Hippocampal lesions, haloperidol, and excessive grooming

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Rats with bilateral hippocampal damage, neocortical lesions, or sham operations were tested for excessive grooming after intracerebroventricular (icv) injection of ACTH₁₋₂₄ or saline. The animals were tested for 3 days after pretreatment with low doses of haloperidol and on the first and last test days after saline pretreatment. The animals with hippocampal lesions evidenced less grooming than did the other groups, after both icv ACTH and icv saline. In addition, their grooming was reduced to a greater extent by low doses of haloperidol than was grooming by controls. This was interpreted to reflect altered dopaminergic sensitivity after hippocampal destruction.

Animals with near-total bilateral hippocampal destruction have been shown to exhibit an altered responsiveness to agents with selective effects on dopaminergic systems (see Isaacson, 1980, for a review) and also to reduce the excessive grooming produced by intraventricular injection of ACTH₁₋₂₄ (Colbern, Isaacson, Bohus, & Gispen, 1977; Elstein, Hannigan, & Isaacson, 1981). Furthermore, both systemic and intraventricular injections of the dopaminergic blocking agent haloperidol, can antagonize both ACTH-induced grooming and that produced by the circumstances related to testing in a novel environment (see Gispen & Isaacson, 1981, for a review). However, the doses of systemically administered haloperidol required to produce a reduction in excessive grooming have been high, typically of the order of 2 mg/kg. The present study was undertaken to extend our knowledge of the mechanisms of action of the neuropeptides by determining whether lower doses would produce an effect on ACTH-induced excessive grooming in animals with hippocampal damage or in control subjects. The paradigm chosen was one in which the lesions of the hippocampus or surgical control procedures were made at the same time cannula guides were implanted into the foramen of Monro (the interventricular foramen). The animals were tested for peptide-induced excessive grooming at various postsurgical times after pretreatment with haloperidol.

Male Long-Evans hooded rats received sham operations, neocortical damage, or neocortical and hippocampal destruction by aspiration as described by Isaacson and Woodruff (1975). At the time of central nervous system damage, polyethylene cannula guides

were implanted into the intraventricular foramen according to the procedures of Brakkee, Weigant, and Gispen (1979). Behavioral tests for grooming were given on the 5th, 7th, 9th, 11th, and 14th days after surgery (Tests 1, 2, 3, 4, and 5, respectively) following the procedure of Gispen, Wiegant, Greven, and de Wied (1975). Different sets of animals were given intracerebroventricular (icv) injections of either 2 µg of ACTH₁₋₂₄ in 2 µl of saline or 2 µl of saline on every test day. Pretreatments with progressive doses of haloperidol (.01, .04, or .08 mg/kg) were given ip on Test Days 2, 3, and 4. These were given 10 min before the icv injection. A saline pretreatment was given ip on Test Days 1 and 5. After the final test, the animals were sacrificed with an overdose of pentobarbital and the brains were recovered and examined histologically for appropriate cannula placement and lesions.

Histological evaluation of the brains revealed that the hippocampal lesions were somewhat smaller than those normally produced in this laboratory (e.g., Isaacson & Woodruff, 1975). They involved the dorsal and middle portions of the hippocampus. The ventral hippocampus was spared in all animals. The amount of hippocampal destruction was approximately 50% of the structure. The neocortical lesions involved the dorsolateral neocortex overlying the hippocampus and were about the same amount of damage as is usually found in lesions.

The excessive grooming induced by either the icv injection of ACTH or by the effects of transport, handling, and exposure to a novel test room (icv saline injection) was reduced in animals with hippocampal damage relative to the cortical and sham-operate groups (see Figure 1).

Figure 1. Means and SEMs of grooming scores of groups receiving icv ACTH₁₋₂₄ or icv saline after pretreatment with saline (Sal) or haloperidol at doses of .01, .04, or .08 mg/kg as indicated.

To reduce the effect of isolated extreme scores, a logarithmic transformation was made on the data before the statistical analyses were performed. Separate within-subjects analyses of variance performed on the scores from the three groups of subjects receiving intraventricular ACTH indicated that the sham and cortical groups did not differ across the first 4 testing days. A significant effect was found in the hippocampal lesion group [$F(3,24) = 4.963$, $p < .01$]. The location of the effect seemed to occur on the 3rd and 4th test days when the animals were given the .04- and .08-mg/kg doses of haloperidol (see Figure 1). A correlated t test was performed between the scores obtained on Test Day 2 and Test Day 3 for the animals with hippocampal lesions and indicated a significant effect ($t = 3.60$, $p < .05$). Similar within-subjects analyses of variance made on the three groups receiving icv saline revealed no differences occurring over the first 4 test days in any group.

On the fifth test, made after pretreatment with saline, all ACTH-injected groups showed reductions in the grooming induced by the icv ACTH relative to the fourth test. Only one animal in all of the groups had a higher score on the fourth test. The levels of all groups were approximately those found on the fifth test in the intraventricular saline group. The reductions in the cortical and sham-operate groups on this final test were significant relative to the previous tests, but the amount of grooming exhibited by the hippocampal group was not different from the amount exhibited on the fourth test, due to the low amounts of grooming found on that test.

