

The nucleus para-retroambiguus: A new group of estrogen receptive cells in the caudal ventrolateral medulla of the female golden hamster

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Abstract

Receptive female hamsters display very rigid lordotic postures. Estradiol facilitates this behavior via activation of estrogen receptors. In the hamster brainstem estrogen receptor- α -immunoreactive neurons (ER- α -IR) are present in various brainstem regions including nucleus retroambiguus (NRA) in the caudal ventrolateral medulla (CVLM) and nucleus of the solitary tract. ER- α -IR neurons in the CVLM project to the thoracic and upper lumbar cord. However, A1 neurons in this region do not project to the spinal cord, in contrast to overlapping C1 neurons. The question now arises: are ER- α -IR cells in the CVLM part of the A1/C1 group, or do they belong to the NRA or do they compose a separate cluster.

A study in ovariectomized female hamsters using a combination of double immunostaining and retrograde tracing techniques and measurement of soma diameters was carried out.

The results showed that A1/C1 neurons in the CVLM are almost never ER- α -positive; neurons inside or bordering the NRA can be divided in two different types: large multipolar and small; the large NRA-neurons, projecting caudally, are neither tyrosine hydroxylase- (TH) nor ER- α -IR; the small neurons, bordering the NRA and projecting caudally, are ER- α -IR but not TH-IR.

From the available evidence and the present findings it can be concluded that the group of small ER- α -IR neurons in the CVLM has to be considered as a distinct entity, probably involved in the autonomic physiological changes concurring with successive phases of the estrous cycle. Because the location is closely related to the NRA itself the nucleus is called nucleus para-retroambiguus, abbreviated (NPRA).

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Introduction

The female golden hamster takes a special position in the study of female sexual behavior. In the estrous phase, she shows an extremely sustained and rigid lordotic posture in response to stimulation of the lower back and/or perineum. The completely suppressed mobility during this stereotypic copulatory stance is indicative for a strongly inhibitory motor control system, blocking all other kinds of motor responses.

In the neural system controlling the lordotic posture, several levels of the neuraxis participate. Originating from the ventromedial hypothalamic nucleus, a critical region for female repro-

ductive behavior, a descending projection influences the periaqueductal gray matter (PAG) region of the mesencephalon (Calizo and Flanagan-Cato, 2003; Canteras et al., 1994; Daniels et al., 1999; Flanagan-Cato et al., 2006; Pfaff and Sakuma, 1979b).

From the PAG, descending projections reach the caudal ventrolateral medulla oblongata (CVLM) including the nucleus retroambiguus (NRA), as described in monkey (Holstege, 1989; VanderHorst et al., 2000a), cat (Holstege, 1989; VanderHorst et al., 1996), rat (Chen and Aston-Jones, 1996; Holstege et al., 1997), and hamster (Krukerink et al., 2003). The latter report (Krukerink et al., 2003) showed the existence of two projections descending ‘in parallel’: from the caudal vIPAG to the ventrolateral part of the NRA and from a more rostral part of the lateral PAG to more medially located cells in this nucleus. The authors suggest that in the hamster at least two distinct

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functional anatomical PAG-NRA-spinal pathways exist. One pathway originating from the lateral part of the NRA, and projecting to the thoracic intermediolateral cell column, may play a role in the control of sympathetic innervation. The other pathway, from more medially located NRA neurons and projecting to motoneuronal areas, may presumably be involved in vocalization, abdominal straining and postural control. In this context, findings in rat (Hardy et al., 1998; McKellar and Loewy, 1982) report that the CVLM inclusive NRA projects directly to sympathetic neurons in the thoracic cord supporting its role in cardiovascular and respiratory control. The finding of a novel pressor area at the medullo-cervical junction projecting to the thoracic cord adds to the role of this area (Seyedabadi et al., 2006).

In monkey (VanderHorst et al., 2000b), cat (VanderHorst and Holstege, 1995, 1996), mouse (VanderHorst, 2005) and hamster (Gerrits and Holstege, 1999; Gerrits et al., 2004, 2000) a distinct monosynaptic pathway projects from the region of the NRA to the spinal cord. The projection onto motoneurons innervating the muscles involved in the lordotic posture is very suggestive for supraspinal control of this posture.

In summary, the PAG-NRA-spinal motoneuron trajectory can be considered as the final common pathway for the lordotic posture and probably for control of sympathetic adjustments during the estrous cycle.

