in receptor sensitivity may contribute to this variation in amphetamine responsiveness. Similarly, we have previously considered the possible role of differential receptor sensitivity in the etiology of depressive illness (*6*).

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17. Skolnick and Daly (*8*) report opposite relative sensitivities for the two strains with respect to NE-accumulated cyclic AMP in midbrain-caudate and cortical slices. They suggest that the cortical system may play an inhibitory role in the elaboration of behavioral arousal. It is conceivable, therefore, that the greater responsiveness of the Buff strain to the infusion of NE may be due to both a relatively greater sensitivity of a midbrain-caudate excitatory system and the relatively lower sensitivity of an inhibitory cortical system.
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Hippocampo-Hypothalamic Connections: Origin in Subicular Cortex, Not Ammon's Horn

Abstract. *An autoradiographic study of the subcortical projections of the rat hippocampal formation shows that the efferent fibers of the hippocampus proper (fields CA1–4 of Ammon's horn) do not project to the hypothalamus but are confined to the precommissural fornix, ending primarily in the septum. The fibers that are distributed by way of the fornix system to the hypothalamus (principally the arcuate-ventromedial region and the mammillary nuclei) and the anterior thalamus arise from the subicular region of the cerebral cortex (that is, the subiculum, presubiculum, and parasubiculum).*

The hippocampal formation (*1*) has been implicated in various behavioral and neuroendocrine functions, and it is generally assumed that these are mediated by way of well-defined subcortical projections from the hippocampus to the anterior thalamus, the hypothalamus, and the septal region (*2*). However, while the connections of the hippocampus have been studied for more than a century and with virtually every available neuroanatomical technique, surprisingly little is known about the origins of the different components of the fornix system, which comprise the principal descending projection from the hippocampal formation. The earlier descriptions based on normal material are clearly inadequate (*3*), and—although it has not always been appreciated—the interpretation of lesion-induced degeneration experiments may be seriously complicated by the interruption of fibers arising from regions distal to the lesion. With the introduction of the autoradiographic method for tracing central fiber pathways [which is based on the selective uptake of tritiated amino acids by neurons and the subsequent transport of labeled proteins along their axons (*4*)] it seemed appropriate to reinvestigate the origin of the various hippocampal projections, not only because fibers of passage do not appear to complicate the interpretation of connections demonstrated by this method, but also because of its unusual sensitivity (*5*).

More than 50 small injections of [^{3}H]-proline (usually 0.4 μc of L4,5; [^{3}H]proline in 20 nl of distilled water) have been made stereotaxically in different parts of the hippocampal formation of adult albino rats. After survival times ranging from 24 to 72 hours, the animals were perfused transcardially with 10 percent formalin, and their brains were prepared for autoradiography (*4*).

Our results demonstrate that the fibers of the postcommissural fornix which project to the hypothalamus arise not in the hippocampus proper but rather in the adjacent subicular region. The fibers which terminate in the mammillary nuclei have their origin in the dorsal part of the subiculum and the adjoining pre- and parasubiculum; those which pass into the medial corticohypothalamic tract, and terminate in relation to the ventromedial and ar-

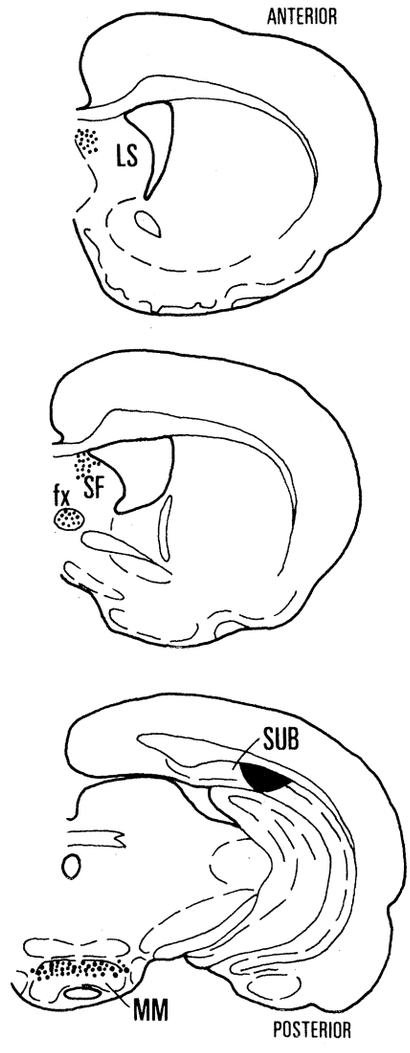

Fig. 1. The distribution of transported label (dots) after an injection of [^{3}H]proline (solid black) into the dorsal part of the subiculum (*SUB*) in one experiment (R176). A subcortical projection to the medial mammillary nucleus (*MM*) and the septal area can be clearly defined. *LS*, lateral septal nucleus; *SF*, septofimbrial nucleus; *fx*, postcommissural fornix. The three tracings are from representative sections through the brain, arranged from anterior to posterior.

