Differential Effects of Aging and Insulin-like Growth Factor-1 on Synapses in CA1 of Rat Hippocampus

Aging-related impairments of learning and memory can be ameliorated by 28 days of intracerebroventricular (icv) infusion of insulin-like growth factor-1 (IGF-1) in old rats. The present study investigated whether there is an aging-related synaptic decline in the stratum radiatum of hippocampal CA1 and whether IGF-1 can ameliorate that decline. Five young (4 months), five middle-aged (18 months) and five old (29 months) Fischer 344×Brown Norway rats received saline infusion; five old (29 months) rats received IGF-1 infusion for 28 days preceding sacrifice. Pyramidal neurons, total synaptic profiles as well as synaptic profiles in multiple spine bouton (MSB) complexes in CA1 were quantified stereologically with the physical disector technique and the postsynaptic density (PSD) length was determined as well. The results indicated a decrease of total synapses between middle and old age but a maintenance of PSD length and MSB synapses throughout life. IGF-1 infusion in old rats did not reverse the aging-related decline in total synapses but did increase PSD length and the number of MSB synapses. These changes in synaptic configurations are morphological correlates of enhanced synaptic efficacy. Thus, aging and IGF-1 affect different, but complementary, aspects of synapses in hippocampal CA1.

Keywords: MSB complex, plasticity, PSD length, quantitative EM, stereology

Introduction

The aging process in rodents is associated with impaired spatial learning and memory as revealed by poor performance on radial arm maze and Morris water maze tasks. While these tasks are hippocampus-dependent (Barnes et al., 1990; Gallagher et al., 1993; Geinisman et al., 1995; Blalock et al., 2003), the specific substrates within the hippocampus for such aging-related cognitive declines have not been defined clearly. It is well established that granular cells in dentate gyrus as well as pyramidal neurons in CA3 and CA1 are maintained throughout life (Gallagher et al., 1996; Rapp and Gallagher, 1996; Morrison and Hof, 1997), suggesting that more subtle changes in synapses may underlie the aging-related learning and memory impairments. Synaptic changes may be reflected either in an actual loss of synapses with age as reported in the dentate gyrus (Geinisman et al., 1992) or in changes in synaptic function such as the impaired synaptic transmission and long-term potentiation observed in the hippocampus of old rats (Barnes, 1994; Auerbach and Segal, 1997; Foster and Norris, 1997; Foster, 1999; Tombaugh et al., 2002). Changes in synaptic function are also reflected in alterations in morphological features of synaptic configuration (Luscher et al., 2000), permitting an indirect assessment of synaptic efficacy in the same biological samples in which synaptic profiles are quantified. Specifically, the length of the postsynaptic density (PSD) and the incidence of synapses in multiple spine bouton (MSB) complexes, i.e. a single presynaptic element contacting more than one postsynaptic targets, are both correlated with measurements of synaptic efficacy (Buchs and Muller, 1996; Jones, 1999; Jones et al., 1999; Toni et al., 1999, 2001; Nikonenko et al., 2002). The present study utilized physical disector technique to quantify ultrastructurally identified synaptic profiles in order to determine whether there is a loss of synapses, either total or those involved in MSB complexes, in the stratum radiatum of hippocampal CA1 region across the lifespan and also addressed the issue of whether there are aging-related changes in PSD length.

The aging-associated learning and memory impairments can be ameliorated by intracerebroventricular (icv) infusion of trophic factors such as nerve growth factor and insulin-like growth factor-1 (IGF-1) (Fischer et al., 1991; Backman et al., 1996; Markowska et al., 1998). Of particular importance for aging studies, IGF-1 has been reported to decrease significantly across the lifespan in a wide variety of species including rats (Amaducci and Tesco, 1994; Sonntag et al., 1999; Arvat et al., 2000; Carter et al., 2002). When the aging-related decline in this trophic factor was reversed by icv infusion for 28 days, the learning and memory impairments on the Morris water maze tasks in old rats were ameliorated (Markowska et al., 1998; Sonntag et al., 2000). However, the mechanism for such IGF-1-induced cognitive changes is unclear. One possibility is that such behavioral improvements were due to an amelioration of aging-related changes in synapses. Consistent with this possibility, IGF-1 supports diverse aspects of neuronal connectivity, including synaptogenesis and axonal sprouting, as well as the maintenance of dendritic length, complexity and spine density (Niblock et al., 2000; O’Kusky et al., 2000; Cheng et al., 2003). Accordingly, the present study also quantified synaptic profiles stereologically in order to determine whether IGF-1 induces changes in synapses in CA1 stratum radiatum of old rats. Thus, in addition to testing the hypothesis that there are aging-related synaptic changes in the stratum radiatum of hippocampal CA1, the present study also tested the hypothesis that 28 days of icv IGF-1 supplementation in old rats can reverse these changes.

