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Differential effect of haloperidol on release of neurotensin in extrapyramidal and limbic systems

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Abstract

The effect of the antipsychotic drug haloperidol on extracellular neurotensin-like immunoreactivity was investigated by microdialysis and compared with the time-dependent response of tissue neurotensin-like immunoreactivity content in brain structures containing dopamine nerve cell bodies and terminals. A single administration of haloperidol (1 mg/kg) increased the extracellular neurotensin-like immunoreactivity levels in nucleus accumbens as measured by microdialysis, but decreased its extracellular concentration in the caudate regions surrounding the probe. The same treatment increased the tissue content of neurotensin-like immunoreactivity in both the nucleus accumbens core and all caudate regions examined within 24 h after the injection. Interestingly, although the neurotensin-like immunoreactivity concentration in the substantia nigra was not altered by the haloperidol treatment, neurotensin-like immunoreactivity levels decreased significantly in the ventral tegmental area. These findings suggest that varied neurotensin systems are associated with nigrostriatal and mesolimbic dopamine pathways and these systems have different responses to haloperidol. The changes in the release of neurotensin may contribute to altered caudate and accumbens neurotensin-like immunoreactivity tissue content induced by haloperidol treatment, but other factors, such as variation in synthesis also likely influence these effects. Differential actions of haloperidol on neurotensin release might be due to regional differences in dopamine or sigma receptor subtypes associated with the neurotensin-containing neurons. © 1997 Elsevier Science B.V.

Keywords: Neurotensin; Haloperidol; Dopamine; Striatum; Nucleus accumbens

1. Introduction

Neurotensin, an endogenous tridecapeptide, is thought to be an important modulator of dopamine neurotransmission in extrapyramidal and limbic regions (Govoni et al., 1980; Kitabgi, 1989). It has been found to be colocalized with dopamine in the prefrontal cortex, but not in the caudate and nucleus accumbens (Kitabgi, 1989). Neurotensin receptors are located on dopamine terminals in both the caudate and nucleus accumbens, suggesting that neurotensin influences the release of this catecholamine (Kitabgi, 1989). Due to the presence of neurons containing mRNA for a neurotensin precursor, it is thought that this peptide originates from neurons with cell bodies in the caudate and nucleus accumbens (Alexander et al., 1989). Although the interaction between neurotensin and dopamine systems is regionally dependent (Gygi et al., 1994), neurotensin's ability to antagonize dopamine-mediated behavior has led to speculation that this neuropeptide can function as an endogenous neuroleptic (Nemeroff et al., 1982; Quirion, 1983; Nemeroff, 1986). Because of its apparent antagonism of dopamine functions, some investigators have speculated that neurotensin plays an important role in the actions of antipsychotic drugs (Govoni et al., 1980; Levant et al., 1989; Myers et al., 1992).

Haloperidol is a widely used antipsychotic drug for the treatment of psychosis such as schizophrenia. This drug has been reported to increase neurotensin concentrations in the nucleus accumbens and caudate nucleus in rats as well as elevate the expression of neurotensin mRNA in these two structures (Govoni et al., 1980; Frey et al., 1986; Merchant et al., 1991, 1992). In addition, reduced neurotensin levels observed in the cerebrospinal fluid of untreated schizophrenic patients appear to return to normal after neuroleptic therapy (Widerlov et al., 1982). Nevertheless, the relationship between the synthesis, release and the tissue content of neurotensin in the presence of haloperidol

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treatment remains unresolved. Therefore, the precise effect of haloperidol on the neurotensin system and the contribution of this neuropeptide to the pharmacological effects of this antipsychotic require elucidation.

In the present study, we measured alterations of extracellular neurotensin in extrapyramidal and limbic terminal fields of dopaminergic pathways by microdialysis and compared the changes in neurotensin release caused by haloperidol with corresponding alterations in surrounding neurotensin tissue content 1–24 h after treatment. The effect of haloperidol treatment on neurotensin tissue levels were also determined in the ventral tegmental area and substantia nigra which contain the corresponding dopaminergic cell bodies.

