Chapter 3
Anatomical Characteristics of Norepinephrine Axons in the Prefrontal Cortex: Unexpected Findings That May Indicate Low Activity State in Naïve Animals

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3.1 Importance of the PFC NE Innervation for Normal Function and Clinical Conditions

The catecholamine norepinephrine (NE) critically regulates information processing within the central nervous system. Along with dopamine (DA) and serotonin (5-HT; 5-hydroxytryptamine), the NE system forms an essential component of the modulatory brainstem innervation that ascends directly to the cerebral cortex without first being relayed through the thalamus. Within the prefrontal cortex (PFC) in particular, NE is known to modulate the essential cognitive and affective functions of this region, with animal studies demonstrating that normal NE innervation to the PFC is necessary for working memory, attention, and arousal (Robbins, 1984; Aston-Jones et al., 1999; Berridge, 2001; Berridge and Waterhouse, 2003; Arnsten and Li, 2005; Lapiz and Morilak, 2006).

Alterations in central NE systems have been observed in patients with depression, posttraumatic stress disorder (PTSD), and attention deficit hyperactivity disorder (ADHD) (Southwick et al., 1993; Pliszka et al., 1996; Klimek et al., 1997; Solanto, 1998; Biederman and Spencer, 1999; Southwick et al., 1999; Zhu et al., 1999) (see also the Chapters 19, 20, and 21 in this volume). These conditions afflict 7–10% of the population, including 3–5% of children, and strain society through lost productivity and poor quality of life. In addition, many more Americans suffer from the effects of chronic levels of stress in their daily lives. Many clinical studies suggest that dysfunction within the PFC may contribute to the symptoms of mental disorders (Drevets et al., 1992; Ernst et al., 1994; Mostofsky et al., 2002; Rauch et al., 2003; Shin et al., 2001; Soares and Mann, 1997; Solanto, 1998; Zametkin et al., 1990), and several studies propose more specifically that alterations of NE transmission in the PFC directly contribute to the pathophysiology of affective disorders and ADHD.
(Meana et al., 1992; Aston-Jones et al., 1994; Charney et al., 1995; Bremner et al., 1996; Pliszka et al., 1996; Callado et al., 1998; Solanto, 1998; Russell et al., 2000).

The essential role of the NE system in mental health is further supported by findings that drugs blocking the reuptake of NE through the NE transporter (NET) effectively treat mood disorders and ADHD (Nelson, 1999; Frazer, 2000; Kent, 2000; Moller, 2000; Bymaster et al., 2002; Spencer et al., 2002; Michelson et al., 2003). Moreover, the therapeutic properties of these drugs may be mediated in part within the PFC itself (Tanda et al., 1994; Frazer, 2000; Bymaster et al., 2002). Reuptake through the NET is a key regulator of NE transmission, in that it controls the temporal dynamics of extracellular NE, the spatial range of NE diffusion, and the synthetic load of NE terminals. Although alterations in NE transmission within the PFC have been associated with both the etiology and treatment of mental disorders, the precise bases for these illnesses and the modes of action of the therapeutic drugs used to treat them are poorly understood. This necessitates a greater understanding of the cellular and molecular control of NE axon terminals within this region.

Our laboratory has initiated a series of studies examining the ultrastructural and phenotypical characteristics of NE axons in the PFC. The initial investigations revealed rather unusual features of these fibers that deviate from traditional expectations of how key proteins are distributed within monoamine axons. This chapter provides a brief historical background on the anatomy of the cortical NE innervation and a review of the atypical characteristics that our research has revealed. We then offer a working hypothesis that seeks to explain these features in a manner amenable to experimental testing. Finally, we review some of the data we have collected to test the model and outline future experiments for challenging the hypothesis.

3.2 General Anatomy of the NE Innervation to the Cerebral Cortex

3.2.1 ORIGIN FROM THE LOCUS COERULEUS (LC)

The general anatomical characteristics of the NE innervation to the cerebral cortex have been well established (Descarries et al., 1984; Fallon and Loughlin, 1987; Berridge and Waterhouse, 2003) and will be summarized only briefly here. Early studies utilizing histochemistry in combination with lesions, retrograde tracers, or anterograde autoradiographic tracing (Ungerstedt, 1971; Pickel et al., 1974; Levitt and Moore, 1978; Morrison et al., 1979; Morrison et al., 1981; Fallon and Loughlin, 1982; Loughlin et al., 1982; Jones and Yang, 1985) have reliably established that the cerebral cortex receives a moderately dense NE innervation from the LC. Evidence for a cortical NE innervation from other brainstem NE cell groups is lacking. Within the LC, cells projecting to the cortex are distributed across the dorsal compact division (Mason and Figiber, 1979; Fallon and Loughlin, 1982; Waterhouse et al., 1983; Loughlin et al., 1986a, b), and the majority are situated within the ipsilateral hemisphere (Ader et al., 1980; Room et al., 1981; Waterhouse et al., 1983; Simpson et al., 1997). Cells projecting to disparate cortical areas are somewhat interspersed with each other (Loughlin et al., 1982). However, a rough anterior to posterior topography