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Review

Serotonin, memory, and the aging brain

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Abstract. Serotonin is widely distributed throughout the central nervous system and is implicated in a variety of neural functions such as pain, feeding, sleep, sexual behavior, cardiac regulation and cognition. This paper is concerned with the last of these. Abnormalities of the serotonergic nervous system are well documented in pathologic studies of Alzheimer's disease and there is evidence suggesting that changes in this system occur in association with non-disease aging. Data on the role of serotonin in learning and memory and on the effects of aging on brain serotonin function are reviewed and discussed in relation to pharmacologic treatment strategies for the memory impairments associated with advancing age.

Key words: Serotonin – Monoamines – Memory – Aging

The role of brain neurochemical systems in cognitive functioning is a subject of increasing research interest as age-related cognitive disorders emerge as major public health problems. The hypothesis, introduced more than a decade ago, that cholinergic deficiency underlies the memory impairment of Alzheimer's disease (AD) launched an intensive effort to find drugs that can restore brain cholinergic function and improve cognition in Alzheimer patients; an effort that, so far, has produced discouraging results. Thus, investigators searching for drugs to improve cognition in demented patients may face a predicament of low expectations.

On the other hand, the neurotransmitter replacement strategy, which has guided most of the pharmacologic research on dementia, may be more fruitful if directed at the more common and modest cognitive impairments associated with non-disease aging. Kral (1962) reported a condition of mild impairment of memory in the elderly, not associated with dementia after 4 years of follow-up, and labeled it "benign senescent forgetfulness." Another state of age-related memory impairment was more recently defined with specific inclusion and exclusion criteria and describes healthy persons over age 50 who have experienced a decline of memory capabilities relative to their level of function in earlier adulthood. This condition is named Age-Associated Memory Impairment or AAMI (Crook et al. 1986). However, investigators have not yet reached general agreement regarding the definition of these mild impairments of memory which are common among non-demented elders (Lane and Snowden 1989; Reinikainen et al. 1990) and may be part of normal aging. Nonetheless, an expanding investigation is underway aimed at developing safe and effective pharmacotherapy for this age-related loss of mnemonic function.

Presently, there is much interest in the role that non-cholinergic neurochemical abnormalities may play in cognitive disorders. Multiple neurochemical deficits are well documented in reports of pathologic studies of AD patients (for review see Rossor and Iversen 1986) and may also underlie the relatively mild cognitive impairments associated with non-disease aging. We recently reviewed data indicating an age-related loss of brain catecholamine (CA) function that may underlie the loss of memory abilities associated with advancing age and discussed the potential implications of combined deficits of CA and acetylcholine (ACh) in research on treatments for this condition (McEntee and Crook 1990).

Neurons containing serotonin (5-hydroxytryptamine, 5-HT) comprise another neurochemical system of the brain, shown to be abnormal in AD (Bowen et al. 1983; Gottfries et al. 1983; Arai et al. 1984; Curcio and Kemper 1984; Palmer et al. 1987) and considered important for learning and memory (for review see Altman and Normile 1988). Data on the effects of serotonergic drugs on learning and memory in animals and in humans with cognitive impairments are being reported with increasing frequency. These data and those from experiments on the state of 5-HT function in the aged brain will be reviewed and discussed in relation to the memory impairments associated with "normal" aging.

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Anatomic features of serotonergic neurons

The serotonergic nervous system is probably the oldest and most widely distributed of all putative neurotransmitter systems of the brain and is implicated in a variety of neural functions. Like other monoaminergic neurons, cell bodies for 5-HT-containing neurons, are relatively few in number, are situated in the brain stem, and have processes which ramify and project throughout the CNS. The cell bodies of neurons that provide 5-HT innervation to the forebrain are in the dorsal and median raphe nuclei of the midbrain and upper pons. In the adult rat, nerve terminals containing 5-HT have a mean density estimated at 5.8 million/mm^3 in anterior cerebral cortex (Audet et al. 1989) and 2.7 million/mm^3 in hippocampus (Oleskevich and Descarries 1990). Taking into account tissue volume and neuronal density, the average range for numbers of these terminals per target neuron is 145–230 in rat cortex (Audet et al. 1989) and 20–130 in rat hippocampus (Oleskevich and Descarries 1990). Nerve terminals containing 5-HT are located at synaptic and non-synaptic sites (Seguela et al. 1989), suggesting that this neurochemical acts as a neurotransmitter and neuromodulator.

Serotonin and the aging brain

In contrast to the substantive evidence indicating a decline of brain CA activity with advancing age in humans and animals (for review see McEntee and Crook 1990), evidence for changes in brain 5-HT function, as a result of aging, is somewhat limited. Analyses of postmortem human and animal brains fail to demonstrate a decline with age in the concentrations of 5-HT or its primary metabolite, 5-hydroxyindoleacetic acid (5-HIAA). In some instances there is an age-related increase in the brain content of these compounds. Table 1 summarizes these data. Likewise, no evidence emerges to suggest that 5-HT-containing presynaptic neural elements are lost as a result of aging. Table 2 gives the results of radioligand-binding studies in postmortem human and animal brains which estimate the density of 5-HT nerve terminals relative to advancing age. The most consistent data for age-related changes in the 5-HT system are radioligand-binding studies that demonstrate diminished populations of 5-HT receptors with age in rat and human brains. Table 3 shows these results.

