oscillatory cycle. In this respect the long IPSP seen in these bursting neurons is quite different from those seen in other systems, where it is attributable to the reduction of a steady (resting) inward sodium current (*16*).

This model also explains why the long IPSP can be reduced in size, but cannot be inverted, as the bursting neuron is hyperpolarized by current injection. If the cell is hyperpolarized to the point where the slow inward current is absent (that is, beyond the negative conductance region), then no long inhibition will be seen and further hyperpolarization has no effect. Our findings that the slow IPSP cannot be inverted and that it is insensitive to potassium changes confirm earlier observations by Pinsker and Kandel (*2*). However, they do not support the suggestion that the long IPSP's might be due to electrogenic pump activation. The conclusion of other workers (*4*, *5*) that the prolonged inhibition in these burst firing neurons is due to a "remote" potassium conductance change is contradicted by our findings (*17*).

The mechanism we have described for the long IPSP in these *Aplysia* burst firing neurons is novel in that it involves synaptic modulation of a regenerative ionic conductance channel. Usually, synaptic transmitters are thought to activate [or, in a few cases (*16*), inactivate] ionic channels that are separate from those involved in excitation processes. In this case, however, the ionic channels being inactivated appear to be the very ones underlying the generation of the oscillating potentials leading to burst firing.

It is especially interesting that synaptic activity as well as the axonal application of transmitter can eliminate the negative resistance characteristic measured for the entire cell. Alving (*18*) showed that the neuronal soma could exhibit burst firing even when ligated from the axon, implying that some slow inward current channels are present at the soma. Although we do not yet understand how events at the axonal site could block the slow inward current for the whole cell, two possibilities seem reasonable. A large proportion of the inward current channels may be at the subsynaptic site. Inactivation of these channels could reduce the slow inward current to a level such that the overall *I-V* curve loses its negative resistance region. Alternatively, the neurotransmitter or some intracellular "messenger" may spread from the synaptic region to other areas of the cell. This would be consistent with the slow time course of the inhibition.

The ability of this synaptic inhibition to directly suppress a voltage-sensitive ionic channel and thereby radically change the *I-V* characteristics of the entire neuron very likely underlies its powerful influence on the burst firing pattern.

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12. Traditionally the chemoreceptive properties of the somatic membrane (the most convenient point for microiontophoresis of transmitter agents onto gastropod neurons) have been considered to exemplify those of the entire neuron, and when we iontophoretically applied ACh to the somas of these cells, we confirmed earlier findings that the slow phase of the response could be reversed at −80 mV. On the other hand, when we applied ACh to the proximal axon (about 100 μm from the soma) and the neuron was voltage clamped to increasingly negative potentials, the slow phase of the axonal ACh response asymptotically approached zero, but no reversal of the axonal slow ACh response was seen, even at a potential of −150 mV. This result was obtained in more than 15 cells.
13. In several other experiments we tested the sensitivity of the L_{10}-produced long IPSP to changes in the extracellular potassium ion concentration and simultaneously monitored the size of the short IPSP. In each case we found that high extracellular potassium reduced both IPSP's by the same percentage, and that low extracellular potassium increased both components by the same percentage. The long IPSP did not reverse under any circumstances. We conclude that the variations in extracellular potassium were altering only transmitter release and had no postsynaptic effect on the long IPSP.
14. Sucrose substitution also reduces extracellular chloride, but previous studies have shown that the long IPSP's are insensitive to changes in the extracellular chloride ion concentration. As expected, the brief chloride-dependent component showed a positive-going shift in its reversal potential. However, the effect of this at the −60 mV point was offset by a small reduction in the conductance of the brief response.
15. It has been demonstrated that calcium also contributes to the slow inward current in invertebrate burst firing neurons and that sodium manipulations can alter intracellular calcium [Eckert and Lux (*11*); D. Johnston, *Brain Res.* **107**, 418 (1976)]. We used low-calcium seawater in some experiments and observed a reduction in the slow inward current and the prolonged inhibition. However, since the low-calcium seawater made the cells unstable, we regard those experiments as inconclusive. On balance, it seems reasonable to infer that some calcium component participates in the production of the long IPSP just as it does in the slow inward current.
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19. Supported by the Veterans Administration, Durham, N.C., and by NIH grant NS 08476. All correspondence should be addressed to W.A.W.