Materials and Methods

Animals

Twenty male Fischer 344×Brown Norway (F344XBN) F1 rats were acquired from the National Center for Toxicology Research and were housed individually with ad libitum access to food and water on a 12 h light–dark cycle. All experimental protocols were approved by the Animal Care and Use Committee of Wake Forest University School of Medicine and were in accordance with the NIH Guide for the Care and Use of Laboratory Animals. Adequate measures were taken to minimize...
pain or discomfort and all of the analyses were performed with the experimenter blind to experimental group.

Animals were divided into 4 groups by age and treatment: young (4 months, n = 5), middle-aged (18 months, n = 5), old (29 months, n = 5) and old with IGF-1 (29 months, n = 5). Rats in the old IGF-1 group received icv infusion of recombinant human IGF-1 (Bachem California, Torrance, CA) delivered at a rate of 50 ng/0.5 ml/h for the 28 days preceding sacrifice. Rats in the other groups received 28 days of saline (vehicle) infusion at the same rate before sacrifice. For icv infusion of IGF-1 or saline, each rat was anesthetized [ketamine (100 mg/ml); xylazine (20 mg/ml) 1:1; 0.1 ml/kg body weight] and a 28-gauge stainless steel cannula was implanted into the right lateral ventricle (Alzet® brain infusion kit; Alza Corporation, Mountain View, CA; bregma -0.8 mm, mediolateral 1.4 mm; Paxinos and Watson, 1986) and was connected to an Alzet® osmotic minipump (Alza Corporation) that was placed subcutaneously between the shoulders at the base of the neck. The pumps were replaced once after 14 days.

Tissue Preparation and Sampling

Twenty-eight days after implantation of the minipumps, animals were anesthetized [ketamine (100 mg/ml); xylazine (20 mg/ml) 1:1; 0.1 ml/kg body weight] and perfused transcardially with 1.3 M cacodylate buffer (pH 7.4) followed by fixative (2% paraformaldehyde/2% gluteraldehyde). Brains were sectioned coronally at 200 μm on a vibratome; the CA1 region was blocked from sections containing the dorsal hippocampus (Fig. 1; bregma -2.3 to -4.3 mm, mediolateral 0-2 mm; Paxinos and Watson, 1986) and blocks were osmicated, dehydrated, embedded in araldite plastic and cut on an ultramicrotome at either 1 μm (semithin sections) or 700 Å (thin sections). Analysis was limited to dorsal hippocampus because this area is more closely associated with spatial learning and memory performance than is the ventral hippocampus in rats (Moser et al., 1995; Moser and Moser, 1998). Stereological quantification of neurons was performed on 15 disector pairs per animal from semithin sections with a disector height of 4 μm. Stereological quantification of synaptic profiles was performed on 30 physical dissectors from 3 blocks per animal. Each physical disector consisted of a pair of photomicrographs (<8000; Zeiss 10-C transmission electron microscope) from serial thin sections through the stratum radiatum of CA1. Pairs of serial section were chosen in a systematically random fashion as described previously (Shi et al., 2002) and consistent with the requirement for stereological analysis (Geinisman et al., 1996). Thin and semithin sections were from alternating sectors in individual blocks in order to provide sampling of synaptic profiles and neurons through coincident anatomical space.

Quantifications of Pyramidal Neurons and Synaptic Profiles in Hippocampal CA1

The numerical density (Nv) of pyramidal neurons in the CA1 stratum pyramidale (Fig. 1) was quantified from semithin sections with the physical disector technique (Sterio, 1984). For each pair of semithin sections, a ‘reference’ and a ‘look-up’ section were designated, a counting frame (a × b) was superimposed and neurons were counted. A neuron was defined by the presence of a definitive neuronal nucleus with a clear nuclear membrane. The number of nuclei per counting frame that were present in the ‘reference’ section but disappeared in the ‘look-up’ section, a count of synaptic profiles and neurons through coincident anatomical space. The numerical density (Nv) of pyramidal neurons in the CA1 stratum pyramidale (Fig. 1) was quantified from semithin sections with the physical disector technique (Sterio, 1984). For each pair of semithin sections, a ‘reference’ and a ‘look-up’ section were designated, a counting frame (a × b) was superimposed and neurons were counted. A neuron was defined by the presence of a definitive neuronal nucleus with a clear nuclear membrane. The number of nuclei per counting frame that were present in the ‘reference’ section but disappeared in the ‘look-up’ section, a count of synaptic profiles and neurons through coincident anatomical space.

