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The Role of the Central Noradrenergic System in Behavioral Inhibition

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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.

Keywords

noradrenergic system; behavioral inhibition; depression; locus coeruleus; seizures

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1. Introduction[1,2]

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).

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 a exposure to a non-threatening fresh cage or running wheel, performance of appetitive operant responses or initial escape responses to swim stress. Much

[1]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-hydroxylasesaporin 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

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

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 nmoles 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 nmoles 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 nmoles 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 and Iversen, 1977; Tsaltas et al., 1989). The animals continued to respond vigorously to conditioned stimuli long after reward was withdrawn suggesting that they were resistant to the stress of non-reward. A theory was proposed that the dorsal noradrenergic system exerted behavioral inhibitory effects via its action on the hippocampus (Gray et al., 1975), an area involved in both behavioral activation (Flicker and Geyer, 1982) and regulation of the hypothalamic-pituitary-adrenal axis (Herman and Mueller, 2006), although direct tests selectively manipulating hippocampal noradrenergic activity were not conducted.

A later seminal study by Weiss and colleagues utilizing acute local pharmacological inactivation of the LC, then confirmed and extended the hypothesis by showing that the stimulation of inhibitory α_2-adrenergic receptors in or near the LC in rats produced powerful anti-immobility effects in the forced swim test and also reversed the increase in swim-immobility produced by previous exposure to inescapable tailshock stress. These authors also found that the converse manipulation, blockade of these receptors with yohimbine, aggravated the immobility (Simson et al., 1986; Weiss et al., 1986). In support of the assumption that the cause of the increased immobility was increased LC neural activity, Weiss and colleagues subsequently found that the firing rate of LC neurons in these depressed rats was elevated above nonstressed controls (Simson and Weiss, 1988) and that virtually all antidepressant drugs strongly inhibited LC activity (West et al., 2009) confirming earlier reports of reduced norepinephrine turnover in the forebrains of rodents treated with these compounds (Nielsen and Braestrup, 1977). Furthermore selective stimulation of postsynaptic receptors in noradrenergic projection areas of the forebrain achieved by infusions of the ß-adrenoceptor agonist, isoproterenol (ISO), or the α_1-agonist, phenylephrine (PE), in the lateral cerebral ventricle also increased the level of inactivity in the forced swim test in rats consistent with the hypothesized role of noradrenergic hyperactivity in behavioral inhibition (Weiss et al., 1986).

Interestingly, the above study by Weiss et al. also showed that behavioral activity under less provocative conditions such as in a holding cage was actually inhibited by the stimulation of these receptors (Weiss et al., 1986) in agreement with what other investigators had found with α_2-receptor stimulation of the LC under similar conditions (Berridge and Waterhouse, 2003; De Sarro et al., 1987). This finding pointed to a critical difference between the mechanism of behavioral activation in tests of depression versus that in less demanding conditions and appeared to parallel a similar differential effect of antidepressant drugs which enhance behavioral activation during forced swim activity but inhibit it in the open field (Cryan et al., 2005). As will be described below, however, this differential effect was much less apparent when the LC was manipulated through its α_1-receptors, which our group showed to be the major inhibitory adrenergic receptor of the mouse nucleus suggesting either a differential function or localization of LC α_1- and α_2-receptors.

Subsequent studies by this author found that high systemic doses of the α_1-adrenoceptor antagonist, prazosin, that penetrated the blood brain barrier as verified by ex vivo receptor binding (Stone et al., 2001b) produced cataleptic behavior in mice in novel cage tests accompanied by intense expression of the immediate early gene, fos, in the LC (Stone et al. 2006b). At the same time these doses markedly inhibited fos expression in a number of forebrain regions known to be involved in behavioral activation including the secondary motor (M2), cingulate (CG) and piriform (PIR) cortex, and nucleus accumbens (NAC) (Stone et al., 2006b). The same close association of heightened LC and inhibited forebrain neural activation with behavioral inactivity was found to occur after administration of the amine depleting agent, reserpine, and to a lesser degree, the cytokine-releasing endotoxin, lipopolysaccharide (Stone et al., 2006a). It is of interest to note that in these experiments high LC activation was associated with reduced neural activity in the NAC which was known to possess α_1-receptors that mediate neural excitation (Grenhoff et al., 1993), behavioral activation and reward (Stone et al., 2004a; Weinshenker and Schroeder, 2007). However, it had been shown that the neural excitation of these neurons only occurs at low or moderate levels of LC activity; at high levels, such as those occurring during stress, accumbens neurons are depressed (Grenhoff et al., 1993) probably due to the release of co-transmitter, galanin, as is discussed below (Weiss et al., 2005).