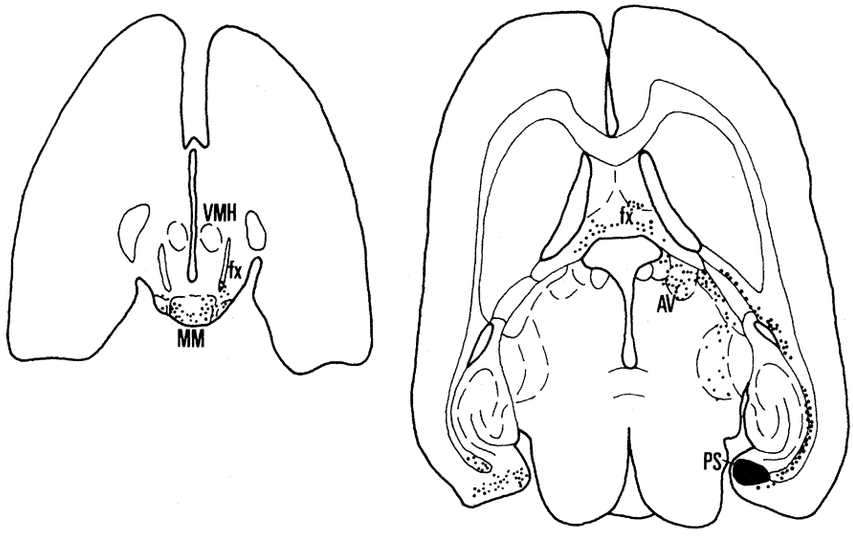

Fig. 2. The distribution of label (dots) after an injection of [^{3}H]proline (solid black area) confined to the pre- and parasubicular cortex (*PS*) in experiment R133. From the injection site, labeled fibers course through the fimbria and fornix system (*fx*) to the anteroventral thalamic nucleus (*AV*) and to the mammillary body. *VMH*, ventromedial nucleus; *MM*, medial mammillary nucleus. Tracing of two representative sections through the brain.

cuate nuclei, arise from the ventral part of the subiculum (*6*).

The evidence for this is as follows. In a large number of brains with injections of [^{3}H]proline into one or more fields of the hippocampus proper [fields CA_1–CA_4 of Lorente de Nó (*7*)], we have been unable to trace labeled fibers in the fimbria or dorsal fornix beyond the septal nuclei. In no case in which the injected isotope was confined to these cytoarchitectonic fields could we find evidence for a projection to the anterior thalamus or to the hypothalamus. It has been possible, however, to show that these fields have a highly ordered topographic projection on the medial and lateral septal and septofimbrial nuclei (*8*).

In a number of experiments in which the isotope injection was either confined to, or had significantly involved, the subicular region, labeled fibers could be readily traced through the dorsal fornix and, by way of the postcommissural fornix, to the anterior thalamus, and to the tuberal and mammillary nuclei of the hypothalamus. When only the dorsal part of the subiculum was labeled (as in the experiment illustrated in Fig. 1), the transported label was found bilaterally within the medial mammillary nucleus, occupying a more-or-less horizontal band across both nuclei. When the injection involved the ventral portion of the subiculum, the labeled fibers were found in the lateral part of the fimbria, and could be followed into the medial corticohypothalamic tract through which they reached the medial preoptic-anterior hypothalamic area, and appeared to terminate in relation to the capsule of the ventromedial and arcuate nuclei of the hypothalamus. In addition, some fibers from the ventral subiculum extend into the precommissural fornix to the septofimbrial and lateral septal nuclei, to the bed nucleus of the stria terminalis, the nucleus accumbens, and the adjoining cortical areas (the taenia tecta, anterior olfactory nucleus, and infralimbic area).

We have studied several brains in which the pre- and parasubiculum were involved by the isotope injection, but only one in which the injection was confined to these two cytoarchitectonic fields (Fig. 2). In this case, evidence of a terminal projection was found in the anterior thalamus (mainly in the anteroventral nucleus), in the mammillary complex (principally the medial mammillary nucleus), and in the entorhinal and subicular regions of the opposite side.

We have not yet examined the brains of other mammals from this point of view; if it can be shown that a similar pattern of connections is common to most mammals (and especially if it could be demonstrated in the primate brain) our entire perspective of the organization of the hippocampal projection system will need to be revised (*9*). Certainly the finding that much, if not all, of the postcommissural projection in the rat brain is derived from the subicular region should serve to focus attention on this poorly understood and, to date, largely unexplored region of the cerebral cortex.

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References and Notes

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10. We thank L. V. Bell and L. Rogers for technical help. Supported in part by NIH grants MH-24604, NS-03777, and NS-10943.

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