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BRAIN RESEARCH

Research Report

Vagal innervation of the aldosterone-sensitive HSD2 neurons in the NTS

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ABSTRACT

The nucleus of the solitary tract (NTS) contains a unique subpopulation of aldosterone-sensitive neurons. These neurons express the enzyme 11-β-hydroxysteroid dehydrogenase type 2 (HSD2) and are activated by sodium deprivation. They are located in the caudal NTS, a region which is densely innervated by the vagus nerve, suggesting that they could receive direct viscerosensory input from the periphery. To test this possibility, we injected the highly sensitive axonal tracer biotinylated dextran amine (BDA) into the left nodose ganglion in rats. Using confocal microscopy, we observed a sparse input from the vagus to most HSD2 neurons. Roughly 80% of the ipsilateral HSD2 neurons exhibited at least one close contact with a BDA-labeled vagal bouton, although most of these cells received only a few total contacts. Most of these contacts were axo-dendritic (~80%), while ~20% were axo-somatic. In contrast, the synaptic vesicular transporters VGLUT2 or GAD7 labeled much larger populations of boutons contacting HSD2-labeled dendrites and somata, suggesting that direct input from the vagus may only account for a minority of the information integrated by these neurons. In summary, the aldosterone-sensitive HSD2 neurons in the NTS appear to receive a small amount of direct viscerosensory input from the vagus nerve. The peripheral sites of origin and functional significance of this projection remain unknown. Combined with previously-identified central sources of input to these cells, the present finding indicates that the HSD2 neurons integrate humoral information with input from a variety of neural afferents.

1. Introduction

The nucleus of the solitary tract (NTS) contains a small subgroup of neurons that are sensitive to aldosterone (Geerling et al., 2006a,b). Due to their expression of the glucocorticoid-inactivating enzyme HSD2 (11-β-hydroxysteroid dehydrogenase type 2), they are referred to as HSD2 neurons. The HSD2 neurons are activated under low-sodium and high-aldosterone conditions including dietary sodium deprivation, hypovolemia, and chronic mineralocorticoid administration, and then inactivated after salt is ingested. This activity pattern, as revealed by c-Fos expression, is the inverse of most other neurons in their region of the NTS (Geerling et al., 2006a; Geerling and Loewy, 2006c, 2007b,a).

The axonal projections of the HSD2 neurons have been identified in rats (Geerling and Loewy, 2006b), and some multisynaptic output pathways as well (Geerling and Loewy, 2006a; Shekhtman et al., 2007), but their sources of synaptic input remain largely unexplored. A minor input arrives from neurons in an adjacent circumventricular organ, the area

