57). Our findings suggest that cerebellar noradrenergic neurons may be affected by age. The decrease in NE content seen in our study may manifest itself in the alterations of other noradrenergic markers, in the aged brain, i.e. binding and second messenger, as seen by different investigators (49–52). NE neurons projecting to cortical and subcortical areas may, in turn, be resistant to age-related deficits. The decrease in NE content in the HYP as a result of MSG treatment may be due to the increased metabolism of NE as seen previously (10). MSG-related changes in NE content in the cerebellum may be due to increased release or metabolism in the adult rats, and a decreased metabolism or release in aged animals.

The striatal DA system appears to be very sensitive to the natural aging process. We demonstrated both a 10% decrease in DA content as well as decreased homovanillic acid content in this region. This would indicate a decreased turnover due to a possible decreased functional state, or loss of DA nerve terminals in the striatum. The reduction in DA stores may most likely be due to a decrease in tyrosine hydroxylase activity in the DA-enriched areas (59). Our results showing decreased striatal DA stores are in agreement with the literature (47,57,58,60). The decrease in DA in the posterior cortex may be due to visual system atrophy associated with the cataracts seen in many of the aged rats at the time of sacrifice. This dysfunction may have resulted in the reduction of DA in the occipital lobe portion of the posterior cortex. There was no change in DA content in the other brain regions examined, although DOPAC was reduced in both the frontal cortex and midbrain of aged rats. This would indicate a reduced function of the DA neurons in this area or enhanced intraneuronal DA metabolism as indicated by an age-related increase in monoamine oxidase activity (47). This finding is in accord

with work done by others in the brainstem (53), midbrain (47,53), hypothalamus (60), and cortex (47). Decreases in DA have been reported in the hypothalamus (47,60) and cortex (58). DA receptors, D_2 in particular, decrease in both humans and animals as result of age (59,61–65). The present findings would appear to substantiate a decreased number or functional state of the DA nerve terminals innervating the striatum of aged rats. The decreases in DA and DOPAC agree with other findings using different rat strains, and the loss of DA receptors reported by others may suggest that DA containing neurons are vulnerable to the aging process and are lost with time.

Our findings suggest that some degree of glutamate/monoamine interaction does exist in adult rats. This is indicated by MSG's ability to decrease NE content in both the hypothalamus and cerebellum of adult rats as well as decreasing DA content in the posterior cortex. MSG had the opposite effect in the striatum of adult rats, producing an increase in DA content. These differences may be due to MSG's ability to alter NE and DA metabolism or release in different brain regions (8–10). This possible interaction is not present in aged rats after an acute, subconvulsive dose of MSG; therefore, this glutamate/monoamine interaction seen in adult rats may be disrupted in aged animals. This would be consistent with reports of decreased numbers of NMDA receptors in the aged brain (66).

There are few reports of age-related changes in 5-HT. Reductions in 5-HT content found in the brains of aged rats were confined to the cortical region, which is similar to that reported elsewhere (58). Age-related decreases in 5-HT have been reported in the brainstem, midbrain (47), and striatum (58) while Bhaskaran et al. found no change in 5-HT content in the cortex, striatum, and cerebellum (47). The impact of serotonergic changes in aging is uncertain, although some markers of serotonergic function are decreased in age-related diseases such as Alzheimer's (67–69). The increase in 5-HIAA content in the striatum may be due to enhanced intraneuronal metabolism (47), increased release or, decreased clearance of the metabolite from the aging brain. These data suggest that 5-HT neurons projecting to cortical regions may be lost as a function of age and that striatal 5-HT metabolism is altered in aged rats.

Glutamate is one of the most abundant of the neuroactive amino acids, and has been implicated in neuronal death associated with age-related pathologies (6,7). In our study, glutamate was reduced in aged animals in both the frontal and posterior cortex. This reduction in GLU may represent a loss of cortical pyramidal neurons in these regions which are thought to form the intracortical association projections. Deficits in GLU content were also seen in the midbrain and brainstem of aged rats. A deficit in aspartate, a putative excitatory amino acid transmitter of the brainstem and climbing fibers of the cerebellum, was found in the brainstem of aged rats. In earlier studies utilizing F-344 rats we examined other indices of glutamatergic function, i.e. release and uptake. There were no difference between adult and aged rats in either GLU release, or uptake measured in frontal cortex slices (70,71). We have also recently found that glutaminase (L-glutamine amidohydrolase, E.C. 3.5.1.2) activity is reduced in the temporal cortex of aged F-344 rats (72). Since glutaminase is one of the enzymes responsible for the formation of neurotransmitter GLU (73); a reduction in its activity may result in the decreases in GLU content seen in the present study. Currently, studies are underway to further examine regional glutaminase activity and regulation. Collectively, these studies suggest that glutamate neurons in the frontal cortex are resistant to changes related to age. The temporal cortex, and the striatum, are affected by age as indicated by decreases in glutaminase activity in the temporal cortex and striatum. Thus, it appears that the temporal cortex may be more sensitive to the aging process and therefore show changes in glutamatergic indices. Further studies are needed to determine the extent and nature of these changes.