2. Materials and methods

2.1. Animal treatment

Male Sprague–Dawley rats (230–280 g, Simonson Laboratories, Gilroy, CA, USA) were housed in a temperature-controlled room for a minimum of two weeks before the experiments. Animals were kept on a 12 h light and dark cycle with free access to food and water.

For microdialysis experiments, rats received a single dose of haloperidol (1 mg/kg per injection, i.p.) routinely used to elicit changes in neurotensin tissue levels (Merchant et al., 1989, 1991) or lactate-saline (1 ml/kg per injection, i.p.).

For tissue neurotensin-like immunoreactivity measurements, rats received the same treatment as used for the microdialysis experiments. Animals were killed by decapitation 1, 3 or 24 h after treatment between 10.00 a.m. and 1.00 p.m. to minimize variability due to diurnal fluctuations.

2.2. Cannula and microdialysis probe construction, placement and perfusion

Guide cannulae were made of 3 mm long 20-gauge needles. Microdialysis probes consisted of 3 cm fused silica tubing inserted into 24-gauge stainless-steel hypodermic tubing measured to correspond with placement into the caudate nucleus and nucleus accumbens, as previously described (Wagstaff et al., 1996). The tubings were joined by polyethylene tubing and 4 mm (for striatum) or 2 mm (for accumbens) exposed dialysis membrane of 40 000 MW cutoff size (Hospal Industrie, France).

The day before the experiment, rats were anesthetized with equithesin (3 ml/kg) and mounted in a stereotaxic apparatus. Guide cannulae were implanted into the caudate and accumbens (from bregma: A + 1.7 mm, L + 1.4 mm for accumbens; A + 1.2 mm, L − 2.0 mm for caudate) (Fig. 1). The guide cannulae were anchored to the skull with dental acrylic and stainless steel screws. Stainless steel stylets were placed in the guide cannulae to maintain patency. The rats were allowed to recover overnight.

On the day of the experiment, the microdialysis probes were inserted though the guide cannulae into the caudate nucleus and nucleus accumbens. The probes were connected to an infusion pump (CMA/100, Carnegie Medicin, Stockholm, Sweden) through a swivel to allow free movement. The animals were perfused at a flow rate of 2 μl/min with sterile filtered artificial cerebrospinal fluid (pH 7.4) containing: sodium chloride (NaCl), 125 mM; potassium chloride (KCl), 2.5 mM; calcium chloride ($CaCl_2$), 1.2 mM; magnesium chloride ($MgCl_2$), 1.0 mM; glucose, 5 mM; 0.25% bovine albumin; sodium phosphate monobasic (NaH_2PO_4), 0.5 mM and sodium phosphate dibasic (Na_2HPO_4), 5 mM. Animals were perfused for 2 h before samples were collected for assaying. Dialysate samples were collected every 25 min. Samples were immedi-

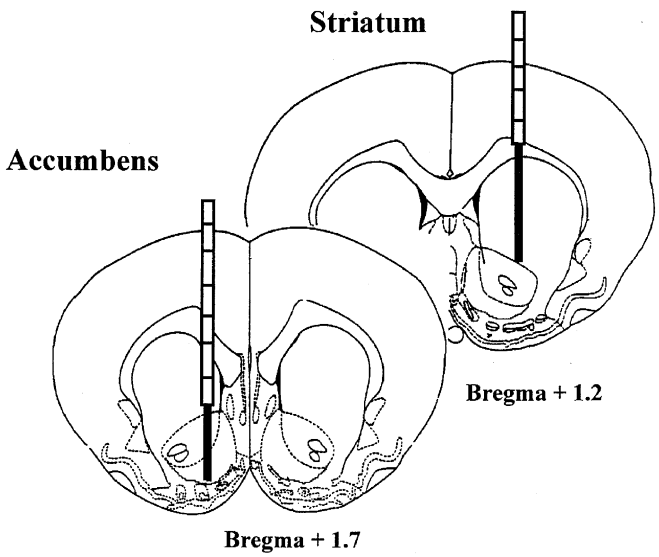

Fig. 1. Regions of probe placement in the nucleus accumbens and anterior caudate. Coordinates are indicated in Section 2.