As autoradiographic studies of the CNS distribution of α_1-adrenoceptors revealed a high concentration of these receptors in the rodent LC (Chamba et al., 1991; Jones et al., 1985), which might be involved in these effects, our group subsequently undertook studies to determine the behavioral effects of stimulation or blockade of these receptors. Because of the unavailability of highly selective agonists and antagonists of the various α_1-receptor subtypes, these studies necessarily used nonselective ligands. An initial study showed that local stimulation of the LC with the selective α_1-agonist, PE, produced modest behavioral activation in rats in the home cage (Stone et al., 2004b). Moreover the effect was reversed by previous systemic treatment with the noradrenergic neurotoxin, DSP4, indicating its dependence on intact noradrenergic innervation of the forebrain. However, since it had been demonstrated that PE was only a partial agonist at central α_1-receptors (Johnson and Minneman, 1986; 1987; Law-Tho et al., 1993), (in contrast to peripheral receptors where it is a full agonist) we followed up these studies by stimulation of the mouse LC with the full α-selective agonist, 6-fluoronorepinephrine (6FNE). Unlike selective α_2-agonists which can produce sedation in nonstimulating environments when infused near the LC (Berridge and Waterhouse, 2003), this compound, which stimulates both α_1- and α_2-adrenoceptors, produced a remarkable disinhibition of a variety of motivated behaviors including wheel running, escape from the home cage, activation of operant behavioral responding (Stone et al., 2009) and increased bar pressing for rewarding brain stimulation with no apparent sedative effect in any of these situations (Lin et al., 2007). The effect of 6FNE on home cage activity, moreover, was significantly attenuated by prior lesion of the LC with 6OHDA

indicating the necessity of this nucleus for the behavioral effect. Coinfusion of selective antagonists of α_1- (terazosin) or α_2-(atipamozole) receptors, furthermore, indicated that the behaviorally activating effect of intracerebral 6FNE in the home cage was mediated primarily by α_1-receptors (Stone et al., 2009).

It was later found that in addition to behavioral activation in the above conditions, 4th ventricular infusion of 6FNE in mice at low or intermediate doses also produced marked and immediate antidepressant actions in a variety of "depressive" tests utilizing both immobility and anhedonia endpoints (Stone et al. In press). Furthermore, these tests included a model of chronic depression in mice, repeated forced swim, that had been shown to be resistant to the acute actions of most available antidepressants .

The α_1-receptors of the LC that were involved in these behaviors also appeared be tonically activated since intraventricular or intracoerulear infusion of terazosin, by itself, produced marked catalepsy in mice (Stone et al., 2001a; 2009). An earlier study in rats by another group had failed to find any effect on behavioral activity of either 3rd ventricular or locus coeruleus infusions of prazosin at 5-40 nmoles suggesting a possible species difference (De Sarro et al., 1987). However, such a difference was not confirmed in a subsequent study in which we demonstrated that infusion of 3 nmoles of terazosin in the 4th ventricle of rats inhibited their gross movements in a novel cage by some 60% and that 10 nmoles produced complete cessation of behavioral activity in this test for at least 30 min (Stone et al., 2003).

Blockade of α_1-receptors also appeared to aggravate depressive behavior although this effect was not as consistent as the reversal of this behavior with stimulation of these receptors. Thus peripheral prazosin injection was found to increase immobility by itself in the rat forced swim (Kitada et al., 1983a) and mouse tail suspension tests (Stone and Quartermain, 1999) and by some, but not others investigators (Borsini et al., 1984; Pulvirenti and Samanin, 1986), to reverse the antidepressant actions of a number of drugs in the forced swimming test (Kitada et al., 1983a; Kostowski, 1985; Poncelet et al., 1987; Schmidt, 1985) and learned helplessness paradigms in rats (Poncelet et al., 1987). In preliminary studies, we have found that ivt. terazosin in mice increases immobility in the tail suspension but not the repeated forced swim test, although it significantly reduced distance swum in the latter, whereas i.p. prazosin, in brain penetrating doses, both increases immobility and reduces distance swum in the latter test (Stone, E.A and Lin, Y. Unpublished observations).

The above behavioral observations prompted a study of what the effect of stimulating or blocking these α_1-receptors was on LC neural activity. Double-label Fos/tyrosine hydroxylase studies of the mouse LC after infusion of this and other adrenergic agonists and antagonists in the fourth ventricle of awake animals were then undertaken and a strong inverse correlation was found between the extent of LC activation and behavioral movements in the home cage (Stone et al., 2009). Infusion of 6FNE, silenced Fos expression in virtually every cell of the mouse LC, despite high levels of gross movement, whereas infusion of the α_1-antagonist, terazosin, activated virtually every cell despite complete behavioral inactivity. The effect of 6FNE on Fos expression, moreover, was blocked more by terazosin than by the α_2-antagonist, atipamezole, indicating primary mediation by α_1-receptors. The α_2-agonist, dexmedetomidine, was also significantly less effective than 6FNE in suppressing LC Fos expression and in disinhibiting active behavior in these experiments (Stone et al., 2009), suggesting that, at least in this species, the key inhibitory adrenergic receptor near or within the LC is the α_1-receptor.

The above findings appeared to contradict the long-held view that α_1-receptors mediate neuroexcitatory processes in the CNS (Bradshaw et al., 1981; Hermann et al., 2005; Osborne et al., 2002) and specifically the finding that stimulation of these receptors with the partial

agonist, PE, in brain slices depolarized LC neurons by suppression of GIRK channel activity (Osborne et al. 2002). However, there had also been reports of inhibitory effects of α_1-neurotransmission on glutamatergic neurotransmission in several other brain regions (see below). We therefore recently attempted to replicate the depolarizing effect of α_1-stimulation of the LC in a mouse brain slice preparation but found only hyperpolarization in response to PE with intracellular recording (Liu R and Stone, EA, unpublished findings). This could reflect a species difference but since rats show an identical inactive behavioral response to blockade of brainstem α_1-receptors (see above), this is deemed unlikely. The reason for the disagreement between these studies is, therefore, not presently apparent. However, it is likely that measures of ex vivo Fos expression in LC neurons from conscious, behaving animals are more relevant to the actual activity of these neurons during the active behavior than are in vitro brain slice determinations.

