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Cardiovascular Deficits After Lesions of C1 Adrenergic Neurons With a Saporin-Based Immunotoxin

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INTRODUCTION

Central nervous system (CNS) adrenergic neurons are located exclusively in the medulla oblongata *(1)*. The metabolism of CNS adrenaline, its turnover rate, and its pharmacology were intensely studied in the late 1970s (reviewed in ref. *2*). Since then, the study of CNS adrenergic neurons has been the purview of integrative physiologists interested in stress, autonomic regulations, and the neural control of blood pressure and glucose. The CNS contains three clusters of adrenergic neurons: C1, C2, and C3 *(1)*. The main focus of this chapter is on the C1 neurons, especially those with spinal projections that are most important for sympathetic control and blood pressure regulation *(3–6)*.

Noradrenergic, dopaminergic, and serotonergic neurons have been selectively lesioned since the 1970s using drugs such as 6-hydroxydopamine (6-OHDA) or 5,7-di-OH tryptamine. These neurotoxins contributed greatly to the understanding of the physiological role of these particular aminergic neurons, but they have proven ineffective to lesion CNS adrenergic neurons *(7)*. Antidopamine β-hydroxylase saporin (anti-DβH-sap), an immunotoxin made of the ribosomal toxin saporin conjugated with an antibody to dopamine β-hydroxylase (DβH) is the first tool available for the selective destruction of CNS adrenergic neurons *(8–10)*. This chapter describes how the use of anti-DβH-sap has helped clarify the role of the C1 neurons.

From: *Molecular Neurosurgery With Targeted Toxins*
Edited by: R. G. Wiley and D. A. Lappi © Humana Press Inc., Totowa, NJ

The C1 Adrenergic Neurons, Unusual Members of the Aminergic Family

The defining characteristic of the C1 group is the presence of phenylethylamine *N*-methyl transferase (PNMT) *(1)*, the enzyme that converts noradrenaline into adrenaline *(2)*. The C1 neurons also contain tyrosine hydroxylase (TH), DβH *(11)*, and a vesicular monoamine transporter *(12)*. The C1 neurons are located in the reticular formation of the medulla oblongata caudal to the facial motor nucleus, and their axonal projections are more restricted than that of CNS noradrenergic neurons *(1)*. The rostral half of the C1 cells project to a variety of lower brainstem and midbrain structures involved in autonomic regulations, but their defining characteristic is a spinal projection that targets sympathetic preganglionic neurons with considerable selectivity *(1,13)*. This connection is largely monosynaptic *(14)*.

Although the spinal terminals of C1 cells contain PNMT, evidence that they contain, no less release, adrenaline remains controversial *(2,15)*. The controversy stems from the still-unresolved technical difficulty in detecting very low levels of adrenaline in the presence of high levels of noradrenaline. The caudal group of C1 cells does not project to the cord. Instead, these cells innervate selected regions of the hypothalamus that regulate blood pressure and many endocrine responses associated with stress *(16–18)*. There is excellent evidence that the hypothalamic projections of C1 cells do synthesize adrenaline *(2)*.

Like all monoaminergic neurons, C1 neurons express a variety of neuropeptides (e.g., neuropeptide Y, enkephalins, cocaine- and amphetamine-regulated transcript [CART]) *(19–22)*. The pattern of expression of these peptides varies according to a neuroanatomical code that is still not understood in functional terms. Contrary to noradrenergic neurons, most adrenergic neurons do not express the noradrenaline transporter (NET) *(23)*, and they have no other known catecholaminergic membrane transporter. This peculiarity of C1 neurons is the most likely reason for their resistance to 6-OHDA and related toxins. The selectivity of 6-OHDA relies on the ability of susceptible neurons to concentrate this chemical via their membrane transporter (e.g., NET for noradrenergic cells) to intracellular levels that are high enough to produce toxic levels of reactive oxygen species *(24)*.

Presympathetic Role of Bulbospinal C1 Cells

The earliest evidence that adrenergic cells must play some role in sympathetic tone generation can be traced to the 1973–1974 immunohistochemical work of Hökfelt et al., who demonstrated that, in the spinal cord, PNMT immunoreactivity is almost exclusively confined to the thoracic and lumbar intermediolateral cell column *(1)*. This histological work also established