periods up to 1 year after experimental infection, and suggests that the persisting viral antigen within macrophages may provide the stimulation for continuing antibody formation in states of prolonged or lifelong immunity to such virus diseases as smallpox, measles, and yellow fever.

In view of the recently demonstrated association between virus infections and demyelinating diseases in human beings and laboratory animals (*16*), however, we may suspect also a pathogenetic role for ependyma and macrophages. While in some diseases the demyelination appears to be the result of a direct cytopathic effect of virus upon oligodendroglial cells, in others immunopathological mechanisms appear to be responsible for myelin destruction. As reservoirs for viral replication, ependyma and macrophages may provide antigenic stimulation for continuing antibody formation as well as a continuing supply of virus for infecting and altering oligodendroglia and myelin membranes.

Investigation of macrophage function thus far has been done mainly on peritoneal macrophages, since they are easily accessible in large numbers and also because a resident macrophage system of the ventricles of the brain has not heretofore been described or proposed. Our findings, taken together with information accumulating about the pathological sequelae of viral invasions of the brain and about macrophage-viral infections in other tissues, indicate another host system requiring further investigation in the attempt to understand pathogenetic mechanisms of certain acute and chronic central nervous system diseases (*17*).

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Strain Differences During Intraventricular Infusion of Norepinephrine: Possible Role of Receptor Sensitivity

Abstract. *Two rat strains previously shown to differ with respect to behavioral activity, regional brain tyrosine hydroxylase activity, and norepinephrine-elicited accumulation of adenosine 3',5'-monophosphate exhibited differential behavioral responsiveness during the intraventricular infusion of norepinephrine. The results are interpreted in terms of differential catecholamine receptor sensitivity.*

Recently we reported an inverse relationship between the behavioral activity of several strains of rats and their respective levels of midbrain and neostriatum tyrosine hydroxylase activity (*1*). This relationship appeared to conflict with the alleged role of central catecholamines (CA) in behavioral arousal (*2, 3*). However, we proposed a possible explanation for this apparent disparity based on the findings that experimental manipulations alleged to impair adrenergic transmission augment central catecholaminergic biosynthetic capacity (*4, 5*) and the converse (*6, 7*). On the basis of these results we suggested that, for the strains examined, both enzyme activity and behavior are influenced by the level of adrenergic transmission. That is, the strain having a high level of functional transmission would manifest relatively reduced enzyme activity and elevated behavioral arousal. The opposite would be expected for a strain with comparatively lower synaptic activity. We further speculated that the primary factor responsible for the differences in transmission might be receptor sensitivity (*1*).

Skolnick and Daly (*8*) tested this hypothesis by measuring norepinephrine (NE)-elicited accumulation of adenosine 3',5'-monophosphate (cyclic AMP) as an index of receptor sensitivity. Evidence suggests that cyclic AMP is intimately associated with neuronal transmission in both the central (*9*) and peripheral (*10*) nervous systems, and in particular that an adenylate cyclase system may, in fact, be the adrenergic receptor itself (*11*). Comparing the combined midbrain-striatal slices of four strains, Skolnick and Daly found a high positive correlation between NE-elicited accumulation of cyclic AMP and the levels of behavioral activity obtained in our study ($r = .99$; $P < .001$). These results support our hypothesis of a direct relationship between the behavioral activity of the various strains and their corresponding adrenergic receptor sensitivity.

We also studied the effects of intraventricular infusion of NE and reported that NE produces a dose-related increase in the behavioral activity of rats (*3, 12*). To ascertain the mechanism by which NE exerts this behavioral effect, we examined the NE-induced behavioral activation under various pharmacological conditions (*13, 14*). Prior treatment with 6-hydroxydopamine (alleged to selectively destroy central CA neurons) markedly potentiated the response to infused NE. Prior treatment with desmethylimipramine (reported to prevent the uptake inactivation of NE) did not alter the effects of NE on behavior. These results suggest a postsynaptic rather than presynaptic mediation of the NE-induced behavioral activation (*13*). Additional evidence for this conclusion stems from the results obtained with intraventricularly infused amphetamine, a drug believed to affect behavior through the release of CA's. The behavioral excitation elicited by amphetamine appears to be de-

pendent upon the endogenous levels of brain CA's since it is suppressed following treatment with CA-depleting agents (α-methyl-*p*-tyrosine or reserpine). Such treatments had either no effect on the response to NE or potentiated that response (*14*). These results provide further evidence for a direct mechanism of action of infused NE and indicate the potential usefulness of NE-induced activity as an index of receptor sensitivity. We now report results in which this procedure was used as a more direct method of testing the hypothesis of differential receptor sensitivities in the various strains.