ately frozen on dry ice and stored at −80°C until assayed for neurotensin-like immunoreactivity. Baseline neurotensin-like immunoreactivity level was determined by collecting four consecutive samples prior to the injection of haloperidol or lactate-saline and the mean of each time point was calculated by determining the average of all animals expressed as percentages of their respective baselines. Ten microdialysis samples were collected after the drug treatment. At the end of each experiment, the animals were sacrificed and probe placement was verified visually from serial coronal sections. In order to establish the neuronal origin of the extracellular neurotensin we were measuring, we previously reported a calcium-dependent potassium-induced release of neurotensin-like immunoreactivity in both caudate and nucleus accumbens (Wagstaff et al., 1996). We also observed that saline injections alone did not significantly alter the extracellular content of neurotensin for 250 min after administration (data not shown due to lack of an effect).

2.3. Microdissection for assessment of neurotensin tissue content

After treatments, the brains were removed and frozen immediately on dry ice and then stored at −80°C. All areas were dissected from consecutive 1 mm thick coronal slices. The caudate nucleus was divided into medial anterior caudate, lateral anterior caudate, medial posterior caudate and lateral posterior caudate regions as described by Gygi et al. (1994): these were the approximate regions of the caudate nucleus surrounding the probes used for the microdialysis experiments. The nucleus accumbens was dissected into core and shell for analysis. The substantia nigra and ventral tegmental area were also removed.

2.4. Tissue neurotensin-like immunoreactivity content

The concentration of neurotensin-like immunoreactivity was determined by a solid-phase radioimmunoassay adapted from the methods described by Maidment et al. (1991). Briefly, tissue samples were homogenized in 0.01 M HCl, centrifuged and the supernatants were lyophilized overnight. An aliquot of the homogenate was used to determine protein for each sample according to the Bradford method (Bradford, 1976). Samples were reconstituted in a phosphate-buffered saline containing 0.1% gelatin. Microdialysate or duplicate aliquots from tissue samples were added to 96-well immunoplates (MaxSorb, Nunc, Roskilde, Denmark) precoated with protein G with attached antibodies from a highly selective neurotensin antiserum used at a 1:20 000 dilution. Samples and standards were incubated at 4°C overnight. ^{125}I-labeled neurotensin (NEN Dupont, Wilmington, DE, USA) was added the next day. The antibody-bound and antibody-free ^{125}I-labeled neurotensin were separated by aspirating the supernatant containing unbound labeled neurotensin. The quantity of neurotensin-like immunoreactivity was determined by comparing bound ^{125}I-labeled peptide from each well to a standard curve. The results were calculated as neurotensin-like immunoreactivity content (pg/mg protein).

2.5. Statistical analysis

Neurotensin-like immunoreactivity concentrations are expressed as percentages of their respective controls to facilitate comparisons between groups.

The average of the first four samples collected by microdialysis prior to the treatment was used as the basal level of extracelluar neurotensin-like immunoreactivity. Extracellular neurotensin-like immunoreactivity levels from each animal were calculated as a percentage of the mean of their respective basal levels (first 4 samples prior to treatment) to eliminate inter-animal variability.