Glycine, a putative inhibitory amino acid neurotransmitter was unchanged by age as was taurine (74). MSG treatment did result in an increased glycine content in the midbrain of aged rats, and therefore, may alter the inhibitory input glycine exerts on other neuronal systems in the midbrain involved in seizure suppression. The complex functional role of glycine makes the interpretation of the MSG-induced glycine increase difficult. Glycine is a putative inhibitory neurotransmitter, modulator (enhancer) of glutamate binding to the NMDA receptor, and is involved in the interconversion of α-ketoglutarate and glutamate via the enzyme glycine α-ketoglutarate transaminase. MSG-induced alterations in any one of these functions could contribute to the increase in glycine content in adult rats.

The work by Banay-Schwartz et. al. (40,41) suggests that decreases in content occur 5–6$\times$ more frequently than do increases. Our work tends to agree with that finding. Although their measurements were very anatomically discrete our findings tend to support the decreases seen in micro-dissected areas of the brain. Our decreases were smaller in magnitude than theirs, but our values are based on wet weight and theirs on per milligram protein which may inflate values if protein content is decreased in aged animals. In summary, from the data presented it is evident that reductions in neurotransmitter

content do exist in the male Fischer 344 rat and these reductions appear to be age-related. Each of the transmitters examined exhibited an age-related reduction in at least one brain region. These reductions are physiologically important when studying the neurochemistry of aged animals, especially male F-344 rats. In light of our studies, it is apparent that cortical regions, i.e. frontal and posterior cortex, are affected more severely than are subcortical regions, with the possible exception of the striatum. These reductions may reflect a loss of noradrenergic, dopaminergic, glutamatergic or serotonergic terminals which may be found in these brain regions. Administration of a subconvulsive dose of MSG resulted in an exacerbation of the age-related deficits in regions such as the hypothalamus (GLU), cerebellum (NE), and brainstem (5-HT). MSG did appear to affect adult animals to a greater degree than aged F-344 rats. This may indicate that a GLU/monoamine relationship exists in both adult and aged rats, but adult rats are more sensitive to exogenously administered excitotoxins in subconvulsive doses, and that although aged rats exhibit a GLU/monoamine relationship, it appears that aged rats may lack the sensitivity of the adult interaction. Moreover, the aged rats may have lost GLU-sensitive postsynaptic neurons as a function of age and could be refractory to exogenous GLU. This interpretation should be taken cautiously since aged rats may exhibit pharmacokinetic differences in MSG distribution or altered peripheral GLU metabolism as evidenced by their delayed or blunted rise in plasma GLU. It is also possible that central differences may exist due to a loss of neurons, thus causing a neuron/glial ratio shift. If aged rats have a loss of glutamatergic neurons, there may be decreased GLU reuptake and reutilization thereby impairing the GLU/monoamine interaction. An impairment of the glutamate metabolic process may exist if there is a concomitant gliosis resulting from the loss of neurons in aged rats. There may be an impairment of glucose metabolism in aged animals and glutamate may be shunted into the Krebs cycle to compensate for a decreased glucose utilization. Aged animals which received MSG may shunt the MSG into the "metabolic" pool of glutamate to compensate for possible deficits in glucose metabolism while adult animals utilize the MSG for the "neuronal" pool of glutamate. Although data from our lab, as well as others, strongly suggest a GLU/monoamine relationship using convulsive doses of neurotoxins, care must be taken in interpreting the results from MSG treatment due to the ubiquitous metabolic nature of glutamate. We do demonstrate that clear age-related changes exist in the Fischer 344 strain, in both amino acids and monoamines and this is one of the first studies to clearly examine both amino acid and monoamine content in a series of brain regions with regards to age.

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