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Effects of neurotensin and bombesin on the secretory and proliferative activity of regenerating rat adrenal cortex

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Summary. Neurotensin (NT) and bombesin (BM)-like peptides are known to be involved in the regulation of the rat hypothalamo-pituitary-adrenal axis. By using selective NT- and BM-receptor antagonists (NT-A and BM-A, respectively) we investigated whether endogenous NT and BM-like peptides play a role in the control of rat adrenal secretion and growth during enucleation-induced regeneration. At day 5 of regeneration, NT-A did not affect the plasma concentrations of aldosterone (PAC) and corticosterone (PBC), but at day 8, it raised both PAC and PBC over the respective baseline value; the simultaneous administration of NT abolished this effect of NT-A. BM-A did not alter PAC and PBC at day 5 of regeneration, while at day 8 it enhanced PBC, an effect reversed by BM. NT-A did not alter mitotic index, and BM-A lowered it at both day 5 and day 8 of regeneration, an effect suppressed by the simultaneous administration of BM. Collectively, these findings allow us to draw the following conclusions: 1) endogenous NT and BM-like peptides influence adrenocortical regeneration in rats; 2) NT exerts a tonic inhibitory action on both aldosterone and corticosterone secretion, without affecting cell-proliferation rate; and 3) BM-like peptides exert a tonic suppressive effect on corticosterone production, coupled with a clear-cut stimulating effect on cell proliferation.

Key words: Neurotensin, Bombesin-like peptides, Steroid-hormone secretion, Adrenocortical-cell proliferation, Adrenal regeneration, Rat

Introduction

Neurotensin (NT) is a 13-amino-acid residue peptide, which plays an important role as neurotransmitter or neuromodulator in the brain and as hormone at the periphery (for review, see Vincent, 1995). NT is involved in the regulation of mammalian neuroendocrine systems, among which the hypothalamo-pituitary-adrenal (HPA) axis (for review, see Malendowicz, 1993; Malendowicz and Markowska, 1994; Nussdorfer, 1996; Rostene and Alexander, 1997). NT stimulates pituitary ACTH secretion, an effect probably mediated by the enhanced release of both CRH and vasopressin (Malendowicz et al., 1991c,d, 1995b; Nussdorfer et al., 1992; Mazzocchi et al., 1993; Malendowicz and Nussdorfer, 1994). NT and neuromedin (NM) N affect aldosterone and corticosterone secretion in rats, their steroidogenic action depending on the dose, time and pharmacological pretreatment of animals (Malendowicz et al., 1991b,c,d, 1992b, 1993, 1996c; Mazzocchi et al., 1991; Lesniewska et al., 1992; Nussdorfer et al., 1992). Moreover, NT and NMN exert a marked proliferogenic action on rat adrenocortical cells, and prevent dexamethasone-induced adrenocortical atrophy (Malendowicz et al., 1991b, 1992a, 1993, 1996c; Lesniewska et al., 1992; Markowska et al., 1992, 1994a,b).

Bombesin (BM) is a 14-amino-acid residue peptide, originally isolated from the skin of the frog *Bombina bombina*, the mammalian counterpart of which is gastrin-releasing peptide (GRP), a brain-gut peptide containg 27-amino acid residues. In mammals, two BM-like NMs have been identified: NMB, a 10-amino acid peptide, and NMC, the C-terminal decapeptide of GRP. All these peptides share structural homologies and exert similar biological effects (for review, see Greeley et al., 1986; Wada et al., 1990). Compelling evidence indicates that BM and BM-like peptides are involved in the regulation of the HPA axis (for review, see Malendowicz, 1993, 1998; Malendowicz and Markowska, 1994; Nussdorfer, 1996). BM-like peptides acutely enhance pituitary ACTH secretion and potentiate CRH effect (Hale et al., 1984; Thomas and Sander, 1985; Familiari et al., 1987; Sander and Porter, 1988; Olsen et al., 1992; Malendowicz et al., 1994, 1995a,c; Malendowicz and Nussdorfer, 1995; Kent et al., 1997),