Each column in the figures for tissue neurotensin-like immunoreactivity content represents a mean ± S.E.M. Multiple comparison was done between the means of each time point and corresponding basal level for microdialysate or control groups for tissue content by using an analysis of variance (ANOVA) test followed by Fisher's PLSD (protected least significant difference) when a dif-

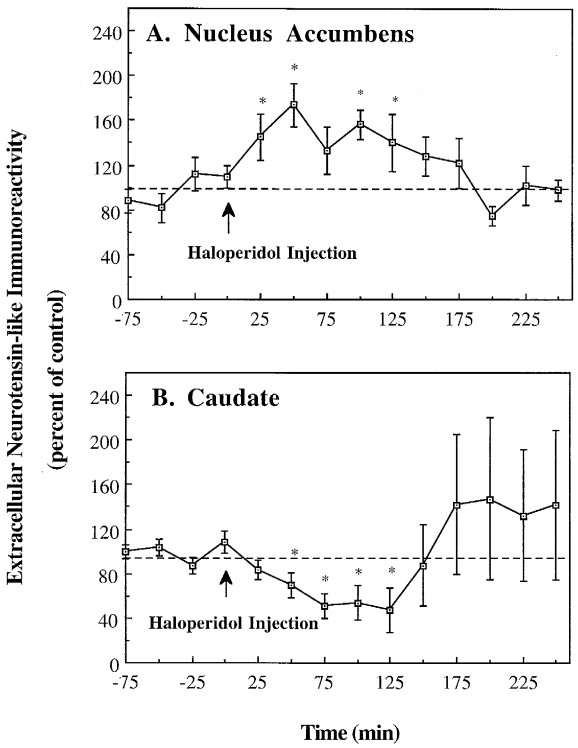

Fig. 2. Effect of a systemic administration of haloperidol on extracellular neurotensin-like immunoreactivity levels in the nucleus accumbens (A) and caudate (B). Haloperidol (1 mg/kg, i.p.) was administered at time 0 as indicated by the arrows. Data (means ± S.E.M. of 8 animals) are expressed as a percentage of the mean of the first 4 time points prior to treatment. * $P < 0.05$ versus corresponding pretreatment baseline.

ference was found. The differences between the means of each time point and control were significant when the possibility that they were the same was less then 0.05.

3. Results

3.1. Effects of haloperidol on extracellular neurotensin-like immunoreactivity levels in caudate and accumbens

In the present study, the in vivo microdialysis technique of Maidment et al. (1991) was employed to measure extracellular neurotensin-like immunoreactivity content in caudate nucleus and nucleus accumbens of awake, behaving rats. After a baseline collection period of 100 min, haloperidol or vehicle was administered (Fig. 2). In the nucleus accumbens, haloperidol significantly elevated extracellular neurotensin-like immunoreactivity level 25 min after the drug injection. The extracellular neurotensin-like immunoreactivity levels remained increased for 150 min before returning to basal level (Fig. 2A). In contrast, haloperidol decreased the extracellular neurotensin-like immunoreactivity level in the caudate nucleus: the neurotensin-like immunoreactivity levels were reduced by 25 min after the treatment and remained depressed for 100 min (Fig. 2B). For control rats receiving only a lactate-saline injection, the extracellular neurotensin-like immunoreactivity level did not significantly vary from the baseline for the entire 350 min collection period in both caudate nucleus and nucleus accumbens (data not shown). The average control values were 1.1 pg/25 min in the nucleus accumbens and 1.2 pg/25 min in the caudate.

