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SEXUAL DIFFERENTIATION OF CENTRAL VASOPRESSIN AND VASOTOCIN SYSTEMS IN VERTEBRATES: DIFFERENT MECHANISMS, SIMILAR ENDPOINTS

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Abstract—Vasopressin neurons in the bed nucleus of the stria terminalis and amygdala and vasotocin neurons in homologous areas in non-mammalian vertebrates show some of the most consistently found neural sex differences, with males having more cells and denser projections than females. These projections have been implicated in social and reproductive behaviors but also in autonomic functions. The sex differences in these projections may cause as well as prevent sex differences in these functions. This paper discusses the anatomy, steroid dependency, and sexual differentiation of these neurons. Although the final steps in sexual differentiation of vasopressin/vasotocin expression may be similar across vertebrate species, what triggers differentiation may vary dramatically. For example, during development, estrogen masculinizes vasopressin expression in rats but feminizes its counterpart in Japanese quail. Apparently, nature consistently finds a way of maintaining sex differences in vasopressin and vasotocin pathways, suggesting that the function of these differences is important enough that it was conserved during evolution. © 2005 Published by Elsevier Ltd on behalf of IBRO.

Key words: sex differences, testosterone, estrogen, bed nucleus of the stria terminalis, amygdala, lateral septum.

Sex differences in vasopressin (AVP) projections of the bed nucleus of the stria terminalis (BST) and medial amygdaloid nucleus (MeA) were first described in rats and were discovered by chance while we were studying what we thought were developing AVP projections of the suprachiasmatic nucleus (SCN) (De Vries et al., 1981). AVP cell bodies in the BST and MeA had yet to be discovered (Van Leeuwen and Caffé, 1983). A study of the development of vasopressin-immunoreactive (AVP-ir) fibers in the lateral septum and habenular nucleus revealed a disturbingly large variability, prompting us to run a second series, separating animals by sex. This revealed a large sex difference with males having a much denser AVP-ir fiber network in the lateral septum and lateral habenular nucleus than females (Fig. 1A). Later we showed that AVP expression in these areas critically depended on circulating gonadal steroids (De Vries et al., 1984), and that AVP-ir cells in the BST and MA showed corresponding sex differences and steroid responsiveness (DeVries et al., 1985; Van Leeuwen et al., 1985). Since these first findings, homologous sex differences have been found in many different species, in mammals as well as other vertebrates (Table 1).

Sources of sexually dimorphic AVP and vasotocin innervation

In rats, the BST and MeA provide a major part of AVP innervation in the forebrain. These two areas belong to the extended amygdala, a cohort of nuclei in the BST and centromedial amygdala with striking similarities in cytoarchitecture and neurochemistry (de Olmos and Heimer, 1999). The sexual dimorphism and steroid responsiveness of AVP neurons in BST as well as MeA underscore these similarities. In vertebrates with less extensive encephalization than mammals, the areas homologous to the BST and amygdala are not physically separated by the internal capsule (Johnston, 1923). In such animals, the sexually dimorphic vasotocin-immunoreactive (AVT-ir) cells typically form a single, undivided cluster (e.g. Boyd et al., 1992; Marler et al., 1999).

Given the wide acceptance of our proposal that the BST and MeA are the sources of sexually dimorphic AVP-ir and, by extension, AVT-ir innervation of the brain, it is important to point out that this idea is based on a rather limited set of experiments (De Vries and Buijs, 1983). To locate the source of the sexually dimorphic AVP-ir innervation of the lateral septum, we used knife cuts ventral to the septum, which showed that AVP-ir fibers enter the septum ventrorostrally. We retrogradely traced connections to the lateral septum (regardless of neuropeptide expression), which favored the BST as a source over other likely candidates, i.e. the SCN and paraventricular nucleus (PVN). Finally, because lesions of the SCN had already disqualified the SCN as a likely source of septal AVP-ir innervation (Hoorneman and Buijs, 1982), we lesioned the PVN bilaterally, which spared septal AVP-ir innervation, and the BST unilaterally, which decimated septal AVP-ir innervation ipsilaterally (bilateral lesions caused high mortality). The conclusion that the BST is an important source of septal AVP-ir fibers therefore rests on solid evidence (De Vries and Buijs, 1983). Evidence for other projections

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Abbreviations: AVP, vasopressin; AVP-ir, vasopressin-immunoreactive; AVT, vasotocin; AVT-ir, vasotocin-immunoreactive; BST, bed nucleus of the stria terminalis; MeA, medial nucleus of the amygdala; POM, medial preoptic nucleus; PVN, paraventricular nucleus of the hypothalamus; SCN, suprachiasmatic nucleus.