Since the lordotic posture can be elicited only during the estrous phase of the female cycle, while ovariectomy completely abolishes this behavior, it is clear that the lordotic posture is under control of ovarian hormones. Interestingly, in addition to many limbic regions, also the brainstem areas mentioned above as composing the ‘final common pathway’ for lordosis contain neurons receptive for estrogen and progesterone (Boers et al., 1999; Calizo and Flanagan-Cato, 2003; Flanagan-Cato et al., 2006; Pfaff, 1989; Turcotte and Blaustein, 1999). This neural circuitry shows functional plasticity related to varying steroid levels (Gerrits et al., 2006). In part of the CVLM this functional plasticity can be observed as variable densities of axon terminals and sprouting dendrites (in the hamster, or as growth cones and increased NRA-terminal profiles onto lumbar motoneuronal dendrites, as demonstrated in the cat and monkey spinal cord (VanderHorst and Holstege, 1997a; VanderHorst et al., 2002).

In the rat a confusing aspect in the neuronal organization of the CVLM concerns the dispersed presence of the catecholaminergic neurons, composing the noradrenergic A1 and adrenergic C1 group, which partially overlap the NRA neurons rostrocaudally. The most distinctive feature is, however, that of these intermingled catecholaminergic neurons, A1 neurons do not project downward into the spinal cord, but instead send their projections upward to innervate several limbic regions like paraventricular hypothalamic (PVN) and supraoptic nuclei (SO) (rat, (Cunningham and Sawchenko, 1988; Sawchenko and Swanson, 1982; Tucker et al., 1987). The C1 group, on the other hand, not only provides ascending adrenergic input both to PVN, lateral hypothalamic area, SO, and median preoptic nuclei (Cunningham et al., 1990; Tucker et al., 1987) but also sends descending projections into the spinal cord (Maisky and Doroshenko, 1991; Tucker et al., 1987).

In hamster and mouse the neuronal organization of the CVLM is similarly complex (Mouton et al., 2006; VanderHorst and Ulfhake, 2006; Vincent, 1988).

In hamster estrogen-receptor-alpha-immunoreactive (ER- α -IR) neurons are numerous in several brainstem areas, like the PAG, the parabrachial nucleus, the region of the NRA and the solitary tract nucleus (Boers et al., 1999). The NRA region, moreover, contains many ER- α -IR neurons projecting directly into the lumbar spinal cord (Boers et al., 1999; Boers and Holstege, 1998). Other ER- α -IR neurons in the CVLM, however, do not project caudally, but appear to belong to the dispersed group of catecholaminergic neurons, collectively labeled A1/C1, as observed in the sheep (Simonian et al., 1998), in the rat (Haywood et al., 1999; Simonian and Herbison, 1997), and in the mouse (VanderHorst et al., 2005). In the latter animal it was found that almost all catecholaminergic positive neurons in the A1 cell group, Sol (A2 group), area postrema, lateral tegmental field between A1 group and Sol contained ER- α -IR nuclei (VanderHorst et al., 2005). Their findings are in agreement with similar studies in rat and sheep (Simonian et al., 1998; Simonian and Herbison, 1997; Voisin et al., 1997), which report high concentrations of neurons double labeled for ER- α and catecholamines in the A1 and A2 group.

Because of the dispersed localization of both the ER- α -IR neurons and the catecholaminergic neurons, it is difficult, however, to subdivide the ER- α -IR neurons in different groups. Therefore, the question arose: which ER- α -IR neurons in the CVLM can be considered as to belong functionally to the NRA, projecting mainly caudally, and which ER- α -IR neurons belong to the A1/C1 catecholaminergic group, projecting respectively rostrally and caudally?

To solve this question we decided to study in ovariectomized female hamsters a combination of double immunostaining methods, retrograde tracing techniques, and measurement of soma diameters. One double immunostaining provided information about ER- α -IR and tyrosine-hydroxylase (TH-IR) (double) labeled cells, and a second for ER- α -IR in combination with a retrograde tracer (cholera toxin B-subunit, CTB). CTB injections were placed in the lower thoracic and upper lumbar cord for identification and localization of spinal cord-projecting neurons in the CVLM that contain ER- α -IR nuclei. In addition to the results of these immunolabeling analysis, data were collected concerning the location and soma diameters of neurons in and along the NRA.

From our findings we conclude that the small ER- α -IR neurons, bordering the NRA, have to be considered as a distinct group, not belonging to the NRA and separate from the A1/C1 group of neurons and we propose to call this group: the nucleus para-retroambiguus (abbreviated NPRA).

Experimental procedures

Animals

The surgical procedures, pre- and postoperative care, and handling and housing of the animals were in accordance with the protocols approved by the University Medical Center Groningen. A total of 7 adult female golden hamsters (*Mesocricetus auratus*; cases H347, H348, H349, H523, H524, H525 and

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