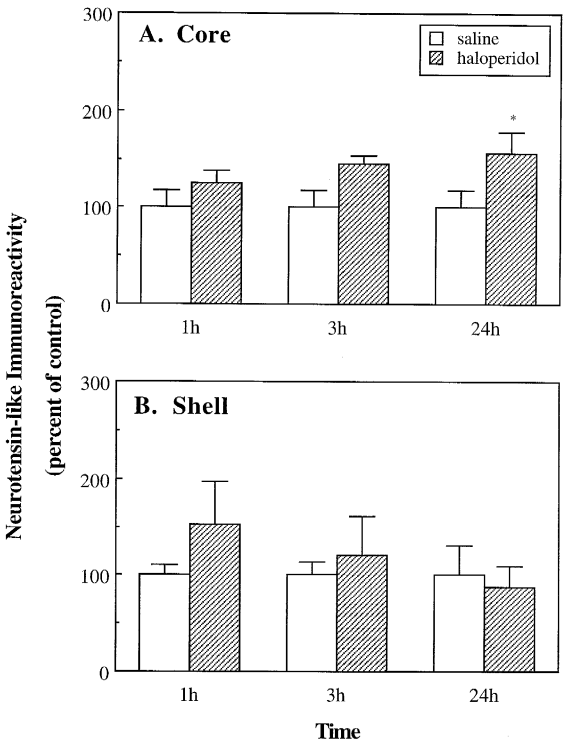

Fig. 3. Tissue neurotensin-like immunoreactivity content in the core (A) and shell (B) regions of nucleus accumbens. Animals were treated with a single 1 mg/kg dose of haloperidol and killed 1, 3 or 24 h after. Neurotensin-like immunoreactivity was analyzed by radioimmunoassay in dissected tissues. Data (means ± S.E.M. of 6 animals) are expressed as a percentage of the mean of vehicle-treated controls. Control values were 243 pg/mg protein in the core, and 1306 pg/mg protein in the shell regions of nucleus accumbens. * $P < 0.05$ versus corresponding vehicle-treated controls.

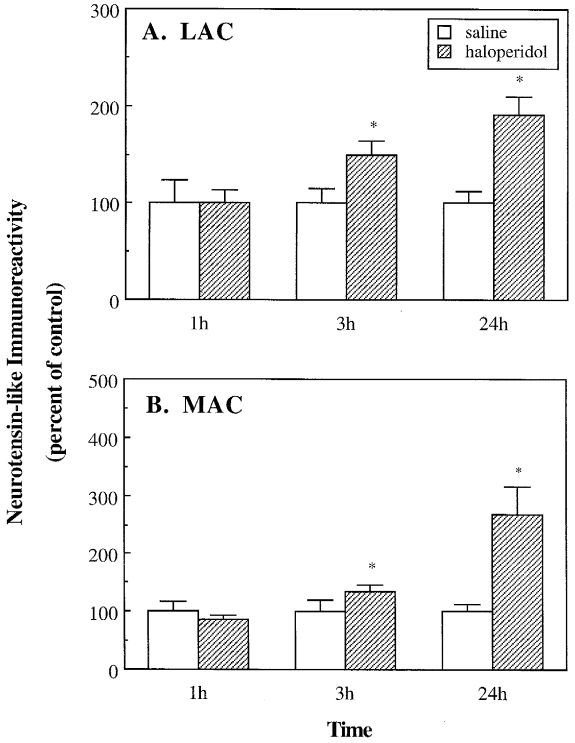

Fig. 4. Tissue neurotensin-like immunoreactivity content in the lateral (LAC) (A) and medial (MAC) (B) anterior caudate. Animals were treated as described for Fig. 3. Neurotensin-like immunoreactivity was analyzed by radioimmunoassay in dissected tissues. Data (means ± S.E.M. of 6 animals) are expressed as a percentage of the mean of vehicle-treated controls. Control values were 68 pg/mg protein in the medial anterior caudate and 97 pg/mg protein in the lateral anterior caudate. * $P < 0.05$ versus corresponding vehicle-treated controls.

3.2. Effects of haloperidol on neurotensin-like immunoreactivity tissue content in the nucleus accumbens and caudate nucleus

Tissue neurotensin-like immunoreactivity content in the caudate and nucleus accumbens was also examined in order to compare with the release of neurotensin in these regions. The nucleus accumbens was dissected into core and shell regions.

In the present study, increased neurotensin-like immunoreactivity tissue levels in the core region of nucleus accumbens was observed 24 h after a single haloperidol injection, but the neurotensin-like immunoreactivity

content did not change significantly in the shell part of the nucleus accumbens during the same time period (Fig. 3).

Haloperidol treatment also increased the tissue levels of neurotensin-like immunoreactivity in all regions of caudate nucleus adjacent to where the probes were placed in microdialysis experiments. In general, these effects occurred early and were more pronounced than those observed in the nucleus accumbens with increases evident by 1 or 3 h after treatment (Figs. 4 and 5).