In addition, age-related data from studies of rat brains suggest increased turnover of 5-HT (Moretti et al. 1987; Brunello et al. 1988), a reduction in 5-HT high-affinity uptake (Brunello et al. 1988), and a decrease, in vitro, in postsynaptic actions of 5-HT on hippocampal granule cells (Baskys et al. 1987). Ebel et al. (1987) point to measures of brain monoamine activities, including 5-HT, that vary between different inbred strains of aged mice. An age-related increase in turnover of 5-HT in hippocampus found in one strain was not present in another strain, leading the authors to suggest that genotype is a factor in the capacity of neurotransmitters and neuromodulators to adapt to aging processes.

Table 1. Age-related changes in the concentrations of 5-HT and 5-HIAA in brain

Species	5-HT	5-HIAA	References
Rat	0	+	Simpkins et al. 1977
Rat	0		Ponzio et al. 1982
Rat	+		Timras et al. 1982
Rat		+	Godefroy et al. 1989
Mouse	+	+	Thurmond and Brown 1984
Human	0	0	Wester et al. 1984; Marcusson et al. 1987

+ (increase), − (decrease), 0 (no change)

Table 2. Age-related changes in the density of radioligand binding sites for 5-HT nerve terminals in brain

Species	Change	References
Rat	+	Brunello et al. 1988
Rat	0	Allen et al. 1983
Mouse	+	Severson 1986
Human	−[a]	Severson et al. 1985
Human	+[b]	Marcusson et al. 1987
Human	0	Allen et al. 1983

+ (increase), − (decrease), 0 (no change)
[a] In cingulate cortex only. No change in frontal cortex, neostriatum, amygdala or hippocampus
[b] In frontal and parietal cortex and hypothalamus

Table 3. Age-related changes in the density of radioligand binding sites for 5-HT receptors in brain

Species	Receptor/Type	Change	References
Rat	5-HT$_2$	−	Brunello et al. 1988
Human	non-specific	−	Marcusson et al. 1984a
Human	5-HT$_1$	−	Shih and Young 1978; Allen et al. 1983; Middlemiss et al. 1986
Human	non-specific[a]	−	Allen et al. 1983

− (decrease)
[a] Authors suggest data indicate postsynaptic receptor density

Overall, the data do not present a clear picture of the state of serotonergic function in the non-disease aged brain, but in part, imply that 5-HT turnover is increased and numbers of 5-HT receptors are reduced, as a result of aging.

Serotonin and memory

Data on the effects of 5-HT on learning and memory are inconsistent. For instance, inhibition of 5-HT synthesis in rodents, by treatment with *p*-chlorophenylalanine, is shown to expedite (Brody 1970), hinder (Valzelli and Pawlowski 1979) or not affect (Kohler and Lorens 1978) learning of an active avoidance paradigm, and treatment

Table 4. Impairment of mnemonic function by experimental measures intended to stimulate 5-HT activity

1. Treatment with several 5-HT receptor agonists, given separately to a group of rats, produced a dose-related impairment of efficiency in performance of a radial maze task (Winter and Petti 1987)
2. Intrahippocampal implantation of neonatal serotonergic nerve grafts impaired performance of rats on a complex spatial learning task (Ramirez et al. 1989)
3. Treatment with the 5-HT agonist, *m*-chlorophenylpiperazine (*m*-CPP), at a dose of 0.1 mg/kg, worsened measures of recent knowledge and memory in patients with AD, but not in elderly controls (Lawlor et al. 1989a)
4. Treatment with *m*-CPP at a dose of 0.08 mg/kg, diminished performance on tests of recent memory in elderly controls, but not in AD subjects (Lawlor et al. 1989b)

Table 5. Enhancement of learning and memory by treatments presumed to impede 5-HT activity

1. Post-training administration of the serotonergic receptor antagonists: pirenperone, ketanserin, mianserin, methysergide and metergoline improved memory in mice for a previously learned aversive behavior (Altman and Normile 1986)
2. Neurotoxin-induced depletion of 5-HT in hippocampus enhanced performance of rats on a complex spatial learning task (Altman et al. 1988)
3. Post-training treatment with the 5-HT antagonists ketanserin and mianserin attenuated deficits in passive avoidance retention normally displayed by middle-aged and aged rats (Normile and Altman 1988)
4. Post-training treatment with ketanserin and mianserin protected rats against a hypoxia-induced deficit in performance of a passive avoidance task (Strek et al. 1989)
5. Treatment with methysergide, a 5-HT receptor antagonist, significantly improved performance on a visual memory task in a group of Korsakoff amnesics (McEntee and Mair 1980)