Two strains of inbred male rats, Buff and F344 (of the strains examined, these were extreme with respect to behavior, regional brain tyrosine hydroxylase, and NE-elicited accumulation of cyclic AMP), were obtained from Microbiological Associates, Inc., Walkersville, Md. One week after their arrival, each animal was implanted with a cannula in the right lateral ventricle (DeGroot coordinates: A 5.4, ML 2.0, H +4.0) and housed individually with unlimited access to food and water for at least 1 week before testing. All rats were approximately 10 weeks old at the start of experimentation. A 12-hour light-dark cycle was maintained.

Animals were placed in experimental chambers and connected to the infusion apparatus described previously (*12*) 1.5 hours before the start of infusion. This preinfusion interval allowed the animals to habituate to the chambers and thus minimized the influence of differential baseline levels on response to infusion. The rats were then continuously infused for 3 hours with either 0.9 percent saline or *l*-norepinephrine bitartrate in 0.9 percent saline vehicle (Winthrop Laboratories) (1.0 μg/μl, free base). This dose was chosen on the basis of dose-response studies demonstrating a moderate behavioral effect with NE at 1.0 μg/μl (*12*). Each animal was infused only once at a constant rate of 20 μl/hour. The behavioral testing apparatus allowed for the automatic, continuous recording of both locomotion and rearing (*14*). After testing, animals were infused with methylene blue dye and the cannula placements were verified by gross dissection of the brain.

During the 1-hour interval immediately before infusion, both strains were relatively inactive (Fig. 1). Similarly, the two strains remained quiescent during the 3 hours of saline infusion. Infusion of NE, however, produced an increase in crossovers and rearings for both groups of animals. The NE-induced excitation was apparent within the first hour and persisted throughout the 3 hours of infusion. However, although both groups were significantly activated by the infusion of NE, the extent of activation was different for the two strains, the Buff animals exhibiting considerably more NE-induced activity with respect to both crossovers (58 ± 6 compared to 27 ± 4; $P < .001$) and rearings (16 ± 3 compared to 4 ± 1; $P < .001$). This difference was readily apparent within the first half hour and continued throughout the entire 3-hour interval of infusion.

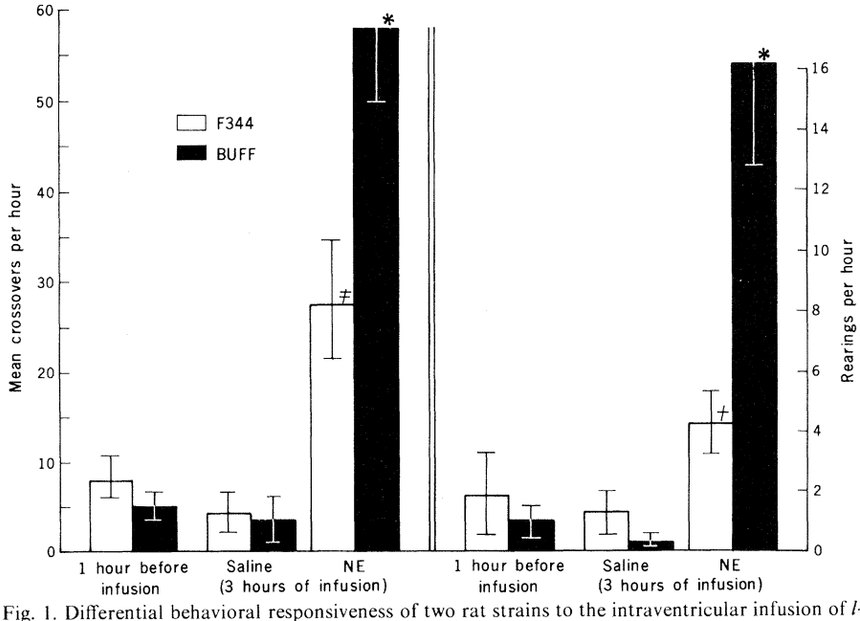

Fig. 1. Differential behavioral responsiveness of two rat strains to the intraventricular infusion of *l*-NE (1.0 μg/μl). The Buff strain ($N = 16$) exhibited significantly more crossovers and rearings than did the F344 strain ($N = 18$) during the 3 hours of NE infusion; *, significantly greater ($P < .001$) than F344 group infused with NE; ‡ and †, significantly greater ($P < .001$ and $< .05$, respectively) than corresponding saline control ($N = 8$ for each control group).