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as well as stimulate glucocorticoid secretion (Gunion et al., 1989; Sander and Thomas, 1991; Malendowicz and Nussdorfer, 1995; Malendowicz et al., 1995a). Conversely, the prolonged administration of BM-like peptides does not significantly affect ACTH blood level, and evokes only moderate rises in corticosterone secretion (Malendowicz et al., 1991a, 1994, 1995a,c, 1996a,b). The effect of BM-like peptides on aldosterone secretion appear to have only a pharmacological relevance (Malendowicz et al., 1996a,b). Like NT, BM-like peptides exert a strong stimulating action on the growth of rat adrenocortical cells (Malendowicz et al., 1991a, 1995c, 1996a,b; Markowska et al., 1993), a finding in keeping with the contention that they can function as autocrine growth factors in several neoplastic tissues (Cuttitta et al., 1985; Dietrich, 1994).

All the above, surveyed *in vivo* findings were obtained by administering exogenous NT or BM-like peptides, thereby not ruling out the possibility that their effects are pharmacological in nature. At present, the availability of potent and specific NT- and BM-receptor antagonists makes it possible to investigate the physiological effects of endogenous NT and BM. Due to the proliferogenic action exerted by both peptides on the adrenal gland, we decided to study their effects on the secretory function and proliferation of regenerating rat adrenal cortices.

Materials and methods

Animals and reagents

Adult female Wistar rats (150±10 g body weight) were kept under a 12:12 h light-dark cycle (illumination onset at 8:00 a.m.) at 22±2 °C, and maintained on a standard diet and tap water *ad libitum*. NT, the NT-receptor antagonist (NT-A) [D-Trp^{11}]-NT (Quirion et al., 1980) and all the laboratory reagents were purchased from Sigma Chemical Co. (St. Louis, MO, USA). BM and the BM-receptor antagonist (BM-A) [Tyr^4, D-Phe^{12}]-BM (Heinz-Erian et al., 1987) were obtained from Bachem (Bubendorf, Switzerland), and vincristin from Gedeon-Richter (Budapest, Hungary).

Experimental procedures

Under ether anaesthesia, the left adrenal gland was enucleated and the contralateral gland removed. Operated rats were given 0.9% NaCl to drink, and were killed 5 or 8 days after surgery. Groups of rats (n=6) were given three subcutaneous injections (28, 16 and 4 h before decapitation) of 30 nmol/kg NT or BM, NT-A or BM-A, and NT plus NT-A or BM plus BM-A, dissolved in 0.2 ml 0.9% NaCl. Control rats were injected with the vehicle only. All groups of animals received an intraperitoneal injection of vincristin (0.1 mg/100 g) 2 h before autopsy. Rats were decapitated at 11:00 a.m.

Cell proliferation assay

Regenerating adrenals were promply removed, fixed in Bouin's solution for 24 h, embedded in paraffin, and sectioned at 5-6 μm. Sections were stained with hematoxylin-eosin, and the mitotic index (i.e., ‰ of metaphase arrested cells) was calculated at x400, by counting 5,000 cells in each regenerating adrenal.

Hormone assay

Trunk blood was collected in the presence of EDTA (1 mg/ml), and plasma was separated. Aldosterone and corticosterone were extracted and purified (Neri et al., 1993), and their concentrations measured by RIA, as previously detailed (Malendowicz et al., 1993). RIA sensitivity was: aldosterone, 5 pg/ml; corticosterone, 50 pg/ml. Intra- and interassay coefficients of variations were: aldosterone, 5% and 7%; corticosterone, 7% and 9%, respectively.

Statistical analysis

Individual results were averaged per experimental group, and SEM was calculated. The statistical comparison of the data was done by ANOVA, followed by the Multiple Range Test of Duncan.

Results

Corticosteroid hormone secretion

As expected, the overall secretion of steroid was higher at day 8 than day 5 of regeneration, due to the increased mass of adrenal parenchyma, while mitotic index did not display significant differences (Figs. 1-4).

At day 5 of adrenocortical regeneration, neither NT nor NT-A affected plasma concentrations of aldosterone (PAC) and corticosterone (PBC). Conversely, at day 8, NT evoked a sizeable decrease in PAC, but not PBC; NT-A raised both PAC and PBC over the respective baseline value, and NT reversed this effect of NT-A (Fig. 1).

