

THE EFFECTS OF HALOPERIDOL ON μ , δ AND κ OPIOID RECEPTOR mRNA EXPRESSION IN THE STRIATUM.

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Haloperidol (HAL) treatment increases the level of proenkephalin (pENK) mRNA in the striatum. Given these mRNA changes lead to large increases in pENK peptides (1,2), this study examined whether HAL treatment produces changes in opioid receptor mRNAs. No generalized changes in μ mRNA were observed in the caudate-putamen (CPu) or nucleus accumbens (Acb) of HAL treated rats. However, in the rostral CPu, an increase in μ mRNA in the ventromedial matrix was noted. No differences in δ mRNA levels were observed between HAL and vehicle (VEH) treated animals. In general, no changes in κ mRNA were observed, although a small increase in κ mRNA was noted in the lateral Acb. These data indicate that although HAL broadly increases pENK mRNA in the striatum, this treatment did not produce generalized changes in striatal opioid receptor mRNAs.

Male Sprague-Dawley rats were given twice daily injections of HAL (2mg/kg) or VEH (1% lactic acid) for seven days. The animals were then killed and the brains processed for *in situ* hybridization. Riboprobes specific for prodynorphin (pDYN), proenkephalin (pENK), μ , δ or κ mRNAs were utilized to identify regions of the striatum that express these molecules, and computerized image analysis (NIH Image) was employed to measure and compare their level of expression in VEH and HAL treated rats. One-way analysis of variance (ANOVA) was used to determine significant differences between HAL and VEH groups. pDYN mRNA was found in striatal patches, the Acb and olfactory tubercle (Tu), while pENK mRNA was more homogeneously distributed across in CPu and localized in the Acb and Tu.

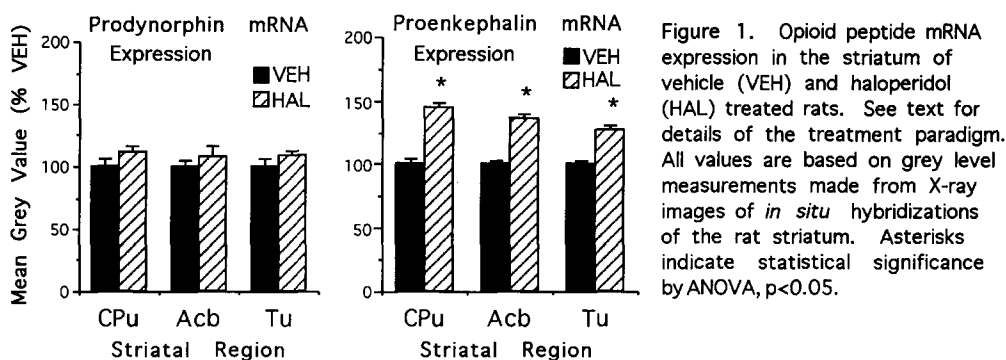


Figure 1. Opioid peptide mRNA expression in the striatum of vehicle (VEH) and haloperidol (HAL) treated rats. See text for details of the treatment paradigm. All values are based on grey level measurements made from X-ray images of *in situ* hybridizations of the rat striatum. Asterisks indicate statistical significance by ANOVA, $p < 0.05$.

HAL treatment had no effect on pDYN mRNA in the rat striatum (Fig. 1), however, it had a dramatic effect on the level of striatal pENK mRNA. HAL treated rats exhibited 45% more pENK mRNA in the CPu ($p=0.0001$; $F=45.83$), 36% more in the Acb ($p=0.0003$; $F=28.12$) and 27% more in the Tu ($p=0.0003$; $F=29.24$) than VEH treated rats (Fig. 1). μ mRNA was localized mainly in striatal patches and the Acb, but it was also found in lower amounts in the rostral striatal matrix (3,4). Whole-region analysis of the CPu and Acb indicated that HAL rats were not significantly different from VEH in these regions, however, HAL treatment did produce a trend toward higher levels of μ mRNA in the CPu (Fig 2).

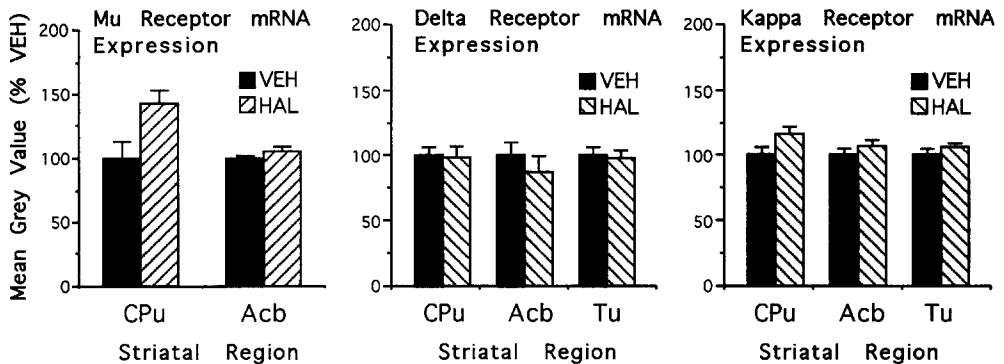


Figure 2. Opioid receptor mRNA expression in the striatum of vehicle (VEH) and haloperidol (HAL) treated rats. See text for details of the treatment paradigm. All values are based on grey level measurements made from X-ray images of *in situ* hybridizations of the rat striatum.

δ mRNA was homogeneously distributed across the CPu, Acb and Tu (5). The levels of δ mRNA were not influenced by HAL treatment (Fig. 2). κ mRNA was localized mainly in the Acb and Tu with some κ positive cells being found in the medial CPu (6). No significant differences were observed between HAL and VEH treated rats, however, a small trend toward an increase in κ mRNA in the lateral Acb was observed in the HAL group (Fig. 2). The intimate interactions between the dopamine and opioid systems are illustrated by the well known effects of dopamine receptor ligands on opioid peptide expression. HAL's effect on striatal pENK mRNA expression is well known, and likely mediated by dopamine D2 receptors on pENK containing striatal neurons (7). Although HAL induces an increase in pENK expression across the entire striatum, it did not produce widespread changes in striatal μ , δ or κ mRNA. However, preliminary data indicate that there may be subregional changes in μ receptor mRNA levels in the striatal matrix. HAL treated rats expressed 63% more μ mRNA than VEH treated rats in the matrix region of the ventromedial CPu ($p=0.002$; $F=19.83$). No differences in μ mRNA were measured between HAL and VEH rats in other striatal regions. A smaller non-significant change in κ mRNA was also observed in a lateral subregion of the nucleus accumbens. Therefore, rather than general changes in opioid receptor expression, receptor expression may be regulated in a subregionally specific manner, the nature and mechanisms of which are currently under investigation.

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