Where $Q$ is the number of counting objects (postsynaptic densities or neuronal nuclei) per counting frame that were present in the ‘reference’ section but disappeared in the ‘look-up’ section, $a$ is the area of the counting frame and $b$ is the height of the physical disector.

Synaptic profiles that are part of MSB complexes (Fig. 2C) also were identified and quantified stereologically with physical disector technique in the same manner as described above. For quantification of MSB synapses, three-dimensional identification of MSBs synapses combined with the disector methods of quantification provide the least biased estimate (Geinisman et al., 2001). However, this technique requires extremely long sets of serial electron micrographs and, as a result, limits the number of sampling sites that can be quantified. The technique used in the present study underestimates the number of MSB synapses (Jones et al., 1997). However, the intention of the present study was not to...
determine absolute number of MSB synapses, but rather to reveal relative differences across the lifespan as well as between IGF-1-infused and saline-infused old rats. Stereological quantification with physical disector has been shown to detect the same differences between experimental groups as the three-dimensional reconstruction method (Buchs and Muller, 1996; Jones et al., 1997; Toni et al., 1999).

For all synaptic profiles identified in CA1 stratum radiatum in the present study, the PSD length was determined. Specifically, the PSD length of all identifiable synaptic profiles in six randomly selected electron micrographs from each animal was determined using the quick line measurement function of Stereoinvestigator software (Microbrightfield Inc.).

In order to avoid the possible confound of differential tissue shrinkage, the numerical densities of total and MSB synapses in CA1 stratum radiatum that were derived from stereological quantification of the synaptic profiles were normalized to the numerical density of CA1 pyramidal cells for individual blocks. Since neuronal density and synapse density were derived from the same resin-embedded samples, any tissue shrinkage would contribute equally to these two sets of data (Jones, 1999; Jones et al., 1999). In this fashion, tissue volume was removed from the resulting synapse per neuron ratio and such a ratio represents a sensitive marker of net changes in synapse density.

Statistics
For the determination of the numerical densities of pyramidal neurons and total as well as MSB synapses, PSD length, total synapse per neuron ratio and MSB synapse per neuron ratio, the average of three blocks from each animal was derived and expressed as mean per animal. Data were analyzed using GraphPad software and ANOVA was performed on pyramidal neuron density, the ratios of total and MSB synapses per neuron, and PSD length among young, middle-aged and old rats. A P value of < 0.05 was considered statistically significant and Bonferroni post hoc tests were performed when there was a significant difference. In addition, pyramidal neuron density, the ratios of total and MSB synapses per neuron, and PSD length were compared between saline-infused and IGF-1-infused old rats with Student’s t-test. A P value of less than 0.05 was considered significant. All data were presented as the mean ± SEM.

Results

Tissue Ultrastructure
The rats in the present study received icv infusion of either saline or IGF-1 for 28 days before sacrifice. Similar icv infusion of saline or IGF-1 has been used in other hippocampal studies without producing neural damage (Lichtenwalner et al., 2001; Poe et al., 2001). In the present study, light microscopic inspection did not reveal evidence of gross tissue abnormalities that could be attributed either to the surgery or the presence of the cannula. Moreover, the ultrastructure of the tissue in all groups appeared healthy without noticeable cell death.

Aging-related Changes in Pyramidal Neurons and Synapses in Hippocampal CA1

The numerical density of CA1 pyramidal neurons was compared across the lifespan with ANOVA. No significant main effect of age on neuronal density was detected (P > 0.05; Table 1). The numerical densities of total and MSB synapses in CA1 stratum radiatum at these ages also were determined (Table 1) and normalized to the numerical density of CA1 pyramidal neurons by deriving the ratios of total and MSB synapses per neuron. Analysis of the ratio of total synapses per neuron across the lifespan with ANOVA indicated a main effect of age (P < 0.05) and post hoc tests revealed a significant decrease in total synapses per neuron in old compared with middle-aged rats (Fig. 3).