At day 5 of regeneration, BM did not affect PAC, but induced a moderate lowering in PBC. BM-A alone did not alter basal values, but evoked a conspicuous rise of both PAC and PBC when co-administered with BM. At day 8, BM enhanced both PAC and PBC, and BM-A alone raised PBC, but not PAC; the simultaneous administration of BM and BM-A did not apparently cause any change in the hormonal values with respect to the baseline (Fig. 2).

Cell proliferation

NT decreased the mitotic index at day 5, but not at day 8 of regeneration, and NT-A reversed this effect of NT, without *per se* changing basal mitotic index (Fig. 3). In contrast, BM did not affect mitotic index at either day

5 or 8 day of regeneration, while BM-A alone markedly decreased it. BM suppressed this effect of BM-A (Fig. 4).

Discussion

It is current knowledge that *in vivo* adrenocortical growth may be distinguished in the following types: 1) maturational growth; 2) ACTH-induced growth; 3) monoadrenalectomy-induced compensatory growth; and 4) growth connected with enucleation-induced regeneration. This last type resembles the maturational growth, and is characterized, especially at its earlier stages, by a low production of aldosterone and corticosterone and a relatively high secretion of 11-deoxycorticosterone (due to the low expression of 11ß/18-hydroxylase enzyme system in proliferating cells) (for review, see Dallman, 1984, 1985; Nussdorfer, 1986). This fact, along with the suppressive effect on aldosterone secretion of 0.9% NaCl (which was given to operated to drink rats for 5 days after surgery) may well explain why results concerning the effect on neuropeptides on hormonal secretion obtained at day 5 of adrenal regeneration are rather confusing and difficult to interpret unequivocally.

Collectively, our findings, obtained at day 8 of regeneration, suggest that endogenous NT and BM exert a tonic inhibitory action on steroid hormone secretion, the effect of NT being addressed on both aldosterone and corticosterone and that of BM only on corticosterone. This contention is based on the evidence that 1) NT-A and BM-A increased PAC/PBC and PBC, respectively, over their baseline values, and 2) NT and BM reversed the effect of their respective receptor antagonist. At

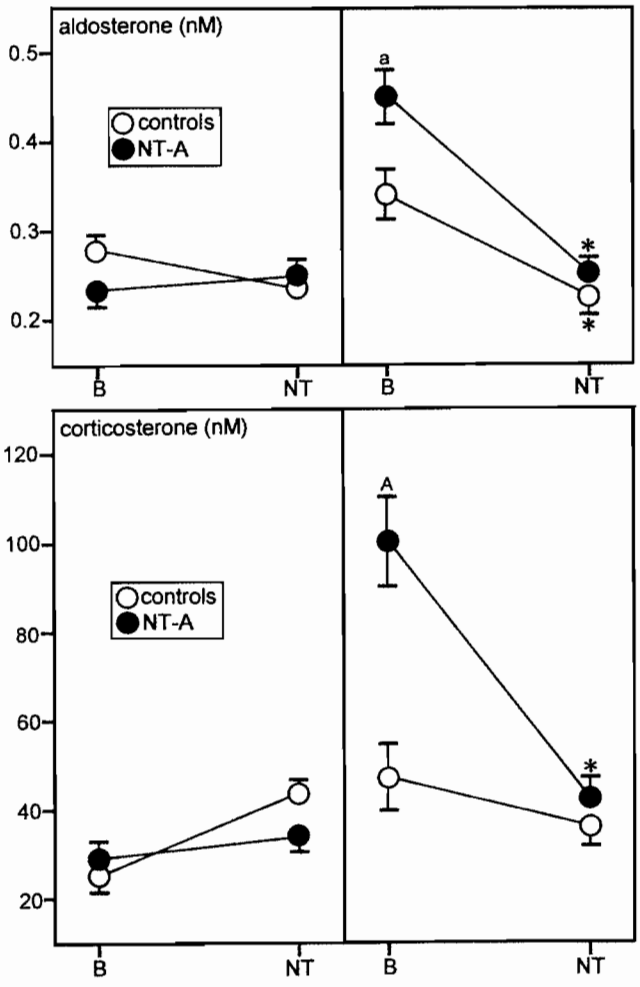

Fig. 1. Effects of NT and NT-A on PAC (upper panels) and PBC (lower panels) in rats at day 5 (left panels) and day 8 (right panels) of adrenal regeneration. Data are means±SEM (n=6). *: P<0.01 from the respective basal value (B); [a]: P<0.05 and [A]: P<0.01 from the respective control value.