Consistent with its behaviorally activating effect, infusion of 6FNE in the mouse LC was also found to enhance Fos expression in several forebrain regions mediating behavioral activity including the NAC and lateral septum, and probably the PIR and M2 as well (Stone et al., In press). This suggests that inhibition of the LC results in disinhibition of output neurons in these forebrain regions with a consequent disinhibition of active behavior.

Further support for the behavioral inhibition hypothesis may come from a study using optogenetic methods to stimulate or inhibit the LC in conscious, freely behaving mice (Carter et al. 2010). These authors have recently shown that high frequency (10 Hz) stimulation of the nucleus produces a striking arrest of active behavior as predicted by the present model. Inexplicably, however, although the stimulation significantly increased Fos expression in the LC, it had the extraordinary effect of reducing rather than increasing the release of NE in the frontal cortex making the effect difficult to evaluate in terms of noradrenergic neurotransmission. As acute treatments with two NE reuptake inhibitors, atomoxetine and reboxetine, were found to attenuate the behavioral arrest, the authors hypothesized that the change resulted from a depletion of terminal levels of NE. However, this is unlikely since they also reported that optogenetic inhibition of the LC, which reduced forebrain NE release to a similar extent, did not produce this arrest. Furthermore, atomoxetine (Ruocco et al. 2010) and reboxetine (Grandoso et al. 2004) have been shown to suppress LC neuron firing rate or NE metabolism, effects which would block behavioral inhibition according to the present hypothesis. It is more likely, therefore, that the arrest resulted from an enhanced release the noradrenergic cotransmitter, galanin, which occurs at high firing rates and can produce inhibition of neural activity in brain areas supporting motivation and motor behaviors (discussed below). However, other effects, such as a depolarization block, cannot be excluded at present (Grace et al. 1997; Stone and Quartermain, 2004).

In contrast to its supportive findings, the above optogenetic study, however, also presented two additional findings that do not appear to be consistent with the present hypothesis but are also difficult to evaluate at present. First, it found that tonic (3 Hz), unlike phasic LC stimulation, increased motor activity, and second that optogenetic inhibition of the nucleus significantly reduced waking EEGs during the animal's dark period. These findings support a direct rather than an inverse relationship between forebrain noradrenergic activity and behavioral activation. However, as no data were presented on forebrain NE release during the tonic LC stimulation, it is not known whether noradrenergic neurotransmission was, in fact, increased or reduced as occurred with the high frequency stimulation. Furthermore the opposing effects of high and low frequency stimulation of the LC on behavioral activation appear at odds with our previous finding of a linear relationship between the degree of drug-induced LC Fos expression and the degree of behavioral inhibition that occurred over a very wide range of LC activities extending from nearly zero (2.6%) to virtually full activation

(88.1%) of the total neuronal population of the nucleus (Stone et al. 2009). In addition, no data were presented on the state of behavioral activity in the optogenetically inhibited animals, which were tested during their dark (active) period during which an inhibition of activity would have been readily apparent.

If the LC is, in fact, mediating behavioral inhibition, then lesions of the nucleus should produce chronic behavioral hyperactivity. As discussed above, earlier dorsal bundle lesion studies had already found reduced extinction of appetitive instrumental responses suggestive of such an effect but had not examined open field behavior, the traditional measure of behavioral activity in rodents. Weiss et al investigated the effect of extensive lesions of central noradrenergic systems on nocturnal home cage behavioral activity and found that the lesions clearly did not produce hypoactivity but did produce extreme hyperactivity in some of the animals (Murrough et al., 2000). Ellison and colleagues, in much earlier work, had also found evidence of chronic hyperactivity, although with a complex time course, in rats living in a naturalistic colony environment after central noradrenergic lesions produced by repeated low dose 6-hydroxydopamine administration (Ellison, 1975).

To re-investigate this question, we recently examined the effect of lesions made with intraventricular injections of the noradrenergic neurotoxins, DSP4, or a dopamine-β-hydroxylase-saporin immunotoxin (DBH-SAP ITX) (Stone et al., Submitted), two novel lesioning methods. Intraventricular rather than peripheral DSP4 was used because the peripheral toxin lesions only axons and acts on peripheral as well as central noradrenergic fibers, which could have different behavioral functions. It was found that ivt. DSP4 and DBHSAP ITX both produced marked chronic behavioral hyperactivity in the open field but that the effect was considerably greater after the former compound. Immunohistochemical cell count verification of the latter lesions, however, revealed that ivt. DSP4, while it partially lesioned the LC (-24%), also lesioned the dorsal raphe (-37.4%) and A7 nuclei (-42.1%) whereas the DBH-SAP ITX more specifically lesioned the LC (-60.9%) although it also had effects on ventral tegmental dopaminergic neurons (-27.9%). The fact that both lesioning methods resulted in significant open field hyperactivity supports the hypothesis that the LC normally limits this behavior. But the finding that the hyperactivity was considerably greater after DSP4 treatment suggests that other brainstem monoaminergic nuclei such as the DR and A7 are also involved in the inhibition of motor activity which is consistent previous findings (Eagle et al., 2009; Martin and van den Buuse, 2008).