Table 6. Experiments with 5-HT uptake blockers that resulted in improved performance on tasks of learning and memory

1. Treatment of mice with alaproclate and zimeldine facilitated retrieval of a learned shock-avoidance behavior (Altman et al. 1984)
2. Mice treated with fluoxetine showed enhanced retrieval of a T-maze active avoidance task (Flood and Cherkin 1987)
3. In rats, post-training treatment with fluoxetine prevented the performance deficit in passive-avoidance behavior produced by exposure to hypoxia (Strek et al. 1989)
4. Attenuation of alcohol-induced memory impairments in adult male human volunteers was effected by treatment with zimeldine (Weingartner et al. 1983)
5. Recall of recently presented information was improved in a group of patients with Korsakoff's psychosis after treatment with fluvoxamine (Martin et al. 1989)

of rodents with 5-HT antagonists generally produces a memory-enhancing effect (Wetzel et al. 1980; Altman and Normile 1986), but there are data to the contrary (Bammer 1982; Kubo et al. 1988). Despite the inconsistencies, the preponderance of evidence shows that stimulation of 5-HT activity in the brain impairs, whereas impedance of its activity enhances learning and memory.

Data that illustrate impairment of mnemonic function by experimental measures intended to stimulate 5-HT activity in the brain are listed in Table 4. Table 5 presents examples of enhanced learning and memory by treatments presumed to impede 5-HT activity in the brain.

Drugs that inhibit uptake of 5-HT into the presynaptic nerve terminals are presumed to increase serotonergic transmission by raising synaptic concentrations of 5-HT. A number of these drugs were studied for their effects on learning and memory. Surprisingly, in most instances these studies showed that treatment with 5-HT uptake inhibitors bettered mnemonic task performance in animals and humans. Table 6 lists experiments that typify this effect.

At first blush, the memory-enhancing effects of 5-HT uptake blockers appear to conflict with the expectation that by increasing 5-HT transmission with these agents, mnemonic performance should deteriorate. However, Altman et al. (1984) showed that the memory-improving effects of the 5-HT uptake inhibitors alaproclate and zimeldine were completely blocked by pretreatment with the 5-HT receptor agonist quipazine, and tended to be potentiated by pretreatment with cyproheptadine, a 5-HT antagonist. The pharmacologic actions to acount for these findings are obscure, however. Altman et al. (1987) speculate that 5-HT uptake blockers may indirectly interfere with, rather than potentiate, 5-HT transmission.

Serotonergic function in amnesic humans

5-HT deficiency is proposed as a cause of amnesia in patients with Korsakoff's psychosis. In Korsakoff patients, diminished urinary excretion of 6-hydroxymelatonin, an end product of melatonin catabolism (Martin et al. 1984a), sleep EEG abnormalities (Martin et al. 1986), and memory test improvement by treatment with fluvoxamine, a specific 5-HT uptake blocker (Martin et al. 1989), are cited in support of a 5-HT hypothesis for this illness. These data, though interesting, are not directly related to 5-HT function in the brain and seem weak in support of this hypothesis.

First, 5-HT is an intermediate in melatonin synthesis from tryptophan, and the pineal body, the primary locus of melatonin production, functions outside of the blood-brain barrier and has no direct neural connections to the brain (for review see Reichlin 1985). We find no evidence, nor is any cited by Martin and colleagues (1984a), to implicate 5-HT systems of the brain in melatonin metabolism. Secondly, the sleep EEG abnormalities reported in Korsakoff patients (Martin et al. 1986) are not specific for diminished 5-HT activity in the brain. Lastly, fluvoxamine-induced memory test improvement in five subjects with Korsakoff's psychosis (Martin et al. 1989) is not strong evidence for a 5-HT deficit in this disorder. As discussed above, the mechanisms for the memory-enhancing effects of 5-HT uptake blockers are not understood.

A more direct estimate of brain 5-HT activity in humans is from measurement of the concentration of 5-

HIAA in CSF (Stanley et al. 1985). Levels of 5-HIAA in CSF from a large group of Korsakoff patients are abnormally low in individual patients, but for the group, the mean CSF level of this metabolite did not significantly differ from the mean control level (McEntee et al. 1984; Mair et al. 1985a). Similar results are reported for six Korsakoff subjects (Martin et al. 1984b). Therefore, a loss of 5-HT may occur in the brains of some patients with the Korsakoff syndrome, but at this time, there is no direct evidence showing that this loss is a consistent feature of the disease or is related to measures of disordered memory (Mair et al. 1985a).