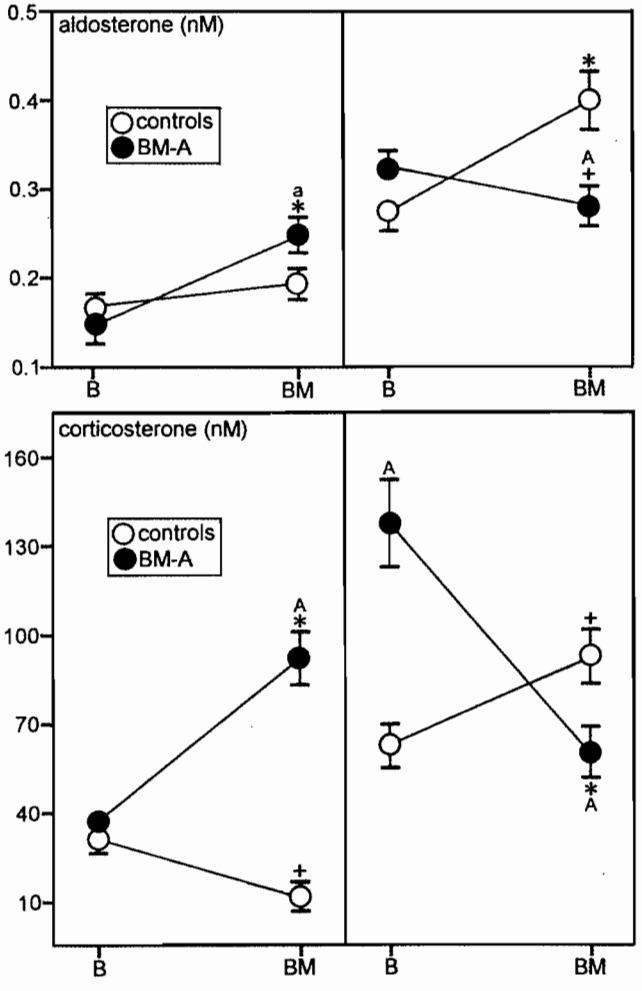

Fig. 2. Effects of BM and BM-A on PAC (upper panels) and PBC (lower panels) in rats at day 5 (left panels) and day 8 (right panels) of adrenal regeneration. Data are means±SEM (n=6). +: P<0.05 and *: P<0.01 from the respective basal value (B); [a]: P<0.05 and [A]: p<0.01 from the respective control value.

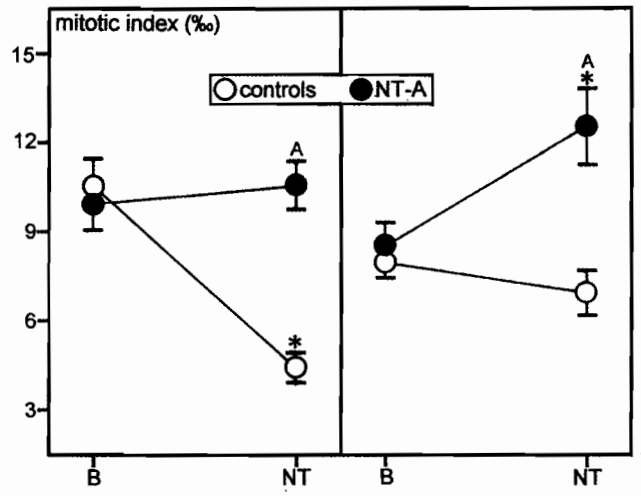

Fig. 3. Effects of NT and NT-A on adrenocortical cell proliferation in rats at day 5 (left panel) and day 8 (right panel) of adrenal regeneration. Data are means±SEM (n=6). *: P<0.01 from the respective basal value; A: P<0.01 from the respective control value.