If depression and behavioral inhibition share a common neurobiological substrate, it would be predicted that noradrenergic lesions should produce significant chronic antidepressant effects. A number of authors, though not all (Esposito et al., 1987; O'Leary et al., 2007), have, in fact, found this effect although it appears to be a weak and unreliable one using intracerebral 6-hydroxydopamine or peripheral DSP4 (Harro et al., 1999; Plaznik et al., 1988; Semba and Takahashi, 1988). In our study, both ivt. DSP4 and the DBH-SAP ITX in mice were found to produce significant anti-immobility effects in the tail suspension and repeated forced swim tests and also to increase distance swum in the latter. Moreover, DSP4 treatment led to a higher intake of sweetened milk, a positively-motivated hedonic behavior, and blunted the reduction in milk intake caused by prior endotoxin administration suggesting that its antidepressant effects were not solely due to increased motor activity (Stone et al., Submitted). In apparent contradiction of the above view, most antidepressant drugs have been found to reduce locomotor activity in the open field test. However, this effect has never been shown to be essential for antidepressant action and might result from the antidepressant-induced noradrenergic stimulation of postsynaptic α_2-receptors in the forebrain, which can aggravate depressive behavior (Garcia-Sevilla et al., 1999; Marcus et al., 2010).

Another prediction of the behavioral inhibition hypothesis is that prior lesions of the noradrenergic system should reverse the behavioral inhibition caused by high doses of α_1-antagonists. To test this we have lesioned mice with ivt. or i.p.DSP4 and then tested for behavioral inhibition in the novel cage test after a high dose of the α_1-antagonist, prazosin (10 mg/kg, i.p.) to activate the LC (Stone EA and Lin Y, unpublished observations). Preliminary results have shown that the both lesions significantly attenuated the prazosin-induced behavioral inactivity but only in the initial 15 min of the test. Thereafter, the animals became profoundly inactive. The cause of the late-occurring inactivity is not presently known.

It is also not clear if the two main noradrenergic nerve bundles, dorsal and ventral, have different functions with respect to behavioral inhibition. Early studies utilizing electrolytic lesions had suggested a significant difference with the dorsal bundle mediating behavioral activation and the ventral, behavioral inhibition (Kostowski et al., 1978), however, more recent studies with neurotoxic lesions have suggested the reverse with the dorsal bundle more closely associated with behavioral depression and the ventral with the anti-immobility effects of antidepressants (Cryan et al., 2002). However, arguing against differential functions, it has been found that injection of lipolysaccharide endotoxin at 180 μg/kg in rats, which produces virtually complete behavioral inactivity, markedly increases Fos expression in A2 (150 fold), A1 (20 fold) and LC neurons (50 fold) suggesting that both systems are hyperactive in the inactive animals (Hare et al., 1995).

Further partial support for the behavioral inhibition hypothesis, but with qualification, has come from studies of genetically epilepsy prone rats (GEPR). These animals have a genetic impairment in noradrenergic function causing reduced turnover of the transmitter in most regions of the brain (Jobe et al., 1986), but also have lower levels of brain 5HT (Merrill et al., 2007). Studies of their behavioral activity in an open field reveals significant chronic hyperactivity (Jobe and Weber, 2006). However, in contrast with DSP4 and DBH-SAP ITX lesioned animals, the GEPR show significantly greater immobility in the forced swim test (Jobe, 2004). Whether the behavioral hyperactivity and increased swim immobility are differentially related to their noradrenergic and serotonergic abnormalities has not yet been determined.

Interestingly, as mentioned above, a difference also seems to be emerging with regard to the function of α_1- and α_2-adrenoceptors in or near the LC in the above behavioral effects. Although Weiss and colleagues (ibid) originally demonstrated an anti-immobility effect of stimulation of α_2-receptors of the rat LC, there has been some controversy as to whether α_2-receptors in neighboring regions are also involved (Cervo et al., 1990; Cervo and Samanin, 1991). In this regard, we have recently found that intraventricular DSP4 abolishes the increased immobility in mice in tail suspension and repeated forced swimming tests caused by 4th ventricular infusion of the α_1-blocker, terazosin, but has no effect on the heightened immobility due to a similar infusion of the α_2-antagonist, atipamezole (Stone EA, Lin Y, and Sarfraz, Y, unpublished observations). This suggests that the depressant effects of blockade of α_2-receptors are less dependent on an intact LC and/or DR than those of the blockade of α_1- and further supports a differential localization or function of the two receptors.

In summary, most of the above neuropharmacological findings support the hypothesis that the LC is involved in the inhibition of behavioral activation under a variety of conditions. Whether the partially conflicting results found with tonic optogenetic stimulation and inhibition of the LC will be borne out, awaits further data on the effects of these treatments on forebrain noradrenergic neurotransmission and dark period behavioral activation, respectively. Assuming the hypothesis will prove to be valid, however, it is still not clear whether the system is equally effective in inhibiting activity in the more behaviorally

demanding tests of depression (forced swim, tail suspension) compared to the less provocative conditions of the open field and home cage although considerable overlap has now been demonstrated in experiments manipulating transmission at LC α_1-receptors. With these caveats, therefore, the findings are in support of the view that a hyperactivity of this system is a contributing etiological factor in depression. Although the present review is concerned primarily with preclinical studies, the hypothesis is also supported by a number of previous clinical studies, reviewed elsewhere (Itoi and Sugimoto, 2010), which have shown evidence of heightened central noradrenergic activity in depressed patients. This has included evidence of elevated levels of NE in CSF (Wong et al., 2000) and of CRF in the LC (Bissette et al., 2003) and CSF (Arborelius et al., 1999) as well as increased tyrosine hydroxylase activity (Ordway, 1997) and glutamatergic neurotransmission in the LC (increased NR2C protein) (Karolewicz et al., 2005). Together these results encourage the further development of therapeutic drugs that reduce LC activity.