3.3. Effects of haloperidol on neurotensin-like immunoreactivity tissue content in the substantia nigra and ventral tegmental area

The nucleus accumbens and caudate nucleus receive dopaminergic projects from ventral tegmental area and substantia nigra, respectively. Therefore, we also examined the effect of haloperidol on neurotensin-like immunoreactivity levels in these dopaminergic cell body regions for comparison with their terminal fields. Haloperidol administration significantly decreased the neurotensin-like immunoreactivity content in the ventral tegmental area 3 h after the treatment. The effect of haloperidol was time-dependent and the neurotensin-like immunoreactivity level

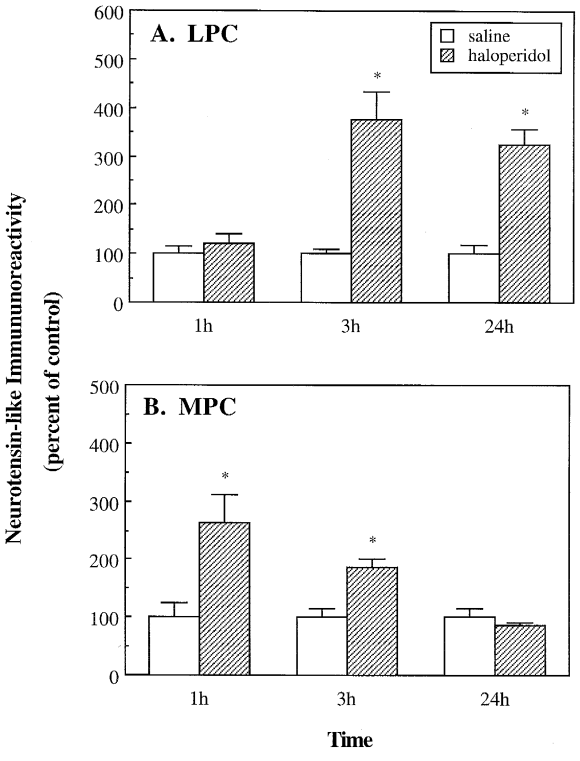

Fig. 5. Tissue neurotensin-like immunoreactivity content in the lateral (LPC) (A) and medial (MPC) (B) posterior caudate. Animals were treated as described for Fig. 3. Neurotensin-like immunoreactivity was analyzed by radioimmunoassay in dissected tissues. Data (means ± S.E.M. of 6 animals) are expressed as a percentage of the mean of vehicle-treated controls. Control values were 61 pg/mg protein in the medial posterior caudate and 39 pg/mg protein in the lateral posterior caudate. * $P < 0.05$ versus corresponding vehicle-treated controls.