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Decrease in Adrenergic Axon Sprouting in the Senescent Rat

Abstract. *When the septal area in young adult rats is denervated by a lesion of the fimbria-fornix, adrenergic fibers proliferate within the denervated area. The same operation performed on aged animals gives rise to a qualitatively similar but quantitatively less pronounced response. This reduction in reactive growth may reflect a decreased capacity of the aged brain to remodel its circuitry and restore lost function.*

The adult mammalian brain is capable of axonal growth in response to various forms of damage including loss of neurons. When neurons are destroyed by lesions, their target cells lose some of their synaptic input. In many cases the remaining projections to those cells form new connections and replace, in the morphological sense, those that were lost. This process, termed reactive synaptogenesis, has been well documented in many areas of immature and adult central nervous systems (*1*). Such responses have not, however, been well investigated in the aged brain.

The plasticity of central neurons in aged animals is a particularly critical issue because the aged brain is most susceptible to neuronal loss. Neuronal loss is a normal consequence of the aging process, as well as the most prominent effect of such common disorders of the aging nervous system as stroke, tumors, and senile dementia. Since reactive sy-

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naptogenesis may ameliorate the functional effects of neuronal loss, we have compared the ability of fibers in aged and young adult rat brains to grow in response to lesions. We report here that growth responses become less extensive with age.

We have studied the capacity of catecholaminergic (CA) fibers to sprout in response to denervation of the septum and hippocampus. The CA fibers are particularly suitable for these studies since their responses to denervation have been well studied and are quite robust and easily followed by histofluorescence methods (*2*). Moreover, CA systems play a central role in the modulation of various behavioral states. We have used a histofluorescence method to localize monoamines in the septum and hippocampus after transection of the fimbria. The septal nuclei receive projections from the hippocampus through the fimbria and from the brain stem through the medial forebrain bundle, a complex tract which includes CA axons. Catecholamine-containing axons proliferate in areas of the septum denervated by a fimbrial transection (*3*). We have also examined the reaction of CA fibers in the hippocampus.