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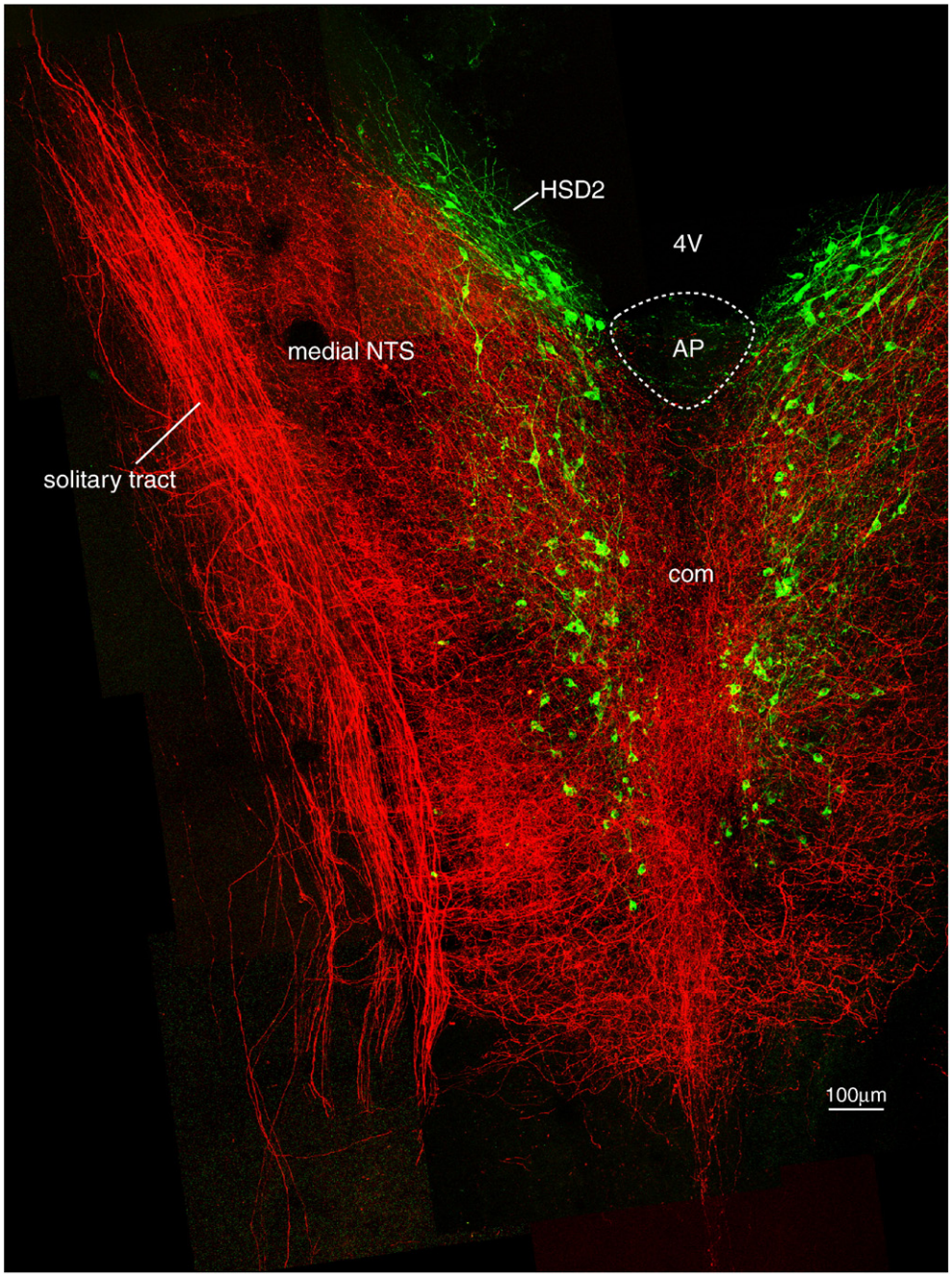

Fig. 1 – This horizontal section through the NTS shows the full extent of vagal innervation in this nucleus (BDA-labeled axons, shown in red) relative to the more restricted distribution of HSD2 neurons. Rostrally, clusters of HSD2 neurons border the posterior wall of the fourth ventricle (4V) on either side of the obex, then extend caudally past the area postrema (AP), and continue through the caudal extent of the NTS, where they form two columns flanking the midline commissural subnucleus (com). Note that the rostral clusters of HSD2 neurons lie in a subregion of the NTS with a low density of vagal fibers relative to the caudal extent of this group. Note also that this figure shows the full 200 µm depth of this section as one compressed plane, and most areas of apparent overlap between vagal fibers and HSD2 neurons did not contain close contacts when examined in individual confocal planes.

postrema, as well as neurotensin-immunoreactive neurons in a neighboring subregion of the NTS that receive baroafferent input (Sequeira et al., 2006). The HSD2 neurons represent a major target of descending axonal projections from neurons in the medial subdivision of the central nucleus of the amygdala (mCeA, Geerling and Loewy, 2006a). Most of the other brain sites that innervate this region of the NTS (Ross et al., 1981; van der Kooy et al., 1984) remain to be explored for direct connections to the HSD2 neurons.

Before identifying central sources of input, we had originally hypothesized that these cells integrate humoral signals from the circulation with neural afferents from the periphery