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The spinal nucleus of the bulbocavernosus: Firsts in androgen-dependent neural sex differences

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Abstract

Cell number in the spinal nucleus of the bulbocavernosus (SNB) of rats was the first neural sex difference shown to differentiate under the control of androgens, acting via classical intracellular androgen receptors. SNB motoneurons reside in the lumbar spinal cord and innervate striated muscles involved in copulation, including the bulbocavernosus (BC) and levator ani (LA). SNB cells are much larger and more numerous in males than in females, and the BC/LA target muscles are reduced or absent in females. The relative simplicity of this neuromuscular system has allowed for considerable progress in pinpointing sites of hormone action, and identifying the cellular bases for androgenic effects. It is now clear that androgens act at virtually every level of the SNB system, in development and throughout adult life. In this review we focus on effects of androgens on developmental cell death of SNB motoneurons and BC/LA muscles; the establishment and maintenance of SNB motoneuron soma size and dendritic length; BC/LA muscle morphology and physiology; and behaviors controlled by the SNB system. We also describe new data on neurotherapeutic effects of androgens on SNB motoneurons after injury in adulthood.

Keywords: Motoneuron; Bulbocavernosus; Levator ani; Androgen; Neuromuscular; Dendrite; Sexual differentiation; Cell death; Testosterone; Dihydrotestosterone

Introduction

In 1980, Marc Breedlove and Art Arnold described a sexually dimorphic group of motoneurons in the lumbar spinal cord of rats (Breedlove and Arnold, 1980). As these motoneurons innervated the striated perineal muscles bulbocavernosus (BC) and levator ani (LA), they named the cell group the spinal nucleus of the bulbocavernosus (SNB). In that first report, SNB motoneurons were shown to be much more numerous in adult males than in females, and to accumulate radiolabeled testosterone or dihydrotestosterone, but not estradiol (Breedlove and Arnold, 1980). In rapid succession the authors demonstrated that the sex difference in cell number could be reversed by neonatal, but not adult treatment with gonadal steroids (Breedlove and Arnold, 1981; Breedlove et al., 1982), and that the SNB nucleus is completely female-like in genetically male rats bearing an inactivating mutation of the androgen receptor (Breedlove and Arnold, 1981). They concluded: "the sexually dimorphic nature of the SNB depends on neither the adult hormone state nor the presence of a Y chromosome, but on the interaction of androgens with their receptors early in development" (Breedlove and Arnold, 1981).

The SNB therefore became the first neural sex difference shown to be due to androgens, acting via classical, intracellular androgen receptors (AR). In the twenty-five-plus years since, the importance of androgens and AR in this system has been repeatedly confirmed, albeit with some interesting twists and turns. The AR so abundantly expressed by SNB cells during adulthood, for example, turn out to be something of a red herring for understanding the sex difference in SNB cell number. Androgens apparently do not act directly at SNB cells to control their number, as is discussed below, although they may act on AR expressed in the motoneurons to control motoneuron soma size.

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The last 25 years has also seen the mushrooming of the field of sexual differentiation of the nervous system in general, and it soon became clear that many sex differences in the brain were primarily dependent on estrogenic metabolites of testosterone (reviewed in Hutchinson, 1997). For some time, the SNB seemed to be unique in its androgen dependence, which led some writers to conclude that testosterone acts through androgenic metabolites and AR to masculinize the spinal cord and periphery, but through estrogen receptors to masculinize the brain. This has turned out to be an oversimplification. Although the SNB remains the premier example of an androgen-dependent neural sex difference, the articles in the current issue attest to the growing awareness of the roles of androgens and AR in other sex differences and neural systems.

At this point, however, more is probably known about the roles of androgens in sexual differentiation of the SNB system than for any other sex difference in the nervous system. The reasons for this are twofold: the androgen-dependence of the SNB has been known for such a long time, and students of the SNB enjoy the advantages offered by any neuromuscular system — very large size of neurons, accessibility of nerve terminals, easy identification of target cells, and relative simplicity of connections. As a result, substantial progress has been made in identifying effects of androgens on multiple processes both in development and in adulthood; in some cases, the cellular and molecular bases for androgenic effects have also been revealed. Here, we first review the evidence for the role of androgens and AR in the determination of SNB cell number and soma size. We next turn to hormone effects on the SNB target muscles, and to the behaviors controlled by this neuromuscular system. Finally, we consider the development and maintenance of SNB dendritic arbors, the study of which has uncovered a novel role for androgens, as well as an unexpected requirement for estrogens in the establishment of SNB motoneuron morphology and function.