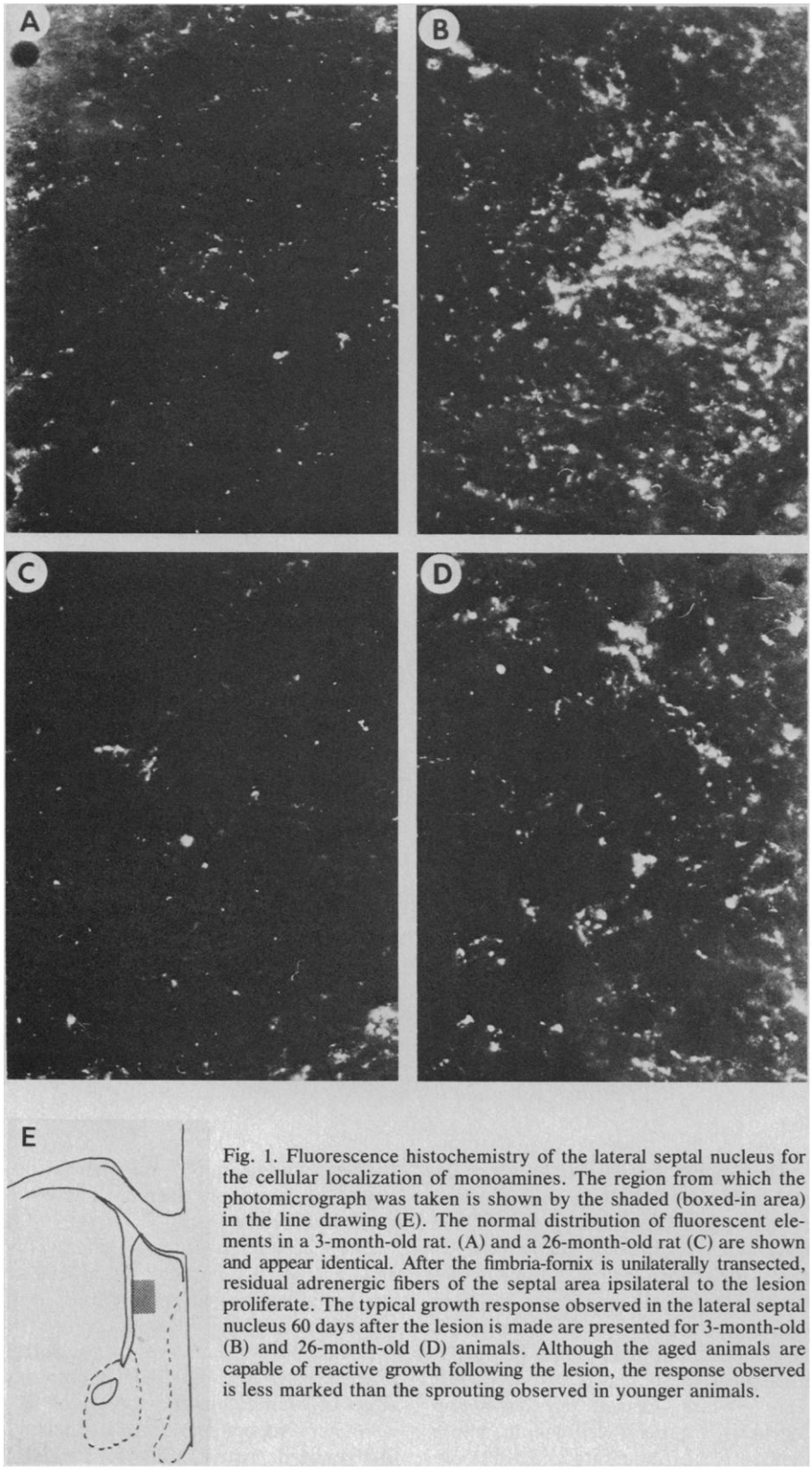

Fig. 1. Fluorescence histochemistry of the lateral septal nucleus for the cellular localization of monoamines. The region from which the photomicrograph was taken is shown by the shaded (boxed-in area) in the line drawing (E). The normal distribution of fluorescent elements in a 3-month-old rat. (A) and a 26-month-old rat (C) are shown and appear identical. After the fimbria-fornix is unilaterally transected, residual adrenergic fibers of the septal area ipsilateral to the lesion proliferate. The typical growth response observed in the lateral septal nucleus 60 days after the lesion is made are presented for 3-month-old (B) and 26-month-old (D) animals. Although the aged animals are capable of reactive growth following the lesion, the response observed is less marked than the sprouting observed in younger animals.

Three-month-old male Sprague-Dawley rats and 26- to 30-month-old barrier-reared rats of the same strain (Charles River) were studied. Animals were anesthetized with pentobarbital, and the fimbria of one side was exposed by aspirating the overlying cortex and part of the striatum. The fibers of the fimbria were than aspirated at a point between the septum and hippocampus. After postoperative periods of 30 and 60 days, animals were decapitated, and the brains were examined for changes in CA innervation by a modified glyoxylic acid histofluorescence method (*4*). Six unoperated rats (three aged and three young adults) and two sham-operated animals were used as controls. Additional animals in which the fimbria was transected were killed 4 days after the operation, and degenerating terminals were stained by a modified Fink-Heimer technique (*5*). Examination of the lesion showed that the operation did not damage the septum or rostral portion of the hippocampus of any of the animals studied.

The septal area of aged rats demonstrated a dense catecholamine fluorescence similar to that of the younger animals. In agreement with previous reports (*3*), the densest catecholamine fluorescence in the septal area was observed in the lateral septal nucleus along the border of the lateral ventricle and at the junction of lateral and medial septal nuclei. The only distinct difference between the age groups was the presence of a yellow-brown autofluorescent material in the septum of the aged animals. This material was intracellular, appearing as fine granules, and may be related to pigments known to accumulate with age (*6*).