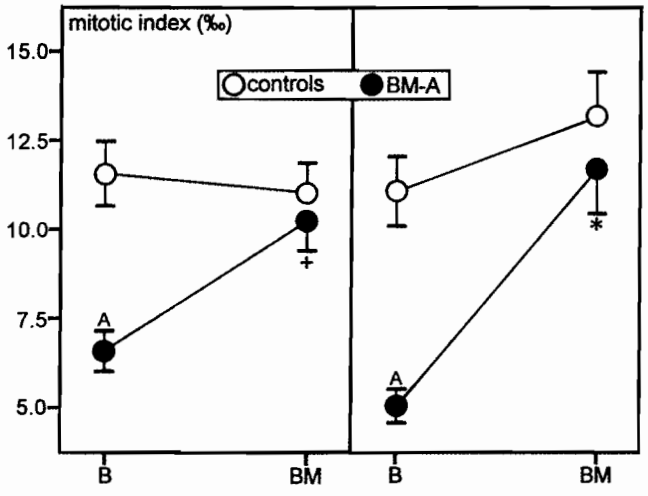

Fig. 4. Effects of BM and BM-A on adrenocortical cell proliferation in rats at day 5 (left panel) and day 8 (right panel) of adrenal regeneration. Data are means±SEM (n=6). +: P<0.05 and *: P<0.01 from the respective basal value; A: P<0.01 from the respective control value.

present, we cannot explain the moderate increase in the hormonal blood levels elicited by the administration of BM alone.

Consistent results were obtained at day 5 and 8 of regeneration as far as the effects of the two neuropeptides on cell proliferation are concerned. NT-A does not affect the mitotic index, while BM-A strikingly lowers it, this effect being annulled by the simultaneous administration of BM. Conversely, NT alone decreases mitotic index at day 5 and when administered together NT-A increases it at day 8. Taken together these observations suggest that 1) endogenous NT does not affect proliferative activity in regenerating adrenals, the action of exogenous NT being conceivably pharmacological in nature and restricted to the early stages of regeneration (Zieleniewski and Zieleniewski, 1995); and 2) endogenous BM exerts a potent tonic stimulatory action on adrenal regeneration, a finding in agreement with the reported growth-factor activity of this peptide (see Introduction).

A large body of investigations stress the functional relevance of the paracrine interactions between cortex and medulla in adrenal glands (for review, see Nussdorfer, 1996; Ehrhart-Bornstein et al., 1998; Mazzocchi et al., 1998). NT and BM-like peptides are contained in adrenal medulla (Nussdorfer, 1996), and it has been recently demonstrated that NT is able to stimulate CRH and ACTH release by rat adrenal chromaffin cells *in vitro* (Mazzocchi et al., 1997). However, a paracrine mechanism of action of endogenous NT and BM-like peptides can be excluded, because at day 5 and 8 of regeneration rat adrenal cortex is deprived of medullary chromaffin cells (Taki and Nickerson, 1985). Since the levels of circulating NT and BM-like peptides are not compatible with their effects on adrenal glands, it seems legitimate to suggest that endogenous peptides originate from preganglionic nerve fibers penetrating the adrenal capsule. In keeping with this possibility, the presence of NT-ergic fibers has been reported in the mammalian adrenal glands (Heym, 1997a,b; Holgert et al., 1998).

In conclusion, our study shows that 1) endogenous NT exerts a tonic inhibitory influence on both mineralocorticoid and glucocorticoid secretion of regenerating rat adrenal cortex, without affecting cell-proliferation rate; and 2) endogenous BM-like peptides exert a tonic stimulating action on regenerating rat adrenal growth, coupled with a suppressive effect on glucocorticoid secretion. Our investigation also emphasizes that adrenal regeneration after enucleation is a very complex process, which is not only controlled by the pituitary ACTH release, but is also modulated by other mechanisms probably involving adrenal innervation by peptidergic fibers.

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