However, it is also clear from these and other studies that the LC is not the only brainstem monoaminergic nucleus involved in behavioral suppression as the DR and possibly lateral tegmental noradrenergic nuclei are also involved as discussed above.

Whether or not the above findings on behavioral inhibition contradict or agree with the functions attributed to the LC listed in the introduction is difficult to assess because of major differences in the measures and methodology employed in the respective studies. Thus the experiments described above on inhibition have primarily utilized measures of gross behavioral activity and relatively gross temporal and pharmacological manipulations of central noradrenergic function whereas the studies of LC function referred to in the introduction have involved electroencephalographic or other electrophysiological measures with more finely resolved or subtle sensory and behavioral processes. Furthermore, most of the earlier hypotheses do not readily lead to specific predictions regarding gross behavioral activation in tests of locomotor activity or models of depression in rodents. However, some general comparisons can be made. First, the present results do not contradict the arousal or sensory regulation hypotheses of LC function since behavioral inhibition may be associated with heightened arousal and/or signal detection (Berridge and Waterhouse, 2003). Second, the present results are also in general agreement with previous findings on the role of α_1-noradrenergic activity during stress on cortical function involved in short term memory processes (Arnsten et al., 1999). Thirdly, several of the earlier LC functions are based to a large degree on observations of close temporal correlations between LC activation and sensory stimulation or changes in behavioral function. While these correlations may, in fact, reflect the role of the noradrenergic system in sensory regulation or decision processes, it is also possible that they function to inhibit the excessive spread of neural activation during these arousing conditions. Exogenous NE and the noradrenergic system have been established to have potent anti-seizure properties that are mediated by primarily by α_1-adrenoceptors in forebrain areas (Ko et al., 1984; Mishra et al., 1993; 1994; Weinshenker et al., 2001; Yan et al., 1998) and possibly also via the release of galanin (Lerner et al., 2008). The activation of this system may function, therefore, to quell this activity throughout the forebrain. This is supported by the finding that Fos expression throughout the CNS to sensory stimulation is greatly enhanced by the systemic blockade of α_2-adrenoceptors (Gubits et al., 1989), which appears to cause a widespread disinhibition of glutamatergic neurotransmission in the forebrain (Marcus et al., 2005; Simson, 2001).

A shortcoming of the above research is its failure thus far to establish the roles and cellular locations of the individual subtypes of α_1-adrenoceptors involved in these functions. Our previous investigation with antagonists administered in the lateral ventricle suggested that the α_{1B}- is the one most closely associated with the regulation of behavioral activation in the mouse (Stone et al., 2001a). Whether this receptor is located in the LC, however, is still

controversial with one immunohistochemical study reporting its absence in mouse brain (Papay et al., 2004) and a second reporting the presence of its mRNA in single rat LC neurons (Osborne et al., 2002). This same receptor appears to be located extensively on the principal neurons in mouse cortical regions involved in behavioral activation (Papay et al., 2004) whereas the α_{1A}-subtype appears to be largely restricted to interneurons (Papay et al., 2006). Because of the lack of highly selective ligands for these receptors, their roles in behavioral activation are still incompletely understood. α_1-Receptors may also be present on afferent terminals to the LC and affect transmitter release at this nucleus since presynaptic α_1-receptors have been found in various brain regions to regulate the release of NE (Aono et al., 2007), DA (Auclair et al., 2002) , glutamate (Marek and Aghajanian, 1999b) and GABA (Lei et al., 2007) and since there is a lack of correlation between α_1-receptor binding sites and the density of LC neurons (Chamba et al., 1991). Furthermore, there is also confusion regarding the endogenous catecholamine ligand for these LC receptors and whether this is epinephrine derived from the n. paragigantocellularis/C1 (Pieribone and Aston-Jones, 1991), norepinephrine from either the LC itself (recurrent collaterals) (Nakamura et al., 1988) or from other noradrenergic nuclei (Maeda et al., 1991), or dopamine from either the ventral tegmental area (Deutch et al., 1986) or A13 cell group in the hypothalamus (Kitahama et al., 2007).

A recent study has demonstrated that whole brain α_{1B}-adrenoceptor overexpression in mice produces pro-depressive effects on the forced swim test and open field hyperactivity whereas expression of a constituitively active mutant α_{1A}-receptor as well as chronic stimulation of the latter receptors with systemic cirazoline has antidepressant actions (Doze et al., 2009). Where in the brain these chronic, systemic effects are operating, however, is not yet known but obviously represent the future direction for research in this area. We have found in preliminary studies that acute systemic treatment with low doses of cirazoline (0.1 mg/kg) depresses behavioral activation in mice in the novel cage test although it is not known whether this is due to stimulation of peripheral, LC or forebrain α_{1A}-receptors (Stone EA and Lin Y, Unpublished experiments).