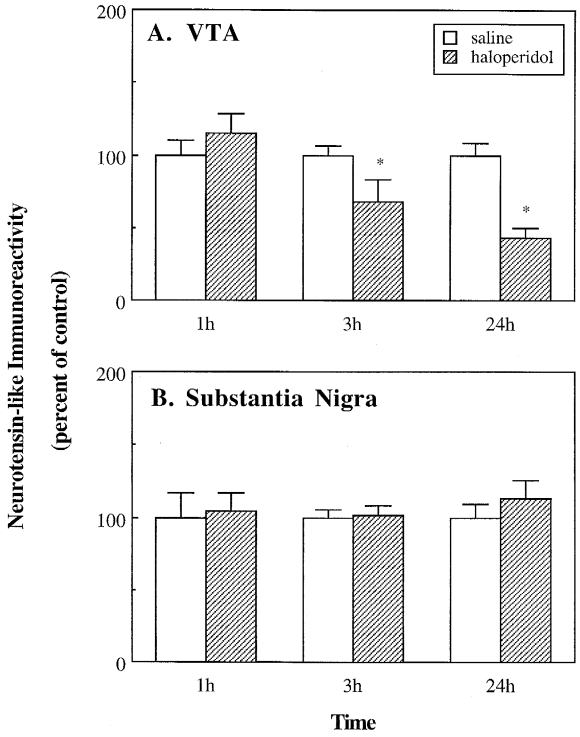

Fig. 6. Tissue neurotensin-like immunoreactivity content in the ventral tegmental area (A) and substantia nigra (B). Animals were treated as described for Fig. 3. Neurotensin-like immunoreactivity was analyzed by radioimmunoassay in dissected tissues. Data (means ± S.E.M. of 6 animals) are expressed as a percentage of the mean of vehicle-treated controls. Control values were 1286 pg/mg protein in the ventral tegmental area and 196 pg/mg protein in the substantia nigra. * $P < 0.05$ versus corresponding vehicle-treated controls.

was lowest at the 24 h time point (Fig. 6A). In contrast, neurotensin-like immunoreactivity concentration in the substantia nigra was not significantly different from respective controls at any of the time points examined (Fig. 6B).

4. Discussion

Many studies have been conducted to elucidate the effects of antipsychotics, such as haloperidol, on the interaction of central dopamine and neurotensin systems. It has been shown that both acute and chronic administration of haloperidol increases the concentration of immunoreactive neurotensin in the whole caudate and nucleus accumbens (Govoni et al., 1980; Frey et al., 1986; Merchant et al., 1989). In addition, it has also been reported that multiple doses of haloperidol differentially influences neurotensin systems in discrete regions of the caudate nucleus and nucleus accumbens (Gygi et al., 1994).

The mechanisms underlying these haloperidol-induced region-specific changes in neurotensin tissue content are still not well understood, although haloperidol-induced expression of mRNA for the precursor of neurotensin has

been reported. Increased expression of neurotensin/neuromedin mRNA in the dorsolateral caudate as well as the shell of the nucleus accumbens occurs after treatment with haloperidol (Merchant et al., 1991, 1992). Changes in tissue levels of neuropeptides may reflect alterations in release, synthesis and/or metabolism. While the dose of haloperidol we used (1 mg/kg) is unlikely to alter neurotensin metabolism (Konkoy et al., 1994), the effect of this haloperidol treatment on the release of neurotensin needs to be studied to understand completely the response of neurotensin systems to this drug and possibly other antipsychotics. It has been speculated that changes in the neurotensin tissue level can inversely correspond to release of this neuropeptide. Therefore, we employed microdialysis to determine the release of neurotensin and compare effects with changes in neurotensin tissue content.

Our results revealed that a single administration of haloperidol decreased the release of neurotensin in the caudate and elevated tissue neurotensin content in the surrounding regions by 1–3 h after drug treatment. Combined with previous observations, our finding suggests that acute haloperidol administration blocks caudate neurotensin release (Fig. 2), resulting in a compensatory synthesis of the peptide (Merchant et al., 1991, 1992) and a relatively rapid elevated tissue level (Figs. 4 and 5).

In contrast, haloperidol had the opposite effect on neurotensin release in nucleus accumbens, i.e., it increased the extracellular neurotensin level. This effect was surprising due to previous reports that neurotensin tissue content and mRNA level increase after haloperidol treatment in this limbic structure. Nevertheless, the response of nucleus accumbens to haloperidol was different from that of caudate regions. Specifically, in caudate regions, the changes in tissue neurotensin content occurred early (by 1 or 3 h) and were more prominent; in contrast, in the nucleus accumbens, we observed either no (in the shell) or a delayed (in the core) change. The differences in the effect of haloperidol on neurotensin tissue levels in the nucleus accumbens and caudate regions may relate to the opposite effect of haloperidol on neurotensin release found in these two brain regions (Fig. 2).

In addition, we observed that neurotensin tissue content in ventral tegmental area, source of dopamine to the accumbens (Kitabgi, 1989), was decreased (Fig. 6A), but unchanged in substantia nigra (Fig. 6B), source of dopamine to caudate (Kitabgi, 1989). This further supports our hypothesis that the caudate and accumbens-related regions are differentially affected by haloperidol treatment resulting in distinct neurotensin responses.