These results indicate that the Buff animals are more responsive than are the F344 animals to the infusion of NE. If NE specifically affects CA receptors, as suggested by our previous studies (*13–15*), then these findings indicate that either the number or sensitivity of central adrenergic receptors is greater in the Buff than in the F344 rats.

To determine the generality of these results, we also examined the effects of intraventricular infusion of amphetamine on the behavior of the two strains. If the amount of amphetamine-induced CA release is approximately the same for the two strains, then the difference in receptor sensitivity would result in a greater response to amphetamine by the Buff animals. The infusion of *d*-amphetamine sulfate (Sigma Chemical Co.) at 1.5 μg/μl, a dose chosen because of its relatively moderate behavioral effects in previous studies (*14, 15*), produced an increase in activity in both of the strains. However, as with NE, the increase in locomotor activity was considerably greater for the Buff rats (147 ± 47 compared to 13 ± 3; $P < .02$). The greater difference between the two strains with amphetamine than with NE suggests that the Buff rats may be more responsive to the NE-releasing action of amphetamine as well as having greater receptor sensitivity than the F344 animals. In a small sample of rats, infusion of methoxamine hydrochloride (Burroughs-Wellcome, Inc.) (2.92 μg/μl, free base), alleged to be a direct-acting alpha agonist (*16*), produced similar results (91 ± 9 and 49 ± 14), thus further indicating the greater receptor sensitivity of the Buff rats. This compound is of particular interest since it does not appear to be taken up into the CA presynaptic terminals (*16*), thus ruling out differences in CA uptake as the mechanism underlying the differential responsiveness of the strains. Our results with NE, amphetamine, and methoxamine, and the findings of Skolnick and Daly (*8*) with regard to NE-elicited accumulation of cyclic AMP in the midbrain and striatum, are all consistent with our hypothesis of a differential receptor sensitivity in the strains tested (*17*).

Drug-induced alterations in receptor sensitivity have been invoked to explain phenomena such as tolerance or sensitization with repeated drug administration (*5, 14, 18*). In addition, genetic or experientially induced differences in receptor sensitivity may influence responsivity to drugs and proneness to psychiatric diseases. For example, Fawcett *et al.* (*19*) have shown that responsiveness to amphetamine may be used as an index for identifying subgroups of depressed patients. It is conceivable that differences

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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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-

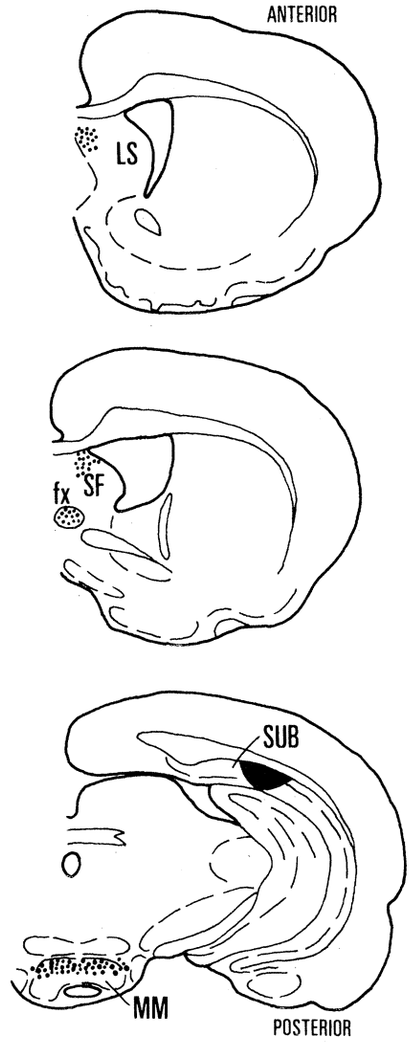

Fig. 1. The distribution of transported label (dots) after an injection of [^{3}H]proline (solid black) into the dorsal part of the subiculum (*SUB*) in one experiment (R176). A subcortical projection to the medial mammillary nucleus (*MM*) and the septal area can be clearly defined. *LS*, lateral septal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