At 4 days after fimbrial transection, degenerating elements revealed by the Fink-Heimer method appeared in the ipsilateral medial and lateral septal nuclei and in portions of the nucleus of the

diagonal band. On the contralateral side, we observed only sparse degeneration predominantly localized in the lateral portions of the septal nucleus. In the hippocampus of both sides, the deep third of the dentate molecular layer and strata radiatum and oriens showed abundant terminal degeneration. The overall pattern of degeneration corresponded to that described in previous studies (*7*). The abundance of degeneration products was indistinguishable in 3- and 26-month-old animals.

By 30 or 60 days after the operation, CA fibers in the 3-month-old animals ($N = 10$) had proliferated in the denervated septal areas in agreement with previous reports (*2*). Figure 1 shows a typical response observed in a portion of the lateral septum. This proliferative reaction began within 30 days after the operation and further increased by 60 days. Similar but less pronounced results were obtained from 26-month-old rats ($N = 7$). The number of CA fluorescent elements increased, particularly in the lateral septal area ipsilateral to the transection, but to a lesser extent than that seen in 3-month-old animals (Fig. 1). These results indicate that central CA fibers can still grow in aged animals but not so well as in younger ones.

The reaction of CA fibers was examined in the hippocampus. Recently Loy and Moore (*8*) reported that CA fibers originating from the superior cervical ganglion grow into certain denervated zones of the dentate gyrus when the fimbria is cut. We examined this reaction as a further index of CA plasticity in brain. Our observations confirmed the findings of Loy and Moore in all 3-month-old animals ($N = 10$). Coarse and intensely fluorescent CA fibers, characteristic of those of sympathetic origin, innervate the hilus and inner molecular layer of the dentate gyrus (Fig. 2). In contrast, such a response was obtained in only one of seven 26-month-old animals, even when they were examined 60 days after surgery. In one 26-month-old animal, a growth reaction similar to that of younger rats was evident at 60 days, but was much smaller (Fig. 2).

The paucity or absence of anomalous growth by sympathetic fibers in older animals is important since it indicates the deficiency is not restricted to central neurons or to any particular brain region. We have obtained similar results in studies of the responses of afferents to the dentate gyrus after removal of perforant path innervation (*9*). Both the septohippocampal and associational-commissural afferents less readily replace the perforant path fibers in 26-month-old rats than in 3-month-old rats. These findings indicate that, as a general rule, reactive growth declines with age.

The reason for this diminished plasticity in aged animals is unknown at present. It may reflect a reduction in the abil-