The intraventricular doses of ACTH given to the sham-operated animals elicited equivalent excessive grooming in the sham-operated and neocortical lesion groups on all days except the last test day. The results from the first 4 test days are consistent with earlier findings that no diminution of excessive grooming is found with repeated injections separated

by 12 or more hours (Colbern, Isaacson, Green, & Gispén, 1978; Jolles, Wiegant, & Gispén, 1978). Furthermore, the grooming scores of neither the sham-operated nor the animals with lesions restricted to the neocortical surface were affected by the low doses of haloperidol used as pretreatments. This would follow from previous observations that indicated that high doses of the drug were required to reduce ACTH-induced excessive grooming. Animals with hippocampal damage showed a reduced amount of grooming after icv ACTH at the .04- or the .08-mg/kg doses. This supports the notion that destruction of the hippocampus alters sensitivity to pharmacologic manipulations of the forebrain dopaminergic (DA) systems (see Isaacson, 1980). The fact that this occurred only in the animals receiving the icv neuropeptide and not in the animals receiving icv saline may reflect the fact that the novelty-induced grooming had approximated a "baseline" level of grooming below which it is not reduced by high doses of either haloperidol or naloxone. Novelty-induced grooming does decline with repeated testing to a "baseline" level (see Colbern et al., 1978).

It is also of interest that ACTH induced excessive grooming in the animals with hippocampal lesions, although the amount was less than that of controls. This indicates that the lesion reduces the sensitivity of the animals to the neuropeptide but does not eliminate responsiveness. A similar effect was observed by Elstein et al. (1981), who found diminished sensitivity to icv ACTH in animals with hippocampal damage but not an inability to exhibit excessive grooming. Since there is presumptive evidence that the excessive grooming found after handling, transport, and placement in a novel environment is due to endogenous ACTH release (Dunn, Green, & Isaacson, 1979), a diminished sensitivity to ACTH-induced effects would also account for the reduced grooming by hippocampally lesioned animals after the icv saline treatments.

The three low doses of haloperidol had an effect that lasted for at least 3 days after the last drug administration. At no time were any overt behavioral signs of lethargy or ataxia noted after the haloperidol injections or on subsequent days. On the 4th test day after pretreatment with saline, the peptide-induced excessive grooming was below that produced by prior treatments of ACTH preceded by systemic haloperidol treatments. This was a surprising result since prolonged daily treatment with icv ACTH or with icv saline does not reduce responsiveness to subsequent ACTH administration (Colbern et al., 1978). This suggests that these low doses of haloperidol given over 3 days produced a relatively long-lasting effect on the dopaminergic systems. Long-term effects of chronic neuroleptic treatments have been

noted (e.g., Moore & Thornburg, 1975), but the effects of single doses or brief regimes of haloperidol administration have been less well studied. Changes in dopamine turnover in olfactory bulb and caudate have been noted up to 8 h and up to 24 h in the median eminence after a single injection of haloperidol (Gudelsky & Moore, 1977). The enhanced turnover in the median eminence could be mediated by prolactin (Gudelsky & Moore, 1976). Changes in dopamine receptors after acute neuroleptic treatment seem to last for longer periods. Increased DA receptor sensitivity lasted for several days after the antagonist effects had terminated (Christensen, Fjalland, & Møller Nielsen, 1976; Møller Nielsen & Christensen, 1975). This supersensitivity may involve dopaminergic excitatory receptors (DA_E) as designated by Cools and Van Rossum (1980). Activation of this receptor system in the caudate has been shown to reduce neuropeptide-induced excessive grooming (Cools, Wiegant, & Gispen, 1978). In their view, neuropeptide-induced excessive grooming can be reduced by an imbalance between excitatory and inhibitory dopamine receptor systems of the basal ganglia. If the destruction of the hippocampus were to disrupt this balance, it should be capable of being restored by appropriate intervention in the basal ganglia system. In line with this view, the injection of a dopaminergic agonist into the nucleus accumbens of animals with hippocampal lesions partially restores normal amounts of novelty-induced excessive grooming (Reinstein, Hannigan, & Isaacson, 1981). The effects of hippocampal damage also affect other behaviors influenced by dopaminergic agents. For example, Fish (1976, cited by Isaacson, 1980), Woodruff (1981), and Woodruff and Isaacson (1977) have found that animals with hippocampal lesions exhibit an altered sensitivity to amphetamine and to haloperidol. Altered sensitivity to drugs with more selective adrenergic effects were not found in animals with hippocampal lesions by Fish or by Schneiderman and Isaacson (1976). These results further support the idea that hippocampal lesions produce long-lasting changes in the responsiveness of animals to dopaminergic agents as measured by several types of behaviors and are not limited to effects on excessive grooming.

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(Manuscript received January 21, 1981;
revision accepted for publication August 7, 1981.)