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Review

The role of the central noradrenergic system in behavioral inhibition☆

Eric A. Stone[a,*], *Yan Lin*[a], *Yasmeen Sarfraz*[a], *David Quartermain*[b]

[a]*Department of Psychiatry, New York University Langone School of Medicine, 550 First Ave., New York, NY 10016, USA*
[b]*Department of Neurology, New York University Langone School of Medicine, 550 First Ave., New York, NY 10016, USA*

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ABSTRACT

Although the central noradrenergic system has been shown to be involved in a number of behavioral and neurophysiological processes, the relation of these to its role in depressive illness has been difficult to define. The present review discusses the hypothesis that one of its chief functions that may be related to affective illness is the inhibition of behavioral activation, a prominent symptom of the disorder. This hypothesis is found to be consistent with most previous neuropsychopharmacological and immunohistochemical experiments on active behavior in rodents in a variety of experimental conditions using manipulation of neurotransmission at both locus coeruleus and forebrain adrenergic receptors. The findings support a mechanism in which high rates of noradrenergic neural activity suppress the neural activity of principal neurons in forebrain regions mediating active behavior. The suppression may be mediated through postsynaptic galaninergic and adrenergic receptors, and via the release of corticotrophin-releasing hormone. The hypothesis is consistent with clinical evidence for central noradrenergic system hyperactivity in depressives and with the view that this hyperactivity is a contributing etiological factor in the disorder. A similar mechanism may underlie the ability of the noradrenergic system to suppress seizure activity suggesting that inhibition of the spread of neural activation may be a unifying function.

Contents

Abbreviations: 6FNE, 6-fluoronorepinephrine; 6OHDA, 6-hydroxydopamine; ADRA, α-adrenergic receptor; atipam, atipamezole; CeA, central nucleus of amygdala; clon, clonidine; CRF, corticotrophin-releasing factor; CRFR1, corticotrophin-releasing factor receptor 1; DMI, desmethylimipramine; DBH, dopamine-β-hydroxylase; DBH-SAP ITX, dopamine-β-hydroxylase-saporin immunotoxin; DSP4, *N*-(2-chloroethyl)-*N*-ethyl-2-bromobenzylamine; EPI, epinephrine; GABA, gamma aminobutyric acid; Gal, galanin; GEPR, genetically epilepsy prone rat; glut, glutamate; ISO, isoproterenol; ivt, intraventricular; LC, locus coeruleus; PGi, paragigantocellularis; PE, phenylephrine; PIR, piriform cortex; praz, prazosin; teraz, terazosin; VTA, ventral tegmental area

☆ (The studies described in this review were carried out in accordance with the *EC Directive 86/609/EEC for research on animals*).

* *Corresponding author at:* Psychiatry MHL HN510, NYU Langone Med Ctr, 550 First Ave., New York, NY 10016, USA. Fax: +1 212 263 0712.
E-mail address:eric.stone@nyumc.org (E.A. Stone).