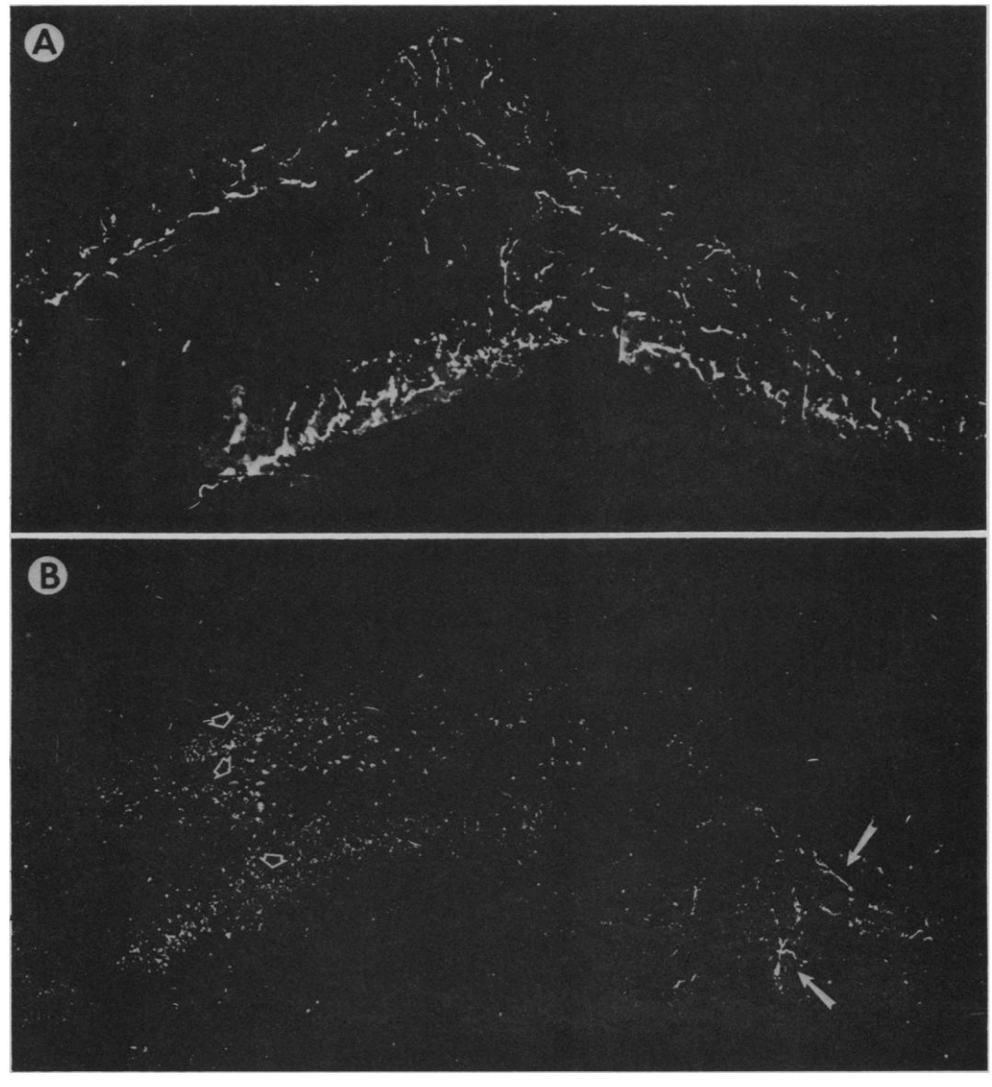

Fig. 2. A photographic montage of the dentate gyrus 60 days after unilateral transection of the fimbria-fornix. After such a lesion, sympathetic fibers arising from the superior cervical ganglion grow into the dentate gyrus. The response in 3-month-old animals (A) is well defined, being localized within the granule cell layer and hilar region. The response in 26-month-old animals (B) is markedly reduced (solid arrows). (B) The maximum growth noted in aged animals. The remaining fluorescent elements (open arrows) are autofluorescent granules that we observe routinely in aged animals.

ity of neurons to synthesize or assemble materials necessary for growth. Alternatively, growth-inducing substances may not be so readily elaborated or perhaps the target cells may be less able to accept new innervation. In the case of sympathetic CA fibers, the diminished growth may be related in part to a reduction in the number of blood vessels in the dentate molecular layer (*9*). However, the reduction in vascular supply is not as great as the reduction in fiber growth, so other factors are probably involved.

Age-related differences in reactive fiber growth may have functional significance. In some instances reactive synaptogenesis appears to underlie recovery or retention of normal function after damage to the central nervous system, but in other instances it seems to cause or contribute to abnormal behavior. In the aged brain we would expect this process to operate not only in cases of severe damage, such as that induced in our study, but also in the replacement of connections lost as a result of the natural aging process. If the new connections can replace the old functionally, then reactive synaptogenesis may be regarded as a compensatory mechanism that counteracts the ill effects of aging. A reduction in growth capacity with age would therefore be detrimental. On the other hand, if the new connections interfere with normal function, reactive synaptogenesis would be harmful and the aged brain would benefit from a diminished growth capacity. Such issues are in need of direct evaluation and must await a more complete understanding of the significance of reactive synaptogenesis. In any case, our finding that neuronal circuitry appears more rigid in old animals needs to be taken into account in considering the end result.

