Perspective

Emerging Evidence for a Central Epinephrine-Innervated α_1-Adrenergic System that Regulates Behavioral Activation and is Impaired in Depression

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Currently, most basic and clinical research on depression is focused on either central serotonergic, noradrenergic, or dopaminergic neurotransmission as affected by various etiological and predisposing factors. Recent evidence suggests that there is another system that consists of a subset of brain α_{1B}-adrenoceptors innervated primarily by brain epinephrine (EPI) that potentially modulates the above three monoamine systems in parallel and plays a critical role in depression. The present review covers the evidence for this system and includes findings that brain α_1-adrenoceptors are instrumental in behavioral activation, are located near the major monoamine cell groups or target areas, receive EPI as their neurotransmitter, are impaired or inhibited in depressed patients or after stress in animal models, and are restored by a number of antidepressants. This 'EPI-α_1 system' may therefore represent a new target system for this disorder.
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INTRODUCTION

Depressive illness is currently believed to result from environmental (stress) and genetically induced alterations in neurotransmission in one or more of the central monoaminergic pathways (noradrenergic, serotonergic, and dopaminergic) mediated by a complex web of factors including corticotropin-releasing factor, hypothalamic–pituitary–adrenal hormones, and cytokines (Anisman *et al*, 2002; Nemeroff, 2002; Nestler *et al*, 2002). With regard to monoaminergic function, most recent basic and clinical research has been focused on the serotonergic system owing to the success of serotonin-selective antidepressants, while the role of the noradrenergic function has been relatively neglected. However, recent work by our group and others, considered in the light of past research, has provided compelling new evidence linking one of the brain's adrenoceptors (α_1) and the 'minor' brain neurotransmitter, epinephrine (EPI), to this disorder. This evidence suggests that there is a putative EPI-innervated α_1-receptor system that is critical for the regulation of active behavior and functions by causing a parallel excitation of the three major monoaminergic systems. This new system appears to be impaired during stress and depression and thus may represent a new target for this disorder. The evidence is reviewed here.

ROLE OF α_1-ADRENOCEPTORS IN BEHAVIORAL ACTIVITY

The new evidence largely concerns a clarification of the role of α_1-adrenoceptors in behavioral activity. One of the core behavioral symptoms of depression is a profound loss of interest in previously pleasurable, nonessential activities. Particularly impaired are those activities that are mediated by positive motivation and entail a fair degree of sustained effort such as hobbies and avocations, sports, socialization, entertainment, 'going out', etc.

From a neurobiological viewpoint, a reduction in positively motivated effortful behavioral activity would most likely be caused by a reduction of central dopaminergic neurotransmission in basal ganglia circuits. In agreement, a number of studies have shown that there is a reduced level of DA and its metabolites in the CSF of depressed patients (Brown and Gershon, 1993) and also a reduced release and metabolism of DA in the basal ganglia of animals subjected to stressors that induce behavioral depression (Cabib and Puglisi-Allegra, 1996). This reduction, however, does not appear to be caused by a direct impairment of the dopaminergic neurons or postsynaptic receptors themselves (Weiss *et al*, 1996; Cabib *et al*, 1998;

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Ossowska et al, 2001; Herman et al, 1984; Zebrowska-Lupina et al, 1988), but may occur instead in an afferent system that modulates dopaminergic function. One such afferent system that is particularly sensitive to stress and has been implicated in depressive illness is the α_1-adrenergic (Lipinski et al, 1987; Stone and Quartermain, 1999).

α_1-Adrenoceptors are G-protein coupled receptors that are widely distributed in the CNS and periphery and that are involved in a wide variety of behavioral, autonomic, and neuroendocrine functions. These include motor activity (see Stone et al, 1999 for references), attention and vigilance (Aston-Jones et al, 1994), fear and anxiety (Arnsten et al, 1999; Fujimaki et al, 2000; Yang et al, 1990), reinforcement (Woolverton, 1987), sensory gating (Bakshi and Geyer, 1999), learning (Ferry et al, 1999; MacDonald and Sirvio, 1999), sexual behavior (Chu and Etgen, 1999), and regulation of blood pressure (Hieble et al, 1999) and of both the hypothalamic–pituitary–adrenal (Feuvrier et al, 1998) and hypothalamic–pituitary–gonadal systems (Dubocovich et al, 1990).