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1. Introduction

The central noradrenergic system has been established to be intimately related to the etiology and/or therapy of depressive illness (Itoi and Sugimoto, 2010; Lopez-Munoz and Alamo, 2009; Millan, 2004). Its precise role in this disorder, however, is controversial with earlier theories attributing depression to its hypoactivity (Schildkraut, 1965) but more recent formulations to its hyperactivity (Gold and Chrousos, 2002; Simson and Weiss, 1988). The function of the noradrenergic system has been variously posited to be stress responding (Arnsten and Li, 2005; Korf et al., 1973; Kvetnansky et al., 2009; Lane-Ladd et al., 1997; Ma and Morilak, 2004; Rasmussen et al., 1986; Stone, 1975; Weiss et al., 2005), arousal (Aston-Jones et al., 2001; Aston-Jones and Bloom, 1981; Berridge and Foote, 1994; Cespuglio et al., 1982), signal detection (Berridge and Waterhouse, 2003), decision making (Aston-Jones and Cohen, 2005), memory retrieval (Bouret and Sara, 2005; Roozendaal et al., 1999), learning (Anlezark et al., 1973; Harley, 1987), psychomotor and cognitive activation (Geyer et al., 1972; Schildkraut, 1965), adaptation and trophic processes (Feeney et al., 1993; Stone, 1983), reward (Segal and Bloom, 1976; Wise and Stein, 1969), drug withdrawal (Christie et al., 1997; Smith and Aston-Jones, 2008; Taylor et al., 1988), depression (Karolewicz et al., 2005; West et al., 2009), behavioral inhibition and nonreward (Mason and Iversen, 1977; Murrough et al., 2000; Tsaltas et al., 1989) and the inhibition of seizure activity (Jobe and Weber, 2006; Yan et al., 1998). Finding a common denominator or mechanism to unite all of these functions with affective illness has proved difficult. Several recent behavioral studies employing local pharmacological inactivation or stimulation, or lesions of the LC, however, are beginning to provide new support for two of these earlier hypotheses regarding the inhibition of behavioral and neural activation that might reconcile some of these functions with depression. This has important implications for our view of this illness, mechanisms of antidepressant therapy and the inhibition of seizures. The following review will therefore discuss these hypotheses in terms of both recent and earlier studies, and how they might relate to the neuropharmacological characteristics of the noradrenergic system.

2. Development of the behavioral inhibition hypothesis

Although depression is a complex and heterogenous disorder, it does have a common behavioral symptom which is the loss of interest or pleasure in virtually all activities (American Psychiatric Association, 2002). Most forms of the disorder are accompanied by a marked reduction in effortful and sustained positively motivated and coping behaviors, which are defined as motor behaviors directed toward a positive reinforcer or the removal or avoidance of a negative reinforcer. This is seen clinically as pervasive anhedonia (Willner, 1997), fatigue at minimal exertion (Demyttenaere et al., 2005), and a lack of participation in virtually all daily activities particularly those associated with active leisure (Barge-Schaapveld et al., 1999; Merrick, 1992) (Table 1).

Behavioral activation responses in animals, which appear analogous to human daily activities, may be modeled in animals using measures of gross behavioral responses to novel or appetitive stimuli, such as exposure to a nonthreatening fresh cage or running wheel, performance of appetitive operant responses or initial escape responses to swim stress. Much previous work has shown that chronic stress, which is etiologically linked to depression in humans, reduces behavioral activation in most or all of these conditions (Garcia-Garcia et al., 2009; Maier et al., 1990; Pechlivanova et al., 2010; Roth and Katz, 1981; Stone et al., 2007) and that these deficits are selectively reversed by antidepressant agents (Farley et al., 2010; Roth and Katz, 1981; Surget et al., 2009). The present review is therefore based on studies utilizing measures of these responses.

Early evidence that the noradrenergic system may have a behaviorally depressant effect came from studies showing that low but not high doses of intracerebral NE could produce behavioral arousal or motor stimulation in inactive rodents. Thus it was found that intracerebral infusion of 0.4 but not 2 nmol into the hypothalamus of hibernating ground squirrels produced behavioral and body temperature arousal (Beckman and Satinoff, 1972), intraventricular (ivt) infusion of 3 but not 6 or 12 nmol of the catecholamine partially restored behavioral activity in a novel cage in inactive hypothermic rats after cold swim stress (Stone and Mendlinger, 1974), and intracoerulear infusion of 2.5 but not 10 nmol stimulated open field activity in rats (Smee et al., 1975). The reason for the effectiveness of low but not high doses was not apparent at the time these studies were conducted but in retrospect appears to have resulted from a preferential action of low doses on more sensitive inhibitory CNS noradrenergic autoreceptors, which were shown to have a seven-fold higher affinity than heteroceptors (Raiteri et al., 1983).

Subsequent studies which examined the effect of lesions of the dorsal noradrenergic bundle in rats on operant learning and extinction experiments also suggested an inhibitory effect on behavioral activation. These experiments showed that animals with virtually no forebrain NE had dramatic deficits in the extinction but not acquisition of operant responses (Mason