One possible explanation for the unique effects of haloperidol on neurotensin release might be due to different populations of haloperidol-responsive receptors in these brain regions. For example, the nucleus accumbens and the caudate nucleus have a different anatomical distribution for dopamine D_3 and D_2 receptor subtypes. Dopamine D_3 receptors are abundant in the nucleus accumbens, whereas dopamine D_2 receptors are located in the nucleus accumbens as well as the caudate nucleus (Griffon et al., 1995b; Sokoloff et al., 1995). A haloperidol-induced decrease in the caudate release of neurotensin is likely due to its action on dopamine D_2 receptors in the caudate nucleus (Wagstaff et al., 1996), whereas an increased release of neurotensin in the nucleus accumbens might be the result of its dopamine D_3 receptor blockade since dopamine D_3 and D_2 receptors are believed to mediate different and sometimes opposite clinical effects (Griffon et al., 1995a; Levesque et al., 1995). This hypothesis is further supported by the observation of neurotensin mRNA changes induced by antipsychotic drug treatment. Blockade of dopamine D_2/D_3 receptors by antipsychotic agents paradoxically decrease neurotensin gene expression in those neurons located in the nucleus accumbens, where dopamine D_3 receptors are mainly present; whereas treatment by these drugs enhances such expression in caudate areas expressing only the dopamine D_2 receptor (Levesque et al., 1995).

An argument against a differential role of dopamine D_2 and D_3 receptors on neurotensin release in the accumbens and caudate is our previous observation that eticlopride, a drug with haloperidol-like affinity for dopamine D_2 versus dopamine D_3 receptor affinity, caused decreased neurotensin release in both caudate nucleus and nucleus accumbens (Wagstaff et al., 1996). The eticlopride observation suggests that the opposite response of the caudate and accumbens neurotensin systems to haloperidol treatment is not entirely a dopamine receptor phenomenon, but may be due to effects of haloperidol on other receptor types. For example, haloperidol has a documented high affinity for sigma receptors (Bowen et al., 1990). The finding by Levant and Nemeroff (1990) that the sigma receptor antagonist BMY 14802 increases neurotensin concentration in the rat nucleus accumbens and caudate suggests that sigma receptors can also modulate neurotensin concentrations in these brain regions. Therefore, this receptor may contribute to the effects by haloperidol. However, it should be noted that BMY 14802 is not a pure sigma antagonist, but also has affinity for dopamine D_2 receptors (Lang et al., 1994); consequently, the effect of this drug on neurotensin system may in part be attributed to its dopamine D_2 receptor blockade.

The interaction between the dopamine and neurotensin system is very complex. Our study clearly demonstrates that the caudate and accumbens neurotensin systems responded differently to haloperidol treatment. Thus, the release of neurotensin increased in limbic regions, whereas it decreased in the extrapyramidal or motor-linked regions after a single haloperidol administration. The differential response patterns of neurotensin systems to haloperidol might contribute to its antipsychotic action and side effect profile. Possibly relevant is the report of Widerlov et al. (1982) that a decrease in cerebrospinal fluid neurotensin level occurs in some untreated schizophrenia patients, but returns to normal after haloperidol treatment. The antipsy-

chotic effects of dopamine antagonists are generally believed to be associated with mesolimbic dopamine neurons, whereas the Parkinsonian side effects are related to the nigrostriatal dopamine neurons (Onn and Grace, 1995; Levesque et al., 1995). Perhaps antipsychotic effects of haloperidol relate to its ability to increase neurotensin release in the limbic region, whereas the extrapyramidal side effects of haloperidol result from decreased release of neurotensin in extrapyramidal or motor-linked regions. This hypothesis requires additional study. Consequently, the response of neurotensin to haloperidol might provide insight to the mechanism of therapeutic and side effect actions of antipsychotic drugs.

Acknowledgements

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