It is currently thought that the α_1-receptors involved in motor activity exert this function in large part via modulatory effects on dopaminergic neuronal firing rate (Berretta et al, 2000; Grenhoff et al, 1993, 1995), presynaptic release of DA (Gioanni et al, 1998; Mathé et al, 1996; Auclair et al, 2002), and/or potentiation of postsynaptic dopaminergic signaling (Eshel et al, 1990). However, DA-independent effects may also be involved since many α_1-receptors are located on motorneurons downstream of dopaminergic neurons (Hou et al, 2002) and also on or near serotonergic and noradrenergic neurons (Morin et al, 1996).

In previous years, it had been difficult to study these α_1-receptors because prazosin, the prototypical α_1-antagonist used by most investigators, is poorly soluble in saline and cannot be given centrally in high enough doses to block the brain's population of these receptors. To address this problem, our group began to study another α_1-antagonist, terazosin, which has the same receptor selectivity as prazosin but is 20 times more soluble.

The initial experiment was a dose–response analysis in mice of the effect of intraventricular (ivt.) terazosin on behavioral activity stimulated by change to a novel cage (Stone et al, 1999). This 'cage-change' test produced sustained exploration in mice for 1–2 h with minimal anxiety, since the novel cage was the same type as that which the animal was housed in. Terazosin produced a striking dose-dependent complete inhibition of all movement, leaving the animals cataleptic at the highest dose (31.6 nmol/mouse). This effect was selective to the α_1-receptor blocker, since similar experiments with an α_2- (RX821002), β_1- (betaxolol), or β_2-antagonist (ICI118551) produced weaker or no effects. The terazosin-treated mice were not significantly sedated since they showed normal righting reflexes and could support themselves for 30 s on a taut horizontal wire; by contrast, akinetic chlordiazepoxide-treated mice fell off within 10 s. The animals showed a slowed respiratory rate and hypothermia but had only a slight reduction in blood pressure (5 mmHg).

To verify that the immobility was the result of α_1-receptor blockade rather than some nonspecific toxic effect of the drug, the agonist, phenylephrine (PE), was coinjected with the terazosin to determine if it would reverse the inactivity, which it did. Furthermore, we showed that terazosin, at the highest dose, retained its selectivity for α_1 vs DAergic or α_2-receptors, as it did not protect D1-receptors from in vivo alkylation by N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) (but did protect α_1-receptors), did not displace a D2-specific ligand from striatal D2-receptors up to 10^{-4} M, and did not reduce the ex vivo binding of an α_2-specific ligand, but did abolish that of an α_1 ligand in the cerebral cortex.

To determine how closely the loss of active behavior paralleled the blockade of brain α_1-receptors, a range of doses of terazosin was injected ivt. and the resulting behavioral inactivity scores of the animals were correlated with measures of the ex vivo binding of [3H]prazosin to α_1-receptors in their cerebral cortices, which were obtained immediately after the behavioral test (Stone et al, 2001c). A very high and significant correlation was obtained ($r = 0.95$). This experiment was next repeated with i.p. prazosin instead of ivt. terazosin. The former drug had to be given at very high doses (16–32 mg/kg) in order to pass the blood–brain barrier in these animals. (The low doses of prazosin generally used in behavioral research (0.5–2.0 mg/kg) did not significantly reduce ex vivo α_1-binding in the cerebral cortex of our mice (male Swiss Webster) in support of similar findings by others for the mouse (Lindroos et al, 1984) and dog (Taylor et al, 1977).) A similar and near-perfect correlation was obtained again between loss of α_1-binding sites and loss of active behavior, which made it virtually certain that these receptors controlled behavioral activity in this species. These close relations between behavior and α_1-receptor binding were in agreement with earlier studies of α_1-binding in the spinal cord and startle behavior (Astrachan et al, 1983a, b).