### Table 1

<table>
<thead>
<tr>
<th>Age</th>
<th>Neuronal density × 10⁶/mm³ (± SEM)</th>
<th>Total synapses × 10⁶/mm³ (± SEM)</th>
<th>MSB synapses × 10⁶/mm³ (± SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young</td>
<td>22.18 (± 0.66)</td>
<td>15.25 (± 0.479)</td>
<td>6.73 (± 1.40)</td>
</tr>
<tr>
<td>Middle age</td>
<td>21.62 (± 0.88)</td>
<td>15.75 (± 0.550)</td>
<td>5.82 (± 0.92)</td>
</tr>
<tr>
<td>Old</td>
<td>22.42 (± 0.30)</td>
<td>12.33 (± 0.710)</td>
<td>4.18 (± 0.69)</td>
</tr>
<tr>
<td>Old + IGF-1</td>
<td>21.05 (± 1.46)</td>
<td>12.27 (± 0.824)</td>
<td>10.24 (± 1.50)</td>
</tr>
</tbody>
</table>

The present study also evaluated whether there were aging-associated changes in MSB synapses or the PSD length. Comparison of the ratio of MSB synapses per neuron across the lifespan with ANOVA did not indicate a significant main effect of age (P > 0.05; Fig. 4). Similarly, analysis of PSD length in CA1 stratum radiatum across the lifespan with ANOVA also did not show a main effect of age (P > 0.05; Fig. 5).

Thus, pyramidal neurons in hippocampal CA1 region are maintained across the lifespan; however, there is a significant overall loss of synapses in stratum radiatum in old compared with middle-aged F344XBN rats. Nevertheless, parameters that are correlated with synaptic efficacy, the prevalence of MSB synapses and PSD length, are maintained across the lifespan.

Effect of IGF-1 on Pyramidal Neurons and Synapses in Hippocampal CA1 of old rats

There was no significant difference in the numerical density of CA1 pyramidal neurons between saline-infused and IGF-1-infused old rats (P > 0.05; Table 1). The numerical densities of synapses in CA1 stratum radiatum also was determined for the two groups (Table 1) and normalized by pyramidal neuron density. The resulting ratio of total synapses per neuron was not
Effects of Aging and IGF-1 on CA1 Synapses

Figure 4. The ratio of multiple spine bouton (MSB) synapses per neuron in the CA1 stratum radiatum of Fischer 344 × Brown Norway rats across the lifespan as well as following IGF-1 infusion in old age. ANOVA among young (4 months), middle-aged (18 months) and old (29 months) rats that were intracerebroventricularly (icv) infused with saline (0.5 μl/h) for 28 days preceding sacrifice indicates no significant difference in the MSB synapse per neuron ratio across the lifespan (P > 0.05). Student’s t-test suggests that the MSB synapse per neuron ratio is increased significantly in old (29 months) rats receiving 28 days of icv IGF-1 infusion (50 ng/0.5 μl/h) compared with old (29 months) rats receiving saline infusion (0.5 μl/h) (*, P < 0.05). * indicates significant difference compared with old, saline-infused rats.

In addition to MSB synapses and PSDs length, the prevalence of perforated synapses (Fig. 2B), i.e. synapses with discontinuities of their PSDs, is also of functional significance. The incidence of perforated synapses is correlated with synaptic complexity, the level of membrane recycling and synaptic efficacy (Sorra et al., 1998; Neuhoff et al., 1999; Nikonenko et al., 2002). Accordingly, the present study quantified perforated synaptic profiles stereologically with the physical dissector technique. However, the 4–6 perforated synaptic profiles counted from the 30 dissector pairs of each rat were too low to meet the criteria for stereological quantification. The main reason for the low counts of perforated synaptic profiles is that the dissector height (700 Å) in the present study was optimized to quantify simple synaptic profiles, precluding accurate quantification of the significantly larger perforated synaptic profiles. For comparison, perforated synapses also were quantified using another technique: one electron micrograph from each dissector pair was selected randomly and the numbers of total and perforated synapses were determined in order to derive the percentage of perforated synapses for that micrograph. Comparison of the percentage of perforated synapses between saline-infused (0.0136 ± 0.0018) and IGF-1-infused (0.0269 ± 0.0038) old rats revealed a significant increase of perforated synapses following 28 days of icv IGF-1 infusion in old rats (P < 0.05). Although we cannot make a definitive statement about changes in perforated synapses because they were not quantified stereologically, such a finding does suggest an increase of this type of synaptic profile following IGF-1 infusion in old rats.