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7. Lesions of the fimbria-fornix disrupt several pathways, among which are the connections between the two hippocampi. The commissural projection which arises in the CA3-CA4 region of one hippocampus and projects to the contralateral hippocampus with specific terminations in the inner one-third of the dentate molecular layer and also strata radiatum and oriens of regio superior and regio inferior [T. W. Blackstad, *J. Comp. Neurol.* **105**, 417 (1956)]. A lesion of the fimbria-fornix also produces degeneration in the septal nuclei because the hippocampal and subicular pyramidal cells project to different parts of the septal area [L. W. Swanson and W. M. Cowan, *J. Comp. Neurol.* **172**, 49 (1977)]. Finally this lesion also removes the adrenergic innervation to the hippocampal formation arising from locus coeruleus because some of these fibers enter the hippocampal formation through the fimbria [R. Y. Moore, in *The Hippocampus*, R. L. Isaacson and K. H. Pribram, Eds. (Plenum, New York, 1975), vol. 1, p. 215].
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Center-Surround Organization of Auditory Receptive Fields in the Owl

Abstract. *The spatial receptive fields of specialized auditory units in the midbrain of the barn owl* (Tyto abla) *contain two functionally antagonistic areas: an excitatory center and an inhibitory surround. The response of these units represents the balance of acoustic activation of the two areas, which in turn depends upon the location, intensity, and spectral content of the sound stimulus.*

The barn owl (*Tyto alba*) derives spatial information from sound signals accurately enough to capture small prey in total darkness. Recently a specialized auditory region in the midbrain of the owl has been implicated in spatial analysis of sound stimuli (*1*). Neurons in this region, which respond to sounds from restricted areas of space (receptive fields) are arranged systematically according to the location of their receptive fields so that they form a physiological map of auditory space. We now describe another space-dependent response property of these units that further supports their implied function in spatial analysis of sound: their receptive fields are subdivided into spatially separate excitatory and inhibitory areas similar to the center-surround receptive field organization described for other sensory systems.

The midbrain region that contains these units is the lateral and anterior region of the auditory nucleus known as mesencephalicus lateralis dorsalis (MLD), the avian homolog of the inferior colliculus. Because of the systematic arrangement of unit receptive fields in this region, it has been called the space-mapped region of MLD (*2*). The receptive fields exhibited by units in the space-mapped region have been classified as limited-field (L-F) receptive fields, to contrast them with other, less restricted field types.

Four barn owls were studied, each owl being prepared for long-term recording (*2*). The statements made here are based on the properties of 63 single units (*3*) that were located in the lateral and anterior portion of the MLD as confirmed by electrode track reconstructions. The experiments were performed in a large anechoic chamber (*4*). Conventional amplification and spike analysis equipment was used (*1, 2*).

Nearly all L-F units (60 of 63) had low ongoing discharge rates. Thus, in order to detect inhibitory effects of sounds presented in areas outside a unit's receptive field, two sound sources were required: one positioned inside the unit's receptive field to drive the unit (driving speaker), and a second to present test sounds at various locations outside its receptive field (roving speaker) (*5*). The position of the roving speaker was remotely controlled from outside the chamber. The speaker moved along a semicircular track to provide changes in sound-source azimuth, and the track itself rotated around a horizontal axis to provide changes in sound-source elevation. The sphere described by the movement of the roving speaker was 1 m in radius. The head of the anesthetized owl (*6*) was secured to a head holder and was centered within the speaker's sphere of movement so that the owl's median and visual planes corresponded to 0° azimuth and 0° elevation of the roving speaker (*7*). The driving speaker was also movable, but not by remote control.

The protocol for testing units was as follows. After a single unit had been isolated, the roving speaker was moved while emitting noise bursts (*8*) to the area of space to which the unit responded most vigorously. This area of space, which is sharply defined for L-F units, is called the unit's best area (*1*). The driving speaker was then manually positioned in the unit's best area, behind the roving speaker. The threshold of the unit to noise bursts from each speaker was measured; sound intensity values refer

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