We next attempted to determine which subtype of α_1-receptor mediated the motor activation. The mammalian brain is known to possess the genes and express the mRNA of three α_1-receptors, 1A, 1B, and 1D. The proteins for only two of these (α_{1A} and α_{1B}) have so far been found in brain tissue (Garcia-Sainz et al, 1999; Schwinn, 2000; Yang et al, 1998). No highly specific antagonists of these subtypes were available that could be used to unambiguously identify the responsible receptor. Therefore a series of α_1-antagonists having a range of affinities for the subtypes was injected ivt and their affinities to inhibit active behavior in the novel cage test (inhibitory dose 50%) was correlated with their known affinities to bind to the cloned receptors (K_i values). A high correlation would identify the receptor in question. Six antagonists were used: terazosin, benoxathian, phentolamine, 5-methylurapidil, BMY7378, and WB4101. Behavioral ID_{50} values were obtained from 9–11 point dose–response curves for each antagonist against activity in the novel cage test. Binding affinities were obtained from the literature by computing the average of all published values (3–11 studies) for these antagonists at cloned α_{1A}-, α_{1B}-, and α_{1D}-receptors. The results showed a high and significant correlation for α_{1B} (0.89), with none for either the α_{1A}- (0.27) or α_{1D}-receptors (0.13). This finding agreed with a previous study that showed that agonists of α_{1B}-receptors, but not of α_{1A} or α_{1D} were effective in the reversal of cataplexy in narcoleptic dogs (Nishino et al, 1993).

These results, however, appeared to be in partial disagreement with findings from genetically altered mouse strains. An α$_{1B}$-receptor deficient mouse strain had been generated (Cavalli et al, 1997) and had been reported to show 'normal' activity in a novel chamber or open field (Spreng et al, 2001); however, a second group did report a significant reduction in the open field activity with this strain (Knauber and Muller, 2000). In order to determine if there was compensation for the loss of the α$_{1B}$-receptor in the mutant mice, we challenged them with large doses of the stimulant, modafinil. The latter drug appears to stimulate motor activity in part by activation of central α$_1$-receptors (Duteil et al, 1990; Simon et al, 1995; Stone et al, 2002a). The mutants were found to be less than half as responsive as their wild-type conspecifics to the highest modafinil dose (40 mg/kg) (Stone et al, 2002a). Drouin et al (2002) had performed a similar experiment using three other stimulants also believed to act in part via α$_1$-receptors, amphetamine, cocaine, and morphine, and had found the α$_1$ mutants to be much less active than wild-type controls in response to each given i.p. In a further preliminary experiment, we found that ivt. terazosin can completely inhibit novel cage activity in the α$_{1B}$ mutant mice (Stone EA, Lin Y, and Quartermain D, unpublished findings), suggesting that the compensation is mediated by another α$_1$-receptor.

Blendy and colleagues have recently generated an α$_{1D}$-deficient strain and have reported that these mice show reduced rearing responses in a novel cage and reduced nocturnal wheel running in the home cage (Saldalge et al, 2002). Our inability to detect the role of the α$_{1D}$-receptor may be explainable by the fact that no one has yet succeeded in demonstrating any α$_{1D}$-binding in the brain of either the rat (Yang et al, 1997), mouse (Yang et al, 1998), or rabbit (Piao et al, 2000) using the above antagonists as displacing agents. Therefore the α$_{1D}$-receptor responsible for behavioral activation must have some unique property such as a potential location in the peripheral nervous system which in some way communicates with the CNS.

The above experiments therefore established that central α$_1$-adrenoceptors are essential for behavioral activation in response to either novelty or psychostimulant drugs. The primary subtype involved in the mouse brain is the α$_{1B}$-adrenoceptor but a second central α$_1$-receptor, as yet unidentified, can partially compensate for its loss during development.