Serotonergic function in thiamine deficient animals

Thiamine deficiency is generally acknowledged as the underlying etiology of Korsakoff's disease and study of animals with experimental depletion of thiamine is a long-established method for research on the causes of amnesia. Brains from rats made thiamine deficient show increased turnover of 5-HT (Van Woert et al. 1979) and decreased uptake of 5-HT into cerebellar synaptosomes (Plaitakis et al. 1978). It cannot be determined if these findings are transient or chronic, as the data were obtained during the acute stage of vitamin depletion. In Korsakoff patients, amnesia persists long after their recovery from the thiamine deficient state, and therefore it is more appropriate to analyze the effects of thiamine deficiency in animals after they recover from the experimental insult. Accordingly, brains from rats with persistent learning impairments for several months following recovery from thiamine depletion have increased levels of 5-HT in midbrain-thalamus and striatum (Mair et al. 1985b; Langlais et al. 1987) and increased levels of 5-HIAA in midbrain-thalamus (Mair et al. 1985b), striatum (Mair et al. 1985b; Langlais et al. 1987) and cerebellum (Mair et al. 1985b), compared to controls.

Neurochemical interactions of 5-HT

Some effects of 5-HT altering drugs on mnemonic processes might be explained by interactions with other neurochemical systems which also influence learning and memory. Of obvious importance are interactions between serotonergic and cholinergic systems. Data from measurements of the release or concentration of 5-HT and ACh in animal brains by various experimental manipulations indicate that the two systems are mutually inhibitory (Robinson 1983; Gillet et al. 1985; Marchi et al. 1986; Maura and Raiteri 1986). Earlier reports of increased turnover of ACh in certain forebrain regions in rats following treatment with putative 5-HT agonists suggest that the two transmitters act in concert with each other (Euvard et al. 1977; Samanin et al. 1978; Ladinski et al. 1981).

Recent animal experiments have examined the effects of different pharmacologic manipulations of the serotonergic and cholinergic systems on measures of learning and memory. Combined treatment with the 5-HT uptake inhibitor alaproclate and oxotremorine, a muscarinic agonist, enhances retrieval of passive avoidance behavior in mice at doses which, when given individually, were too low for either drug to produce an effect (Altman et al. 1987). In rats, neurotoxin-induced denervation of forebrain 5-HT superimposed on a lesion of the cholinergic septohippocampal pathway produced an increase in impairment of performance on a spatial learning task, compared to that caused by the cholinergic lesion alone; although denervation of forebrain 5-HT by itself did not significantly affect task performance (Nilsson et al. 1988). On the other hand, depletion of 5-HT in rats by systemic administration of *p*-chloroamphetamine improved acquisition of a complex spatial discrimination task; an effect completely blocked by lesioning cholinergic neurons in nucleus basalis magnocellularis (NBM), whereas NBM lesions alone did not alter task performance (Normile et al. 1989).

The data above, while indicating that important interactions between 5-HT and ACh affect learning and memory, do not demonstrate a consistent relationship between the two systems. These inconsistencies might be explained by the suggestion that 5-HT-ACh interactions occur at different sites with different functional roles (Altman et al. 1987), but presently, definitive explanations for these complex neurochemical events seem distant.

Interactions between serotonergic and noradrenergic systems are also of interest. Several studies suggest a functional reciprocal relationship between these two systems in the brain (Lewis et al. 1976; Crespi et al. 1980; Reader and Jasper 1984; McRae-Degueurce et al. 1985; Rappaport et al. 1985), and an anatomical relationship is indicated by identification of 5-HT nerve terminals in the locus ceruleus (Leger and Descarries 1978). Pretreatment with NE blocks the memory impairment produced by injection of 5-HT into hippocampus (Essman 1978). The facilitating effects of pirenperone, a 5-HT receptor antagonist, on retention of a learned aversive routine in mice is entirely reversed by pretreatment with an alpha-adrenergic blocker, but not by beta-adrenergic, muscarinic or dopaminergic blocking agents (Normile and Altman 1987). The findings cited suggest that, in respect to learning and memory, 5-HT and NE systems act mainly in opposition to one another, but again, at this time, data on this complex subject are insufficient to draw firm conclusions.

Lost learning and memory capabilities may result from a disrupted balance among multiple interacting neurochemical systems. The significance of such balance is portrayed by the view that different effects will be produced at different concentrations of 5-HT and other monoamines in various cellular locations, particularly in relation to non-synaptic versus synaptic sites (Seguela et al. 1989).

Implications for treatment of age-related memory impairment

The predominant theme emerging from this review suggests that 5-HT exerts an inhibitory influence on learning and memory; a view also held by Altman and Normile (1986). Hence, a reasonable argument can be made for treatment trials of 5-HT antagonists in elderly hu-

mans with impaired memory. This might seem paradoxical to some investigators, who believe that the deficiency of 5-HT shown in postmortem brains of patients with AD, makes a case for testing 5-HT agonists in persons with disordered memory. However, the part played by the 5-HT deficit in the cognitive abnormalities of AD is unknown and presently, available evidence points to 5-HT antagonists, rather than agonists, as serotonergic drugs with promise as memory enhancers. Although the pharmacologic actions by which 5-HT uptake inhibitors improve memory are obscure, these agents also appear to have potential as treatments for memory dysfunction.