Motoneuron death and the establishment of SNB cell number

In male rats, the SNB [also known as the dorsomedial nucleus or DM (Schrøder, 1980)] consists of approximately 200 motoneurons that innervate the perineal muscle complex consisting of the bulbocavernosus (BC) and levator ani (LA; collectively, BC/LA), as well as the external anal sphincter (Breedlove and Arnold, 1980; Schrøder, 1980; McKenna and Nadelhaft, 1986). The SNB in mature females, who lack or have greatly reduced perineal musculature (Hayes, 1965; Čihák et al., 1970; Tobin and Joubert, 1991), is comprised of only approximately 60 motoneurons, innervating primarily the external anal sphincter (McKenna and Nadelhaft, 1986; Ueyama et al., 1987).

This sex difference in SNB motoneuron number develops perinatally. Before birth, the number of motoneurons in the SNB increases in both male and female rats, the result of a migration of developing SNB cells into their characteristic medial location (Sengelaub and Arnold, 1986). SNB motoneuron numbers reach their maxima in both sexes just before birth, and this peak is followed by a decline through postnatal day (P)10, when cell number reaches its adult range (Fig. 1). The decline is due to sexually dimorphic cell death, as revealed by counts of degenerating cells in the SNB (Nordeen et al., 1985). Females typically lose up to 70% of their SNB motoneurons, whereas males lose about 25%.

Gonadal hormones act in the establishment of sex differences in SNB motoneuron number by regulating this normally-occurring motoneuron death. Females treated perinatally with testosterone propionate (TP) have reduced cell death during development and significantly more SNB motoneurons in adulthood than do normal females (Breedlove and Arnold, 1983b; Nordeen et al., 1985; Sengelaub and Arnold, 1986). Conversely, male rats with a mutation of the androgen receptor

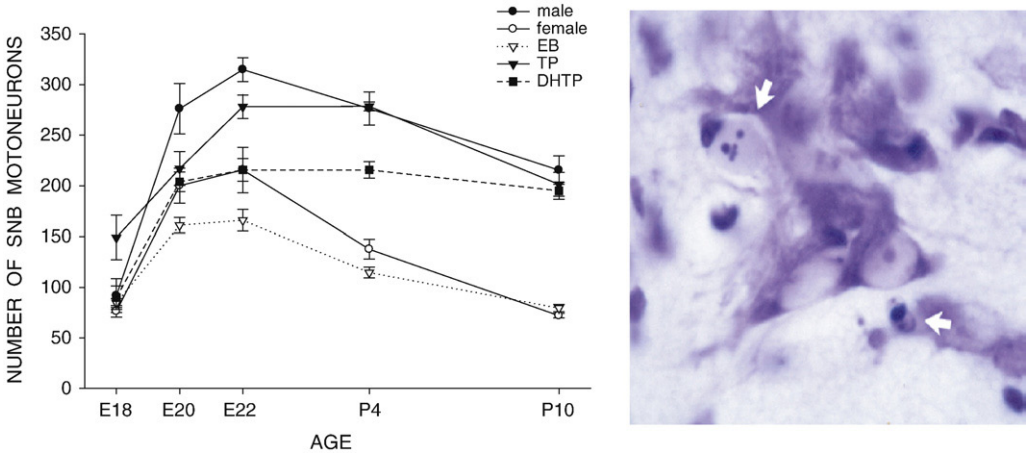

Fig. 1. Development of SNB motoneuron number is regulated through an androgen-mediated normally occurring cell death. (Left) Counts of motoneurons in the SNB from embryonic day (E)18 through postnatal day (P)10 for normal males and females, as well as females treated both pre- and postnatally with either estradiol benzoate- (EB), testosterone propionate- (TP), and dihydrotestosterone propionate- (DHTP). Females treated with TP or DHTP have a masculine number of SNB cells on P10, whereas females treated with EB do not differ from controls. Points represent means±S.E.M. (Right) Photomicrograph of a transverse, cresylecht violet-stained section through the SNB at P2 showing both normal motoneurons and degenerating cells (arrows). (*Compiled from data originally published in Nordeen et al., 1985; Goldstein and Sengelaub, 1990, 1992.*)