3. Mechanisms for Neural and Behavioral inhibition

The most obvious mechanism by which noradrenergic activity could inhibit behavioral activation is via the inhibition of synaptic transmission of afferents to output neurons in brain regions that mediate the organization and execution of motor programs. Consistent with this mechanism, noradrenergic activity has been found to inhibit baseline (background) neuronal firing rates in output neurons in a wide range of forebrain structures including the hippocampus (Segal and Bloom, 1974; 1976), prefrontal (Mantz et al., 1988; Olpe et al., 1980), cingulate (Olpe et al., 1980), parietal (Lecas, 2004; Taylor and Stone, 1980), visual (Olpe et al., 1980; Sato et al., 1989), and cerebellar cortex (Bickford-Wimer et al., 1991), amygdala (Chen and Sara, 2007) and motor thalamus (Rivner and Sutin, 1981) although not in several midbrain structures including the dorsal raphe (Baraban and Aghajanian, 1980) and lateral geniculate (Menkes et al., 1981). The inhibitory changes have been found to be mediated most often by ß-adrenoceptors (Chen and Sara, 2007; Olpe et al., 1980; Sato et al., 1989). An inhibitory effect on baseline firing has also been observed in the ventral tegmental dopaminergic neurons although only at high rates of LC activity (Grenhoff et al., 1993). In contrast to baseline activity, however, neuronal activity that is evoked by sensory input does not appear to be uniformly inhibited as a number of investigators have shown increased activation of sensory and motor neurons, frequently, but not always, during low or moderate levels of LC activation (Berridge and Waterhouse, 2003; Waterhouse et al., 1998). How these opposing effects on background and evoked activity are integrated and affect behavioral output is not presently clear. However, in contrast with low/moderate rates of LC impulses, high rates, which occur with stress, seem to reduce both background and evoked

activity in these regions (Berridge and Waterhouse, 2003). Several factors have been discovered which may mediate the latter inhibitory actions.

3a. Galanin release in the ventral tegmental and forebrain areas

Dopaminergic neurons of the ventral tegmental area (VTA) represent the chief motivational and behavioral activation system of the brain via afferents to mesolimbic and mesocortical regions. Dorsal noradrenergic input to this structure has a biphasic action, accelerating the firing rate of dopaminergic neurons with single pulse LC stimulation and inhibiting it at burst-type stimulation (Grenhoff et al., 1993). The excitatory effect appears to be mediated by the activation of α_1-receptors and is blocked by prazosin whereas the inhibitory effect had been suggested to be the result of the release of the noradrenergic cotransmitter galanin, a peptide known to inhibit VTA neurons (Gopalan et al., 1993) and to be released at high noradrenergic firing rates (Grenhoff et al., 1993). Weiss and colleagues proposed that depressive-like behavior occurring during stress therefore is due to galanin release in the VTA and have presented confirmatory evidence for this hypothesis (Weiss et al., 2005). Since galanin is also present in other forebrain noradrenergic afferents (Chepurnov et al., 1998), this inhibitory action might occur widely in cortical and subcortical regions subserving behavioral organization and activation and form the basis for the potent antidepressant actions of the galanin antagonists M35, SNAP-37889 and SNAP-398299 (Ogren et al., 2006). Galanin also has potent anti-seizure activity at both GalR1 and GalR2 receptors (Lerner et al., 2008) which could contribute to the anti-seizure activity of the noradrenergic system.

It should be noted that the galanin hypothesis may also finally clarify the mechanism by which NE depleting drugs produce behavioral inactivity. It had been commonly assumed that the latter effect is due to a depletion of the catecholamine in noradrenergic projection areas in the forebrain. However, the galanin hypothesis suggests that the inactivity results instead from a loss of NE in the LC causing hyperactivity of this nucleus, due to the reduced stimulation of inhibitory α_1- and α_2-receptors, with a consequent high release of galanin in forebrain structures. It would therefore be of interest to determine if galanin antagonists block the behavioral inactivity produced by brain NE depletion.

In this regard it is also relevant to consider another type of depletion of brain NE, that caused by the knock-out of the dopamine-β-hydroxylase gene (Thomas and Palmiter, 1997). These animals totally lack brain NE and have been shown to have normal or reduced home cage activity as well as reduced motor function in a swimming task. They also do not respond to noradrenergic antidepressants in the tail suspension or forced swim tests (Cryan et al., 2004). As they lack the noradrenergic neurotransmitter it would be expected that they would have low or no neurotransmission at α_1-receptors. However, it was found that infusion of the α_1-antagonist, terazosin, in the dorsal pons near the LC produced marked behavioral inactivity in these animals that was as profound as that shown by similarly infused wild-type mice suggesting that α_1-receptors are, in fact, active in the KO mice (Lin et al., 2008). The only catecholamine present in these animals is DA and it was therefore suggested that DA was partially activating α_1-receptors possibly accounting for the modest impairment of motor function and the resistance to noradrenergic but not serotonergic antidepressants. Furthermore, the fact that reserpine, which depletes DA as well as NE, produces the same profound inactivity as α_1-blockade is consistent with this view. However, this finding is not yet definitive since reserpine also depletes brain 5HT, which also plays a major role in behavioral activation (Mignon and Wolf, 2007).

