Castration and Male Peripheral Neurons

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This entry deals with the influence of androgens (testosterone) on pelvic autonomic pathways in male mammals. The vast majority of the relevant information has been gained in experiments involving castration (testosterone deprivation) performed in male rats, and recently, in male pigs. In both species, testosterone significantly affects the biology of the pathway components, including the pelvic neurons. However, there are great differences between rats and pigs in this respect. The most significant alteration is that testosterone deprivation accomplished a few days after birth results some months later in the excessive loss (approximately 90%) of pelvic and urinary bladder trigone intramural neurons in the male pig, while no changes in the number of pelvic neurons are observed in male rats (rats do not have the intramural ganglia). In the castrated pigs, much greater numbers of pelvic neurons than in the non-castrated animals express CGRP, GAL, VIP (peptides known to have neuroprotective properties), and caspase 3, suggesting that neurons die due to apoptosis triggered by androgen deprivation. In contrast, only some morpho-electrophysiological changes affecting neurons following castration are found in male rats. Certain clinicopathological consequences of testosterone deprivation for the functioning of urogenital organs are also discussed.

Keywords: male genitourinary system ; autonomic innervation ; testosterone deprivation ; androgen receptor ; castration ; apoptosis

1. Introduction

Gonadal steroids exert powerful effects on the growth and maintenance of many neurons, and their substantial role in establishing sexually dimorphic neuronal circuits in the mammalian central nervous system has been widely studied and now is quite well understood [1][2][3][4][5]. However, significantly less attention has been paid to steroid action on peripheral neurons, and the ganglia involved in male pelvic nerve pathways are one of the few identified targets of androgens in the peripheral nervous system. Until recently, virtually all the data came from investigations performed in male rats, and the most relevant and comprehensive contributions published in the second half of the 1990s were compiled by Prof. Janet R. Keast and her collaborators. The knowledge, already relatively comprehensive and complete at that time, has been summarized in some excellent reviews [6][7][8][9] and remains valid until today. The above-mentioned studies show that one of the most important issues is identifying which neurons are sensitive to the effects of testosterone. This can be determined using two approaches. The first is to ascertain if neurons express androgen receptor (AR); if so, this allows us to presume that they are directly influenced by testosterone. The second is to examine the effects of androgen deprivation either by surgical or chemical castration. These should reveal the traits typically maintained by androgens.

Recently, a few contributions in the field have been published [10][11][12], which provide some new and interesting findings. First, these studies were performed in male pigs; second, they considered elements of both above-mentioned approaches combining the surgical removal of testes (castration) with immunohistochemical and/or quantitative real-time PCR (qPCR) investigations of AR expression in neurons of the anterior pelvic ganglion (APG) and intramural ganglia of the urinary bladder (UB) trigone (UBT); third, the comparison of the corresponding findings obtained in male rats and pigs reveals substantial differences, which may be of great importance for planning further investigations aimed at obtaining results important for human and veterinary medicine. It should be noted that the pig is obviously an important animal for veterinary medicine and agriculture, but on the other hand, it has become a critically important experimental animal in biomedical research [13].

Therefore, this short entry addresses the above issues and especially focuses on the comparative analysis of the influence of castration on the pelvic and UB intramural neurons. It should be borne in mind that while laboratory male rats are castrated for experimental purposes only, surgical or chemical castration are treatments widely used in human and veterinary medicine. Moreover, certain clinicopathological consequences of testosterone deprivation for the functioning of urogenital organs are also discussed.

2. Castration and Male Peripheral Neurons

It appears that castration performed in males of larger mammalian species may be much more harmful than previously believed. It can result in the excessive loss of pelvic neurons which presumably supply urogenital organs including the UB and urethra, and UB intramural neurons in at least the trigone area. These organs therefore become deprived of an important part of their innervation. Because these changes are almost certainly a consequence of gonadal steroid deprivation, it is tempting to assume that they may occur following not only surgical, but also any form of hormonal castration, and not only in males but also in females. It can thus be further speculated that in larger mammalian species (including humans) gonadectomy, or more generally, reproductive hormone disorders can lead to the specific partial denervation of lower urinary tract organ tissues, which, in turn, may cause problems in their proper functioning. It should be emphasized, that the literature dealing with morphofunctional abnormalities concerning especially the UB and urethra observed following gonadectomy (steroid deprivation) or associated with the hormonal disorders is relatively immense [63-70].

Furthermore, the potential neuronal loss-derived unfavourable consequences should be taken into account while applying certain forms of treatments, such as those employed in prostate cancer, involving elimination of circulating testosterone. It should also be noted that UBT intramural neurons are probably involved in the neural control of the urethral sphincter [71,72]; thus, their loss can have a negative impact on urinary continence status.

Obviously, the above-mentioned assumptions require comprehensive research validation, and the subsequent studies should seek to answer the following questions:

- would the neuronal loss found in male pigs castrated a few days after birth be observed also in the castrated adult animals,

- which structures are innervated by the porcine male apoptotic neurons,

- whether castration is followed by significant loss of nerve fibres in the organs of the porcine male urogenital system (in either juvenile or adult individuals),

- whether in adult individuals of both sexes of other species (including humans) any significant loss of pelvic or UB intramural neurons can be observed after castration (female and male cats, male horses) or following/during natural (menopausal women) or therapeutic (prostate cancer patients) sex steroid deprivation. The same question applies to nerve fibres supplying especially the pelvic organs.

Accordingly, the possible results would (a) significantly expand the knowledge on the peripheral neuroendocrine relationships (as mentioned, the corresponding information on the central mechanisms is much more extensive), (b) provide information that can contribute to, or even revise, the current view on causes of disorders in the functioning of the lower urinary tract following gonadectomy (and those associated with severe hormonal disorders) not only in animals but also in humans, and (c) contribute to the veterinary knowledge about the possible consequences of both surgical or pharmacological gonadectomy commonly performed in domestic animals due to various, other than experimental, requirements.

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