BRAIN LOCALIZATION

A fundamental question regarding the motoric α$_1$-receptors concerns the brain sites that they operate in. α$_1$-Receptors are present in a broad range of structures including most motor, sensory, autonomic, and neuroendocrine-related areas (Acosta-Martinez et al, 1999; Day et al, 1997; Jones et al, 1985; Volgin et al, 2001; Williams and Morilak, 1997; Zilles et al, 1993). They are present at low densities in basal ganglia structures (corpus striatum, nucleus accumbens, ventral tegmental area, substantia nigra), at higher densities in prefrontal and motor cortices, hypothalamus, brainstem motor nuclei, cerebellum, and spinal motorneurons, and at very high densities in the olfactory bulb, thalamus, locus

coeruleus (LC), dorsal raphe (DR), piriform cortex, and amygdala. There is a species difference with regard to the hippocampus, which has a very low concentration in rodents, but in primates, including humans, has a very high concentration of these receptors primarily in the dentate gyrus (Palacios et al, 1987).

To investigate the localization, we tested the ability of microinjections of terazosin in discrete regions of the mouse brain to induce immobility in a 10 min exposure to a novel cage (Lin et al, 2002; Lin and Stone, 2001). At present we have tested 23 brain areas of which four have given definite positive responses (ie inactivity) and two potentially positive responses. The definite areas are the dorsal pons in or near the LC, the DR, the nucleus accumbens, and the cerebellum lobules lying dorsal to the fourth ventricle. Positive responses have also been obtained from the IV ventricle which suggests diffusion to nearby periventricular sites of either or both the dorsal pons and cerebellum. The potential areas are the medullary C2 area and medial preoptic area in which partial responses have been encountered.

It should be noted that two of the above definite sites, the dorsal pons and DR, are known to possess very high densities of α$_1$-receptors (Chamba et al, 1991; Jones et al, 1985; Zilles et al, 1993), whereas the cerebellum has been reported by some (Acosta-Martinez et al, 1999; Jones et al, 1985; Zilles et al, 1993), but not others (Palacios et al, 1987), to have a moderately high density. We have confirmed that there is a moderately high density of α$_1$-receptors in the cerebellum of the mouse strain used in the above experiments (male Swiss Webster) (Stone EA, Ahsan R, and Lin Y, unpublished results). As noted above, the nucleus accumbens also possesses α$_1$-receptors but at a lower density (Jones et al, 1985).

To control for nonspecific effects, we have shown further that the terazosin-induced immobility at each site can be reversed completely by coinfusion of the full α$_1$/α$_2$-agonist, 6-fluoronorepinephrine. A selective full α$_2$-agonist, dexmedetomidine, was ineffective in reversing the terazosin immobility. The selective α$_1$-agonist, PE, has been less reliable in reversing this immobility, probably owing to the fact that it is only a partial agonist at rodent brain α$_1$-receptors mediating phosphatidylinositol hydrolysis or potentiation of cAMP responses (Johnson and Minneman, 1986).

Owing to the small size of the mouse brain and the possibility of diffusion of terazosin to noninjected sites, the above conclusions remain tentative and will need to be confirmed by other methods and in larger animals. Nevertheless, the nucleus accumbens findings agree with previous work by Cools (1991), who has shown that stimulation of α$_1$-receptors in this area elicits motor activity in the rat. Others have found evidence for motoric α$_1$-receptors in the rat prefrontal cortex (Blanc et al, 1994; Gioanni et al, 1998; Trovero et al, 1992) and hippocampus (Plaznik et al, 1984). However, we have not found terazosin to induce immobility in either of these structures of the mouse brain, but this may be the result of the use of stimulant drugs or different behavioral tests, time periods, and species.

Surprisingly, we found that the terazosin produced the opposite effect, that is, an enhancement of motor activity, when injected into the dorsal hippocampus or lateral

septum. This suggests that α_1-receptors in the latter two regions suppress rather than excite behavioral activity. A similar effect had been reported by Kelsey (1976) for the rat septum. As will be discussed in the next section, the latter findings may be relevant to the role of α_1-receptors in vigilance and anxiety.

In preliminary work, we have examined the ability of α_1-agonists injected alone locally into these regions to induce behavioral activation in animals inactive in their home cages during the light period. So far we have found that 6FNE injected into the dorsal pons elicits sustained motor and exploratory behavior in the home cage (Stone EA, Lin Y, and Quartermain D, unpublished findings). The partial agonist PE has been less reliable in this regard.