3b. Activation of CRF-neurons in stress-related and other nuclei by the ventral noradrenergic bundle

The ventral noradrenergic bundle carries afferents from the lateral tegmental noradrenergic nuclei (A1 and A2) to corticotrophin releasing factor (CRF)-containing neurons in stress nuclei of the paraventricular hypothalamus (PVH) (Kiss and Aguilera, 2000), bed nucleus of the stria terminalis (BNST) (Delfs et al., 2000; Forray and Gysling, 2004; Gray, 1993; Khoshbouei et al., 2002; Phelix et al., 1994) and central nucleus of the amygdala (CeA) (Nunez et al., 2010; Raber et al., 1995), and may activate these neurons by stimulation of α_1- (Cecchi et al., 2002; Forray and Gysling, 2004; Kiss and Aguilera, 2000; Koob, 1999) or β-adrenoceptors (Aston-Jones et al., 1999). Noradrenergic afferents may also contact CRF-containing neurons in a variety of other forebrain structures as well (Gray, 1993). The CRF-containing neurons of the BNST and CeA communicate with a wide range of forebrain structures (Gray, 1993; Heinrichs and Koob, 2004; Swanson et al., 1983). High densities of CRFR1 receptors are found on pyramidal cells throughout the neo- and paleocortex and hippocampus (Chen et al., 2000), regions involved in the organization and activation of motor activity. While the precise behavioral functions of the various CRF receptors in forebrain areas are still incompletely understood, nevertheless, it is possible that the CRFR1 relays a ventral noradrenergic α_1-adrenergic signal to inhibit ongoing behavioral activity via the inhibition of excitatory glutamatergic neurotransmission in these areas (Forray and Gysling, 2004; Koob, 1999). Thus, the ventral noradrenergic bundle may trigger a widespread inhibition of forebrain output neuronal activity and induce behavioral inhibition via this stress network.

3c. Inhibition of glutamatergic neurotransmission by forebrain α_1-adrenoceptors

Although the above galanin mechanism would seem to rule out a participation of forebrain NE itself in behavioral inhibition there are still two types of findings that support its possible role: the inhibition of glutamatergic neurotransmission in principal forebrain neurons by NE acting at adrenergic receptors and the ability of selective pharmacological stimulation of these forebrain receptors to suppress behavioral activation. These are considered below for the α_1-, α_2- and β-adrenoceptor. Moreover, the postsynaptic α_1- adrenergic receptors in the forebrain, which would be strongly activated and inhibit glutamatergic neurotransmission during high LC activity, are directly involved in the anticonvulsant action of this system (Seo et al., 2000) and thus would contribute to the correlation between the anti-behavioral activity and anti-convulsant functions of the noradrenergic system.

Although α_1-adrenoceptors had been thought to uniformly mediate neuronal excitation throughout the CNS (Bradshaw et al., 1981; Hermann et al., 2005; Marek and Aghajanian, 1999a), several groups have now demonstrated that these receptors can inhibit glutamatergic neurotransmission in several forebrain structures including the medial prefrontal, temporal and entorhinal cortex and BNST (Dinh et al., 2009; Law-Tho et al., 1993; Lei et al., 2007; McElligott and Winder, 2008). One group has observed that the stimulation of α_1-receptors in the monkey prefrontal cortex silences pyramidal neurons normally active during memory trace experiments (Arnsten et al., 1999). The location of the responsible α_1-receptors has not, however, been established. One subgroup of these receptors, α_{1A}-, however, appears to be located on forebrain interneurons and to cause excitation with release of GABA (Braga et al., 2004; Papay et al., 2006).

In support of an inhibitory role of forebrain α_1-receptors in active behavior, Weiss and colleagues showed that infusion of the α_1-agonist, PE, in the lateral ventricle inhibited activity in the forced swim test of rats (Weiss et al., 1986). However, another group found only enhanced behavioral activity in the same test with a higher dose of PE in the lateral ventricle (Kitada et al., 1983a). Neither group, however, employed a full agonist, and it

would therefore be of interest to repeat this experiment with 6FNE and measure the activity of forebrain pyramidal neurons in the swimming animals using Fos expression.

An inhibitory role of forebrain α_1-receptors on seizure activity has been supported by the reduction of audiogenic seizures after intraventricular infusion of PE (Ko et al., 1984) and infusion of PE or methoxamine into the superior colliculus of GEPR rats (Yan et al., 1998). The latter effect was reversed by co-infusion of prazosin which also blocked a similar anticonvulsant effect of infusion of the NE reuptake inhibitor, nisoxetine. α_1-Receptor stimulation also produces anti-convulsant effects in the metrazol model and in mice genetically depleted of NE (Weinshenker et al., 2001). It should be noted, however, that because of the opposing actions on forebrain noradrenergic neurotransmission of activation of α_1-receptors in the LC versus those in the forebrain, the functional effects of stimulation of receptors in these two locations will be opposite for both behavioral activation and seizure activity although these two functions will remain correlated under each condition.

3d. Inhibitory α_2-adrenoceptors in forebrain structures

Postsynaptic α_2-adrenoceptors are also known to inhibit glutamatergic neurotransmission in forebrain pyramidal neurons (Ji et al., 2008), although in some regions excitatory effects have been observed (Carr et al., 2007). Presynaptic α_2-receptors, possibly located on dopaminergic terminals, in the prefrontal cortex may also have an inhibitory effect in association with D2 dopaminergic neurotransmission (Marcus et al., 2010). Several groups have found that selective stimulation of postsynaptic α_2-receptors produces hypoactivity in open field tests in rats (Herman et al., 1976; Nassif et al., 1983; Spyraki and Fibiger, 1982) but not in mice (Heal et al., 1989) possibly reflecting a difference in the sensitivity of postsynaptic receptors between the two species. In agreement, local selective blockade of α_2-receptors in the monkey prefrontal cortex has been shown to lead to behavioral hyperactivity (Ma et al., 2005). Clozapine, which facilitates prefrontal cortical glutamatergic neurotransmission via combined blockade of α_2-adrenergic and D2 dopamine receptors, has been shown to enhance frontal cortical cognitive function and reduce suicidality in schizoaffective disorders (Meltzer et al., 2003). In addition, blockade of NE reuptake with desmethylimipramine (DMI) has long been known to produce hypoactivity in rodents which might be the result of stimulation of postsynaptic α_2-receptors in forebrain regions by endogenous NE. In agreement, we and others recently found that prior blockade of these receptors with systemic atipamezole in mice attenuates the hypoactivity in mice in the open field after DMI as well as enhances Fos expression throughout the neocortex (Boyce-Rustay et al. 2008; Stone, EA and Lin, Y, unpublished observations).