Multiple 5-HT receptor types and subtypes are identified in brain tissue (for review see Schmidt and Peroutka 1989), and ongoing research is likely to spawn additional subtypes. Consequently, receptor type and subtype specificity has become an important aspect of serotonergic drug research and has important implications in treatment strategies for finding drugs to improve learning and memory.

Most of the memory-enhancing 5-HT receptor antagonists discussed in this paper have varying degrees of affinity for 5-HT_2 sites. Strek et al. (1989) found that among the 5-HT blockers they tested, only those with selective affinity for 5-HT_2 receptors were effective in preventing hypoxia-induced amnesia. Thus, investigation of selective 5-HT_2 antagonists may be worthwhile in drug treatment studies of people with an age-related decline in learning and memory abilities.

Results from animal experiments suggest that 5-HT_3 receptor antagonists also have memory-enhancing properties. Marmosets treated with a 5-HT_3 antagonist demonstrate a dose-dependent improvement in performance on an object discrimination reversal task (Costall et al. 1989a). In rats, deficits in performance of a T-maze reinforced alternation task, produced by scopolamine treatment, are attenuated by co-treatment with each of four 5-HT_3 blockers (Costall et al. 1989b). These findings are supported by data of Ashby et al. (1990) showing that microiontophoretic application of the selective 5-HT_3 agonist 2-methyl serotonin to rat medial frontal cortex, a brain region associated with spatial learning, inhibits neuronal activity. This effect is blocked by a number of putative 5-HT_3 antagonists, but not by 5-HT_1 or 5-HT_2 antagonists. Clinical treatment trials with some 5-HT_3 antagonists are already underway in memory-impaired elders.

Available data are insufficient to determine if changes in the 5-HT system of the brain underlie the decline of mnemonic function associated with advancing age. Nonetheless, there is ample evidence indicating that 5-HT mechanisms play a significant role in learning and memory processes. Therefore, it seems important and logical to proceed with clinical research to learn if serotonergic drugs have a place in the treatment of this model of memory impairment.

References

Allen SJ, Benton JS, Goodhardt MJ, Hann EA, Sims NR, Smith CCT, Spillane JA, Bowen DM, Davison AN (1983) Biochemical evidence of selective nerve cell changes in the normal ageing human and rat brain. J Neurochem 41:256–265

Altman HJ, Normile HJ (1986) Enhancement of the memory of a previously learned aversive habit following pre-test administration of a variety of serotonergic anatgonists in mice. Psychopharmcology 90:24–27

Altman HJ, Normile HJ (1988) What is the nature of the role of the serotonergic nervous system in learning and memory: prospects for development of an effective treatment strategy for senile dementia. Neurobiol Aging 9:627–638

Altman HJ, Nordy DA, Ogren SO (1984) Role of serotonin in memory: facilitation by alaproclate and zimeldine. Psychopharmacology 84:496–502

Altman HJ, Stone WS, Ogren SO (1987) Evidence for a possible functional interaction between serotonergic and cholinergic mechanisms in memory retrieval. Behav Neural Biol 48:49–62

Altman HJ, Normile HJ, Galloway MP, Ramirez T, Azmitia EC (1988) Facilitation of complex maze learning in rats following selective deafferentation of the dorsal hippocampus. Soc Neurosci Abstr 14:725

Arai H, Kosaka K, Iizuka T (1984) Changes of biogenic amines and their metabolites in postmortem brains from patients with Alzheimer-type dementia. J Neurochem 43:388–393

Ashby CR, Edwards E, Harkins K, Wang RY (1990) Characterization of 5-hydroxytryptamine$_3$, receptors in the rat medial prefrontal cortex. Eur J Pharmacol 173:193–196

Audet MA, Descarries L, Doucet G (1989) Quantified regional and laminar distribution of the serotonin innervation in the anterior half of adult rat cerebral cortex. J Chem Neuroanat 2:29–44

Bammer G (1982) Pharmacological investigations of neurotransmitter involved in passive avoidance responding: a review and some new results. Neurosci Biobehav Rev 6:247–296

Baskys A, Niesen CE, Carlen PL (1987) Altered modulatory actions of serotonin on dentate granule cells of aged rats. Brain Res 419:112–118

Bowen DN, Allen SJ, Benton JS, Goodhardt MJ, Hann EA, Palmer AM, Sims NR, Smith CCT, Spillane JA, Esiri MM, Neary D, Snowdon JS, Wilcock GK, Davison AN (1983) Biochemical assessment of sertonergic and cholinergic dysfunction and cerebral atrophy in Alzheimer's disease. J Neurochem 41:266–272

Brody JF (1978) Behavioral effects of serotonin depletion and of *p*-chlorophenylalanine (a serotonin depletor) in rats. Psychopharmacology 17:14–33

Brunello N, Riva M, Rovescalli AC, Galimberti R, Racasni G (1988) Age-related changes in rat serotonergic and adrenergic systems and in receptor responsiveness to subchronic desipramine treatment. Pharmacol Toxicol 63:150–155