The finding of positive motor sites in the DR, dorsal pons, and nucleus accumbens suggests that α_1-receptors regulate motor activity via effects on three major monoaminergic systems of the brain: the serotonergic, noradrenergic, and dopaminergic. Stimulation of α_1-receptors can produce excitation of neurons in the DR (Baraban and Aghajanian, 1980; Menkes *et al*, 1981; Ohliger-Frerking *et al*, 2002; Reinhard Jr *et al*, 1983; Rouquier *et al*, 1994), the LC (Nakamura *et al*, 1988; Williams and Marshall, 1987), and the pontine reticular formation (Stevens *et al*, 1994) and, as discussed above, can facilitate the release of DA in the nucleus accumbens. In addition, neurons in the vermis cortex of the cerebellum are known to send efferent fibers to the LC and ventral tegmental area (Snider *et al*, 1976) and to the DR (Chan-Palay, 1977), which regulate the activity of these monoaminergic nuclei (Cano *et al*, 1980; Snider and Snider, 1979). The above brain localization of the motoric α_1-receptors is consistent with the hypothesis that the α_1-system coordinates and controls behavioral activation.

EPI AS AN ENDOGENOUS NEUROTRANSMITTER AT α_1-RECEPTORS

A second fundamental question regarding this system concerns the identity of its endogenous catecholamine neurotransmitter. It has been widely assumed that it is NE, since the latter is the chief endogenous α_1-agonist in the brain and since early studies showed that ivt. NE injections elicited motor activity (Geyer *et al*, 1972; Segal *et al*, 1974) via an α-receptor (Kleinrok and Zebrowska-Lupina, 1971; Zebrowska-Lupina *et al*, 1977), while electrolytic lesions of the LC impaired motor activity (Donaldson *et al*, 1976; Kostowski *et al*, 1978). However, a role for NE was not supported by many subsequent lesion studies, showing that the destruction of central noradrenergic pathways by the more selective neurotoxin, 6-hydroxydopamine (6-OHDA), did not induce hypoactivity in rats (McNaughton and Mason, 1980) and that a virtually complete elimination of this catecholamine from the brain produced by multiple-site central 6-OHDA lesions, failed to affect the nocturnal activity of rats (Murrough *et al*, 2000). However, it should be noted that compensatory changes are known to occur after these lesions and that the lesion of the dorsal noradrenergic bundle by 6-OHDA can potentiate the catalepsy induced by morphine (but not by neuroleptics) (Mason *et al*, 1978). These findings suggest that NE has a limited role in neurotransmission at motoric α_1-receptors.

On the other hand, there is accumulating evidence of the fact that EPI is an important transmitter for these receptors. Although the tissue concentration of EPI is only a few percent of that of NE, the extracellular concentration of EPI in the rat hypothalamus measured by microdialysis (Routledge and Marsden, 1987a) or push-pull cannula (Phillipu *et al*, 1979) is equal to that of NE. EPI has traditionally been thought to be the endogenous ligand for brain postsynaptic α_2-adrenoceptors, based on the finding that α_2-receptors are upregulated in the brainstems of rats genetically low in brain EPI (BUF strain) (Vantini *et al*, 1984) or in animals treated chronically with inhibitors of phenylethanolamine-*N*-methyl transferase (PNMT) (U'Prichard *et al*, 1988). However, both rats of the latter strain and animals treated with PNMT inhibitors also show an equal upregulation of the density of brainstem α_1-adrenoceptors (presumably postsynaptic to the source of EPI) and, in addition, an enhanced motor response to ivt. catecholamine injection (Segal *et al*, 1975), suggesting that brain α_1- as well as α_2-adrenoceptors are innervated by EPI. This agrees with the finding that EPI has the highest efficacy of all tested catecholamines at α_1-receptors coupled to phosphatidyli-nositol hydrolysis or potentiation of cAMP responses in rat brain slices (Johnson and Minneman, 1986). Furthermore, pharmacological inhibition of PNMT, which causes a depletion of extracellular EPI but not of NE (Routledge and Marsden, 1987a), has been found to produce marked behavioral inactivity (Katz *et al*, 1978) and to abolish appetitive hypothalamic self-stimulation in rats and mice (Katz and Carroll, 1978), while stressors that release EPI, peripheral administration of EPI (Chopde *et al*, 1995; Yntema and Korf, 1987), and glucocorticoids that induce PNMT (Chopde *et al*, 1995) have all been found to reverse the catalepsy induced by neuroleptics probably via α_1-receptor stimulation. Ivt. EPI administration has also been shown to markedly enhance hypothalamic self-stimulation in rats (Hasegawa, 1975).