Therefore, 28 days of icv IGF-1 infusion in old rats does not affect pyramidal neuron density or ameliorate the decline of total synapses between middle and old age in the CA1 region of hippocampus. However, such a treatment is associated with increases in MSB synapses, perforated synapses, as well as in PSD length.

Discussion

Effect of Aging on Neurons and Synapses in Rat Hippocampus

Like humans and monkeys, aged rats exhibit cognitive impairments including compromised spatial learning and rapid loss of newly acquired information (Barnes et al., 1990; Gallagher et al., 1993; Markowska et al., 1998; Blalock et al., 2003). The structural and electrophysiological changes associated with these aging-related behavioral deficits have not been defined clearly. It is possible that either a loss of hippocampal neurons and/or a loss of synaptic connections contribute to the observed impairments in old rats. However, the present study indicates that CA1 neurons are not lost with age. This finding, together with previous reports of a maintenance of dentate gyrus granular cells and CA3 pyramidal neurons across the lifespan (Rapp and Gallagher, 1996; Morrison and Hof, 1997; Poe et al., 2001), indicate that that the aging-related learning and memory impairments may be due to more subtle changes in synaptic organization.

Earlier studies investigating aging-associated changes in hippocampal synapses have yielded inconsistent results due in
large part to use of non-stereological techniques (Geinisman et al., 1995). Stereological quantification of ultrastructurally identified synaptic profiles is recognized to offer the most accurate estimation of synapse density (Smith et al., 2000). Using that technique, the present study revealed a significant decrease in synapses per neuron in CA1 stratum radiatum between middle and old age. In contrast, two morphological correlates of synaptic efficacy, MSB synapses and PSD length, were maintained across the lifespan. Interestingly, another recent stereological study did not reveal an aging-related change in CA1 stratum radiatum synapses (Geinisman et al., 2004). However, that study compared synapse number only in young and old rats, ages that also did not differ on any measures in the present study. In the dentate gyrus, stereological quantification revealed a synaptic decline in old compared with very young (5 months of age) male F344 rats (Geinisman et al., 1992), although recent findings from our laboratory suggest a maintenance in DG synapses between more mature young adult (10 months of age) and old F344×Brown Norway rats (Newton et al., unpublished observations). In CA3, Poe et al. (2001) showed maintenance of ultrastructurally identified synaptic profiles in the stratum lucidum in young, middle-aged and old rats. These findings appear to indicate differences among hippocampal sub-regions in the degree of susceptibility to an aging-related loss of synapses. It is also noteworthy that synaptic changes in the aging hippocampus occur in a layer-specific pattern (Smith et al., 2000), and further stereological studies in other layers of dentate gyrus, CA3 and CA1 will be needed to fully elucidate aging-related hippocampal synaptic changes. Nevertheless, it is clear that hippocampal synapses are more susceptible than pyramidal neurons and granular cells to loss during normal aging. Consequently, declines in synapses between middle and old age in the stratum radiatum of CA1 may contribute to the reported learning and memory impairments in senescent rats.

Effect of IGF-1 on Hippocampal Synapses

Synapses are highly labile structures that are affected by changes in the microenvironment of the brain such as a loss of the trophic factor IGF-1 (Adams et al., 1997; Causing et al., 1997). The levels of IGF-1 protein as well as type 1 IGF receptors decrease across the lifespan (Sonntag et al., 1999) and IGF-1 signal transduction is compromised in the aging brain (Xu et al., 1995). These findings, together with reports that IGF-1 can support diverse aspects of synaptic functions such as nerve regeneration, establishment of contacts at the neuromuscular junction and synaptogenesis (Recio-Pinto et al., 1986; Gehrmann et al., 1994; Ishii et al., 1994; Fernandez et al., 1999; O’Kusky et al., 2000), indicate that diminishing levels of this trophic factor may be responsible for the loss of CA1 synapses between middle and old age. Moreover, IGF-1 is important for both the pre- and postsynaptic compartments of neuronal connectivity. Presynaptically, the extent of dentate gyrus axonal sprouting has been correlated with the level of IGF-1 expression (Woods et al., 1998). Postsynaptically, IGF-1 stimulates dendritic branching of cortical neurons in organotypic slice culture (Niblock et al., 2000) as well as maintains dendritic length, complexity and spine density on pyramidal cells in frontoparietal cortex (Cheng et al., 2003). Taken together, these findings implicate a decline of brain IGF-1 in the loss of CA1 synapses between middle and old age.