Costall B, Domeney AM, Gerrard PA, Jones DNC, Naylor RJ, Tyers MB (1989a) Effects of GR38032F on performance of common marmosets (*Callithrix jacchus*) in an object discrimination reversal task. Br J Phamracol [Suppl] 98:637P

Costall B, Coughlan J, Kelly ME, Naylor RJ, Tyers MB (1989b) Scopolamine-induced deficits in a T-maze reinforced alternation task are attenuated by 5-HT_3 receptor antagonists. Br J Pharmacol [Suppl] 98:636P

Crespi F, Buda M, McRae-Degueurce A, Pujol JF (1980) Alteration of tyrosine hydroxylase activity in the locus coeruleus after administration of *p*-chlorophenylalanine. Brain Res 191:501–509

Crook T, Bartus RT, Ferris SH, Whitehouse P, Cohen GD, Gershon S (1986) Age-associated memory impairment. Proposed diagnostic criteria and measures of clinical change: report of a National Institute of Health work group. Dev Neuropsychol 2:261–276

Curcio CA, Kemper T (1984) Nucleus raphe dorsalis in dementia of the Alzheimer type; neurofibrillary changes and neuronal packing density. J Neuropathol Exp Neurol 43:359–368

Ebel A, Strosser HT, Kempf E (1987) Genotypic differences in central neurotransmitter responses to aging in mice. Neurobiol Aging 8:417–427

Essman WB (1978) Serotonin in learning and memory. In: Essman WB (ed) Serotonin in health and disease. Spectrum, New York, pp 69–143

Euvard D, Javoy F, Herbert A, Glowinski J (1977) Effect of quipazine, a serotonin-like drug, on striatal cholinergic interneurons. Eur J Pharmacol 41:281–289

Flood JF, Cherkin A (1987) Fluoxetine enhances memory processing in mice. Psychopharmacology 93:36–43

Gillet G, Ammor S, Fillion G (1985) Serotonin inhibits acetylcholine release from rat striatum slices: evidence for a presynaptic receptor-mediated effect. J Neurochem 45:1687–1691

Godefroy F, Bassant MH, Weil-Fugazza J, Lamour Y (1989) Age-related changes in dopaminergic and serotonergic indices in the rat forebrain. Neurobiol Aging 10:187–190

Gottfries C-G, Adolfsson R, Aquilonius S-M, Carlsson A, Eckernas A, Nordberg A, Oreland L, Svennerholm L, Wiberg A, Winblad B (1983) Biochemical changes in dementia disorders of Alzheimer type. Neurobiol Aging 4:261–271

Kohler C, Lorens SA (1978) Open field activity and avoidance behavior following serotonin depletion: a comparison of the effects of parachlorophenylalanine and electrolytic midbrain raphe lesions. Pharmacol Biochem Behav 8:223–233

Kral VA (1962) Senescent forgetfulness: benign and malignant. J Can Med Assoc 86:257–260

Kubo T, Shibanoki S, Matsumoto A, Tsuda K, Ishikawa K (1988) Portacaval anastomosis attenuates the impairing effect of cyproheptadine on avoidance learning in rats – an involvement of the serotonergic system. Behav Brain Res 30:279–287

Ladinski H, Consolo S, Tirelli AS, Forloni GL, Segal M (1981) Regulation of chlonergic activity in the rat hippocampus: in vivo effects of oxotremorine and fenfluramine. In: Pepeu G, Ladinski H (eds) Cholinergic mechanisms: phylogenetic aspects, central and peripheral synapses and clinical significance. Advances in behavioral biology, vol 25. Plenum, New York, pp 289–296

Lane F, Snowden F (1989) Memory and dementia: a longitudinal survey of suburban elderly. In: Lovibond P, Wilson P (eds) Clinical and abnormal psychology. Elsevier, North-Holland, pp 365–376

Langlais PJ, Mair RG, Anderson CD, McEntee WJ (1987) Monoamines and metabolites in cortex and subcortical structures: normal regional distribution and the effects of thiamine deficiency in the rat. Brain Res 421:140–149

Lawlor BA, Sunderland T, Mellow AM, Hill JL, Molchan SE, Murphy DL (1989a) Hyperresponsivity to the serotonin agonist *m*-chlorophenylpiperazine in Alzheimer's disease. Arch Gen Psychiatry 46:542–549

Lawlor BA, Sunderland T, Mellow AM, Hill JL, Newhouse PA, Murphy DL (1989b) A preliminary study of the effects of intravenous *m*-chlorophenylpiperazine, a serotonin agonist, in elderly subjects. Biol Psychiatry 25:679–686

Leger L, Descarries L (1978) Serotonin nerve terminals in the locus coeruleus of adult rat. A radioautographic study. Brain Res 145:1–13

Lewis BD, Renaud B, Buda M, Pujol JF (1976) Time-course variation in tyrosine hydroxylase activity in the rat locus coeruleus after electrolytic destruction of the nucleus raphe dorsalis or raphe centralis. Brain Res 108:339–344