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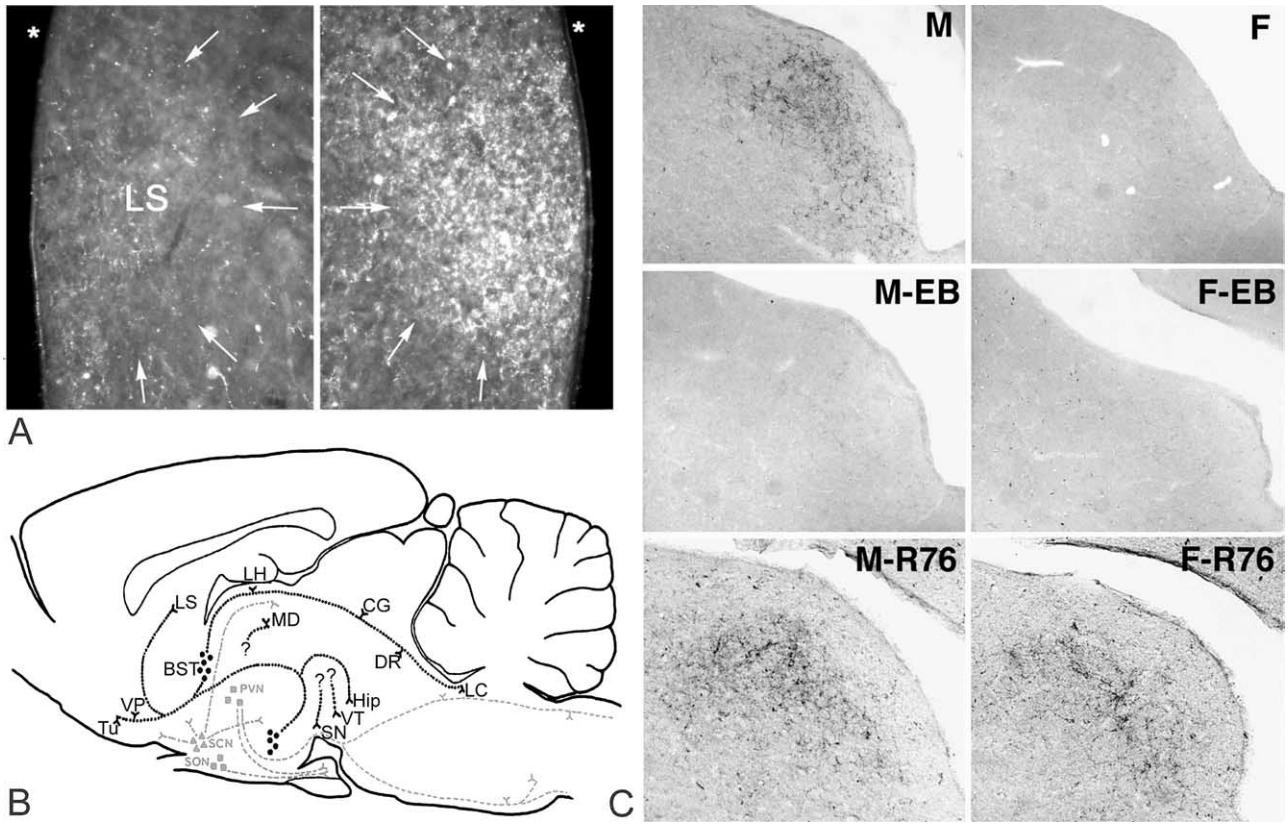

Fig. 1. Sexually dimorphic AVP and vasotocin (AVT) projections in rat and quail brains. (A) Dark-field microphotographs of AVP-ir fiber networks (arrows) in the lateral septum (LS) of a female (left) and male rat (right); * lateral ventricle. (B) Diagram of most prominent AVP-ir projections in rats, modified from De Vries et al. (1985). Steroid-sensitive projections (black lines) run from BST (circles) and MeA (MA, circles) to LS, ventral pallidum (VP), olfactory tubercle (Tu), lateral habenular nucleus (LH), midbrain central gray (CG), dorsal raphe nucleus (DR), locus coeruleus (LC), and ventral hippocampus (Hip). Question marks indicate projections to Hip, mediodorsal nucleus of the thalamus (MD), ventral tegmental area (VT), substantia nigra (SN), which disappeared after castration but not after lesioning the BST. Steroid-insensitive projections (gray lines) originate in SCN (triangles), PVN (squares), and supraoptic nucleus (SON, squares). (C) Bright-field photomicrographs of AVT-ir fiber networks in the lateral septum of male (M) and female Japanese quail (F), treated during development with oil (top panels), estradiol benzoate (EB; middle panels), or the aromatase inhibitor R76 (R76; bottom panels), gonadectomized three weeks post-hatching, and treated with testosterone for another two weeks. Note that AVT fibers are absent in the oil-treated female and EB-treated male and female quail.

from the BST and MeA is less firm. When we found that castration deleted AVP-ir cell bodies in the BST and MeA but not in other areas, and AVP-ir fibers in all areas where unilateral lesions of the BST had eliminated AVP-ir fibers, we proposed that the BST and MeA projects to all areas where castration eliminated AVP immunoreactivity and not to areas where AVP immunoreactivity remained (Fig. 1B; DeVries et al., 1985). Later Caffé et al. (1987) combined retrograde tracing with AVP immunocytochemistry to confirm that the BST projects to the lateral septum and show that the MeA projects to the ventral hippocampus as well as lateral septum. Differences in the effects of BST and MeA lesions on septal AVP innervation, however, suggest that the BST provides the lion's share of the septal AVP-ir innervation (Al Shamma and De Vries, unpublished observations). None of the other BST and MeA projections have been independently confirmed. Even less certainty exists about homologous projections in other vertebrates. The only other tracing study was done in Japanese quail, which demonstrated that AVT-ir neurons in the BST project to the medial preoptic nucleus (POM; Absil et al., 2002). However, given the often striking similarity in distribution, sexual dimorphism, and steroid sensitivity of AVP and AVT systems across vertebrates, it is unlikely that the anatomy of these systems differs fundamentally among species.

There are some intriguing species differences, however. For example, Moore et al. (2000) find similar sex differences in roughskin newts as are found in rats. However, they also find more AVT-expressing cell groups than have been found in any other species. Some of these cell groups exhibit differences favoring males, others females. Any number of these cell groups could contribute to sexually dimorphic AVT-ir innervation. One could even imagine that some of these cell groups cancel out differences in fiber density if cell groups with opposite differences project to overlapping areas. Like roughskin newts, Japanese quail show similar differences in the BST as do rats, but male quail also have more AVT-ir cell bodies in the POM than do females (Panzica et al., 2001). As the POM projects to the lateral septum (Balthazart et al., 1994), these cell bodies may contribute to differences in septal AVT-ir innerva-