In the present study, we investigated whether the loss of CA1 synapses can be reversed by IGF-1 supplementation. Icv IGF-1 infusion for 28 days has been shown to increase IGF-1 protein in the hippocampus by 100% (Sonntag et al., 2000) and to ameliorate aging-related declines in learning and memory (Markowska et al., 1998). Nevertheless, such a treatment did not ameliorate the CA1 synaptic decline between middle and old age. It is unlikely that 28 days of IGF-1 infusion is too short a period for synaptic changes to occur since synaptogenesis is enhanced in the developing rat dentate gyrus following one month of elevated IGF-1 (O’Kusky et al., 2000). A more likely explanation is that the aging-related decrease of synapses in CA1 is an irreversible process and, once synapses are lost as IGF-1 declines with age, they cannot be restored. Although IGF-1 supplementation was not able to restore CA1 synapses in old rats, it increased PSD length as well as MSB synapses. The PSD represents localization of cytoskeletal elements and scaffolding molecules that are critical for signal transduction and both NMDA and AMPA subtypes of glutamate receptors are clustered in the PSDs (Ziff, 1997; Luscher et al., 2000). The PSD elongation induced by IGF-1 is a morphological correlate of an increased active transmission zone as well as enhanced synaptic complexity, membrane recycling and synaptic efficacy (Sorra et al., 1998; Neuhoff et al., 1999; Geinisman et al., 2001; Nikonenko et al., 2002).

The present study also indicated an increased incidence of synapses in MSB complexes following IGF-1 infusion. MSB complexes evolve from rearrangement of pre-existing simple synapses and can be formed following induction of long-term potentiation, the synaptic model of learning and memory (Toni et al., 1999, 2001). MSB complexes also increase in rats housed in complex environments (Jones et al., 1997), and those trained on motor and associative learning tasks (Jones, 1999; Jones et al., 1999; Geinisman et al., 2001). Thus, the IGF-1-induced increase in MSB synapses may be associated with enhanced synaptic efficacy and consequently underlie the improved cognitive abilities in IGF-1 infused old rats. In summary, IGF-1 infusion in old rats changed the morphology of CA1 synapses in a way consistent with enhanced synaptic efficacy (Nikonenko et al., 2002).

Possible Mechanism for IGF-1-induced CA1 Synaptic Changes

The PSD elongation and increased MSB synapses represent different phases of a continuous process following synaptic strengthening involving both the NMDA and AMPA subtypes of glutamate receptor (Luscher et al., 2000). Specifically, IGF-1 infusion increases NMDA2A and NMDA2B receptors subunits in the hippocampus of old rats (Sonntag et al., 2000) and the IGF-1 signaling pathway interacts with the intracellular cascade of NMDA receptors (Zhang et al., 1998). Following the enhancement and the subsequent activation of NMDA receptors induced by IGF-1, calcium would enter the cell more readily. Such calcium influx elicits the phosphorylation of the GluR1-containing AMPA receptors and the subsequent transposition of these AMPA receptors into the PSD which is associated with increased PSD length and subsequent synaptic perforation (Luscher et al., 2000). These IGF-1-induced morphological changes could be early steps leading to a splitting of some perforated synapses to produce a second spine contacting the same presynaptic bouton (Hering and Sheng, 2001). This
scenario could explain the increase of MSB synapses in old rats following IGF-1 infusion.

Conclusion

Hippocampal synapses are highly labile structures and the present study revealed a loss of synapses in stratum radiatum of hippocampal CA1 between middle and old age that may contribute to the spatial learning and memory impairments in aged rats. Although 28 days of IGF-1 infusion in old rats did not ameliorate the aging-related synaptic decline, the configuration of remaining synapses changed in a manner that is consistent with enhancement of synaptic efficacy. Such improved synaptic function, together with the augmentation of CA1 glucose utilization (Lynch et al., 2001), enhancement of dentate gyrus neurogenesis (Lichtenwalner et al., 2001) and increase of hippocampal NMDA receptors (Sonntag et al., 2000) following 28 days of ivc IGF-1 infusion in old rats, may provide the foundation for reversing the aging-related cognitive impairments (Markowska et al., 1998).

Notes

This work was sponsored by NIA grant AG11370 and was completed in partial fulfillment of the requirements for the Ph.D. degree in the Department of Neurobiology and Anatomy, Wake Forest University School of Medicine (L.S.).

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