Mair RG, McEntee WJ, Zatorre RJ (1985a) monoamine activity correlates with psychometric deficits in Korsakoff's disease. Behav Brain Res 15:247–254

Mair RG, Anderson CD, Langlais PJ, McEntee WJ (1985b) Thiamine deficiency depletes cortical norepinephrine and impairs learning processes in the rat. Brain Res 360:273–284

Marchi M, Paudice P, Bella M, Raiteri M (1986) Dicyclomine- and pirenzapine-sensitive muscarinic receptors mediate inhibition of ^{3}H-serotonin release in different rat brain areas. Eur J Pharmacol 129:353–357

Marcusson J, Oreland L, Winblad B (1984a) Effect of age on human brain serotonin (S-1) binding sites. J Neurochem 43:1699–1705

Marcusson JO, Morgon DG, Winblad B, Finch CE (1984b) Serotonin-2 binding sites in human frontal cortex and hippocampus. Selective loss of S-2A sites with age. Brain Res 311:51–56

Marcusson JO, Alafuzoff I, Backstrom IT, Ericson E, Gottfries CG, Winblad B (1987) 5-Hydroxytryptamine-sensitive ^{3}H-imipramine binding of protein nature in the human brain. II. Effect of normal aging and dementia disorders. Brain Res 425:137–145

Martin PR, Higa S, Burns RS, Tamarkin L, Ebert MH, Markey SP (1984a) Decreased 6-hydroxymelatonin excretion in Korsakoff's psychosis. Neurology 34:966–968

Martin PR, Weingartner H, Gordon EK, Burns S, Linnoila M, Kopin IJ, Ebert MH (1984b) Central nervous system catecholamine metabolism in Korsakoff's psychosis. Ann Neurol 15:184–187

Martin PR, Lowenstein RJ, Kaye WH, Ebert MH, Weingartner H, Gillin JC (1986) Sleep EEG in Korsakoff's psychosis and Alzheimer's disease. Neurology 36:411–414

Martin PR, Adinoff B, Eckardt MJ, Stapleton JM, Bone GAH, Rubinow DR, Lane EA, Linnoila M (1989) Effective pharmacotherpay of alcoholic amnestic disorder with fluvoxamine. Arch Gen Psychiatry 46:617–621

Marua G, Raiteri M (1986) Cholinergic terminals in rat hippocampus possess 5-HT_{1B} receptors mediating inhibition of acetylcholine release. Eur J Pharmacol 129:333–337

McEntee WJ, Crook TH (1990) Age-associated memory impairment: a role for catecholamines. Neurology 40:526–530

McEntee WJ, Mair RG (1980) Memory enhancement in Korskoff's psychosis with clonidine: further evidence for a noradrenergic deficit. Ann Neurol 7:466–470

McEntee WJ, Mair RG, Langlais PJ (1984) Neurochemical pathology in Korsakoff's psychosis: implications for other cognitive disorders. Neurology 34:648–652

McRae-Degueurce A, Dennis T, Leger L, Scatton B (1985) Regulation of neuronal activity in the rat locus coeruleus by serotonergic afferents. Physiol Psychol 344:158–161

Middlemiss DN, Palmer AM, Edel N, Bowen DM (1986) Binding of the novel serotonin agonist 8-hydroxy-2(di-n-propylamino) tetralin in normal and Alzheimer brain. J Neurochem 46:993–996

Moretti A, Carfagna N, Trunzo F (1987) Effect of aging on monoamines and their metabolites in the rat brain. Neurochem Res 12:1035–1039

Nilsson OG, Strecker RE, Daszuta A, Bjorklund A (1988) Combined cholinergic and serotonergic denervation of the forebrain produces severe deficits in a spatial learning task in the rat. Brain Res 453:235–246

Normile HJ, Altman HJ (1987) Evidence for a possible interaction between noradrenergic and serotonergic transmission in the retrieval of a previously learned aversive habit in mice. Psychopharmacology 92:388–392

Normile HJ, Altman HJ (1988) Enhanced passive avoidance retention following posttrain serotonergic receptor antagonist administration in middle-aged and aged rats. Neurobiol Aging 9:377–382

Normile HJ, Jenden DJ, Kuhn DM, Wolf WA, Altman HJ (1989) Effects of combined serotonin depletion and lesions of the nucleus basalis magnocellularis on acquisition of a complex spatial discrimination task. Soc Neurosci Abstr 15:465

Oleskevich S, Descarries L (1990) Quantified distribution of the serotonin innervation in adult rat hippocampus. Neuroscience 34:19–33

Palmer AM, Francis PT, Benton JS, Sims NR, Mann DMA, Neary D, Snowden JS, Bown DM (1987) Presynaptic serotonergic dysfunction in patients with Alzheimer's disease. J Neurochem 8:8–15