3e. ß-adrenoceptors

β-adrenoceptors have also been shown to inhibit excitatory neurotransmission in forebrain pyramidal neurons (Chen and Sara, 2007; Olpe et al., 1980; Sato et al., 1989). Two groups have reported behavioral inhibition in the forced swim test in rats after selective stimulation of postsynaptic β-receptors in forebrain regions by ivt. infusion of ISO (Kitada et al., 1983b; Weiss et al., 1986) although a third has reported antidepressant effects of this compound in a differential reinforcement of low rates task (Zhang et al., 2001). As above, it would be of interest to examine Fos expression in forebrain pyramidal neurons after ivt ISO in these two tasks. Findings on the relationship of β-receptor activity and seizure activity, however, have been inconsistent (Ko et al., 1984; Luchowska et al., 2001; Weinshenker et al., 2001).

4. Summary

A broad range of behavioral, and neuropharmacological studies now support the hypothesis that one of the functions of the central noradrenergic system is the inhibition of behavioral

activation during stressful conditions and that this function may be related to its involvement in depressive illness. This behavioral effect appears to occur as a result of the inhibition of neural activity in output neurons in forebrain regions during period of elevated noradrenergic activity and may be mediated by neurotransmission at galanin, CRF or the adrenergic receptors themselves. The hypothesis is consistent with clinical evidence of central noradrenergic hyperactivity in depressed patients, supports the view that it is the hyperactivity rather than hypoactivity of this system that plays an etiological role in the disorder, and encourages the development of new and improved therapeutic methods to selectively inhibit LC function.

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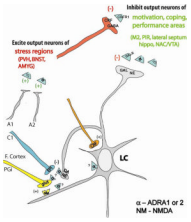

Fig 1.

Depicts the noradrenergic elements hypothesized to be involved in behavioral inhibition. LC neuron firing rates are regulated by a variety of afferent inputs including glutamatergic neurons from the PGi (Ennis et al., 1992) and neocortex (Zhu et al., 2004) acting at NMDA receptors (Ennis and Aston-Jones, 1988), CRF from the AMYG (Van Bockstaele et al., 1998), EPI from C1(Pieribone et al., 1988) and NE and possibly DA from recurrent collaterals of the LC itself (Nakamura et al., 1988) or from other brainstem noradrenergic nuclei acting at α_1-, α_2- and β-adrenoceptors (not shown). The LC projects primarily to forebrain regions involved in sensorimotor organization and motivational processes which are assumed to be inhibited during high rates of LC discharge via galanergic and adrenergic receptors (see text). Stress areas of the PVH, BNST and AMYG receive noradrenergic innervation chiefly from the lateral tegmental brainstem nuclei, A1 and A2 (Aston-Jones et al., 1999), and partially from the LC, all via α and β-adrenoceptors (Koob, 1999; Ma and Morilak, 2004) . Stress areas send inhibitory efferents containing CRF and GABA to the sensorimotor and motivational regions and thus convey the noradrenergic signal from A1 and A2 neurons to these areas (see text for details).

Table 1

Simplified summary of main lines of evidence for noradrenergic behavioral inhibition hypothesis. The upper three rows represent the clearest conditions in which the inhibition or activation of the LC function by alpha receptor agonists, LC lesions or alpha antagonists produces parallel changes in NE and Gal release in forebrain regions causing parallel changes between behavioral activation and seizure vulnerability and reciprocal changes of each with depressive behavior. More complex conditions are represented in the bottom four rows in which the manipulation causes or may cause a differential effect on terminal release of NE and Gal which presumably disrupts the correlations between the three functions.

MANIPULATION	FOREBRAIN NORADRENERGIC TRANSMISSION		BEHAVIORAL ACTIVATION	DEPRESSION	SEIZURES
	NE	GAL			
Stimulation of LC alpha-1/2 receptors: -6FNE, PE, clon, DMT	↓	↓	↑	↓	↑
LC lesions (Ivt DSP4, ITX, 60HDA)	↓	↓	↑	↓	↑
Blockade of LC alpha-1/2 receptors: -praz, teraz, yoh, atipam	↑	↑	↓	↑	↓
GEPR	↓	?	↑	↑	↑
Antidepressants (noradrenergic)	↑	↓[1]	↓	↓	↓
DBH-/-	↓	**0**	↓?[2]	↑?[3]	↑
NE depleting drugs (reserpine et al)	↓	↑?	↓	↑	↑

[1] presumed reduction

[2] indicates disagreement between findings of stimulant- and non-stimulant-induced motor activation (Weinshenker et al. 2003)

[3] indicates reduced response to some antidepressants without change in baseline depressive behavior (Cryan et al. 2004)