Plaitakis A, Nicklas WJ, Berl S (1978) Thiamine deficiency: selective impairment of the cerebellar serotonergic system. Neurology 23:691–698

Ponzio F, Calderini G, Lomuscio G, Vantini G, Toffano G, Algeri S (1982) Changes in monoamines and their metabolite levels

in some brain regions of aged rats. Neurobiol Aging 3:23–29

Ramirez TM, Altman HJ, Normile HJ, Kuhn DM, Azmitia EC (1989) The effects of serotonergic intrahippocampal neonatal grafts on learning and memory in the Stone 14-unit T-maze. Soc Neurosci Abstr 15:465

Rappaport A, Sturtz F, Guicheney P (1985) Regulation of central alpha adrenoceptors by serotonergic denervation. Brain Res 344:158–161

Reader TA, Jasper HH (1984) Interaction between monoamines and other transmitters in cerebral cortex. In: Descarries L, Reader TR, Jasper HH (eds) Monoamine innervation of cerebral cortex. Liss, New York, pp 195–225

Reichlin S (1985) The pineal. In: Wilson JD, Foster DW (eds), Williams textbook of endocrinology. Saunders, Philadelphia, pp 535–538

Reinikainen KJ, Koivisto K, Mykkanen L, Hanninen T, Laakso M, Pyorala K, Riekkinen PJ (1990) Age-associated memory impairment in aged population: an epidemiological study. Neurology [Suppl 1] 40:177

Robinson SE (1983) Effect of specific serotonergic lesions on cholinergic neurons in the hippocampus, cortex and striatum. Life Sci 32:345–353

Rossor M, Iversen LL (1986) Non-cholinergic neurotransmitter abnormalities in Alzheimer's disease. Br Med Bull 42:70–74

Samanin R, Quattrone A, Perri G, Ladinski H, Consolo S (1978) Evidence for an interaction between serotonergic and cholinergic neurons in the corpus striatum and hippocampus of the rat brain. Brain Res 151:73–82

Schmidt AW, Peroutka SJ (1989) 5-hydroxytryptamine receptor families. FASEB J 3:2242–2249

Seguela P, Watkins KC, Descarries L (1989) Ultrastructural relationships of serotonin axon terminals in the cerebral cortex of adult rat. J Comp Neurol 289:129–142

Severson JA (1986) ^{3}H-Imipramine binding in aged mouse brain: regulation by ions and serotonin. Neurobiol Aging 7:83–87

Severson JA, Marcusson JO, Osterburg HH, Finch CE, Winblad B (1985) Elevated density of ^{3}H-imipramine binding in aged human brain. J Neurochem 45:1382–1389

Shih JC, Young H (1978) The alteration of serotonin binding sites in aged human brain. Life Sci 23:1441–1448

Simpkins JW, Mueller GP, Huang HH, Meites J (1977) Evidence for depressed catecholamine and enhanced serotonin metabolism in ageing male rats. Endocrinology 100:1672–1678

Stanley M, Traskman-Bendz L, Dorovini ZK (1985) Correlations between aminergic metabolites simultaneously obtained from human CSF and brain. Life Sci 37:1279–1286

Strek KF, Spencer KR, DeNoble VJ (1989) Manipulation of serotonin protects against an hypoxia-induced deficit of a passive avoidance response in rats. Pharmacol Biochem Behav 33:241–244

Thurmond JB, Brown JW (1984) Effect of brain monoamine precursors on stress-induced behavioral and neurochemical changes in aged mice. Brain Res 296:93–102

Timras PS, Hudson DB, Miller C (1982) Developing and aging brain serotonergic systems. In: Giacobini E, Filogamo G, Giacobini G, Vernadakis A (eds) The aging brain: cellular and molecular mechanisms of aging in the central nervous system. Aging, vol 20. Raven Press, New York, pp 173–184

Valzelli L, Pawlowski L (1979) Effect of *p*-chlorophenylalanine on avoidance learning of two differentially housed mouse strains. Neuropsychobiology 5:121–128

Van Woert MH, Plaitakis A, Hwang EC, Berl S (1979) Effect of thiamine deficiency on brain serotonin turnover. Brain Res 179:103–110

Weingartner H, Rudorfer MV, Buchsbaum MS, Linnoila M (1983) Effects of serotonin on memory impairments produced by ethanol. Science 221:472–474

Wester P, Hardy JA, Marcusson J, Nybers P, Winblad B (1984) Serotonin concentrations in normal aging human brains: relation to serotonin receptors. Neurobiol Aging 5:199–203

Wetzel W, Getsova VM, Jork R, Matthies H (1980) Effect of serotonin on Y-maze retention and hippocampal protein synthesis in rats. Phrmacol Biochem Behav 12:319–322

Winter JC, Petti DT (1987) The effects of 8-hydroxy-2-(di-n-propylamino) tetralin and other serotonergic agonists on performance in a radial maze: a possible role for 5-HT_{1A} receptors in memory. Pharmacol Biochem Behav 27:625–628