Although the above studies showed that inhibition of PNMT produces behavioral inactivity and a concomitant depletion of extracellular EPI, they did not test whether the behavioral change was the result of the neurochemical one. To test this, we therefore determined if ivt. injection of EPI would selectively reverse the behavioral inactivity in PNMT-inhibited mice (Stone *et al*, in press). Mice given one of two PNMT inhibitors, 1,2-dichloro-α-methylbenzylamine (DCMB) or LY134046 received, after 30 min, an ivt. injection of EPI (1–100 nmol), and were screened for gross movement in a novel cage test for the following hour. In support of the hypothesis, exogenous EPI was found to dose-dependently reverse the PNMT-inhibitor-induced in-activity starting at about 3 nmol/mouse and reaching a maximal effect (60% reversal) at 10–30 nmol. It was also found that a higher dose of ivt. EPI (100 nmol) could reverse the behavioral inactivity of untreated animals in their home cages during the light period (10.00–12.00 h). The home cage during the light period is, of course, a low-stimulation environment for mice during the trough of their circadian activity cycle and is likely to produce a low release of brain EPI (Roth *et al*, 1982; Sauter *et al*, 1980). The reason why higher EPI doses were required to activate the home-caged compared to the PNMT-inhibited mice is most likely due to the fact that depletion of the transmitter sensitizes (ie

reverses the ongoing desensitization of) the receptors (Katz *et al*, 1978; Watson *et al*, 2002).

Subsequent experiments with selective adrenoceptor antagonists infused ivt. with EPI showed that the above stimulatory effects of this amine in both the PNMT-inhibited and home-caged mice were due to activation of α_1-receptors. Furthermore, it was found that, in addition to EPI, three other α_1-agonists, NE, 6FNE, and PE also reversed the PNMT-inhibitor-induced inactivity and that the rank order of their maximal behavioral responses, EPI > 6F-NE > PE, matched the rank order of their maximal phosphatidylinositol hydrolysis responses *in vitro* in cells transfected with α_{1B}-receptors (NE was not tested).

The fact that three other agonists also reversed the PNMT-inhibitor-induced inactivity, however, appeared to argue against the uniqueness of EPI as a transmitter for the above α_1-receptors. This doubt was further reinforced by the additional finding that a noncatecholamine, 5-HT, was also capable of reversing DCMB inactivity. However, in support of EPI's role, we showed that its ability to reverse the DCMB-induced inactivity was the greatest of this group of agonists and also that EPI was the only agonist of the four that was capable of stimulating behavioral activity in the home-caged mice during the light period.

The above evidence therefore supports the hypothesis that EPI is an important endogenous catecholamine neurotransmitter at brain α_1-receptors involved in motor activity. The neurophysiological significance of this finding may be elucidated by a comparison of the neuroanatomic distributions of motoric α_1-adrenoceptors and EPI-containing neurons. As discussed above, motor-activating α_1-receptors have been detected in the dorsal pons in or near the LC, DR, cerebellum, and nucleus accumbens with the first three regions also showing high or moderately high densities of α_1-receptor binding sites. Also, as discussed above, the activation of α_1-receptors in these brain regions is known to enhance neuronal firing rates and/or the release or postsynaptic action of their monoamine neurotransmitters (Rouqier *et al*, 1994; Stevens *et al*, 1994; Williams and Marshall, 1987). PNMT-containing nerve endings have been shown to innervate the LC and DR (Hokfelt *et al*, 1984), while both EPI and its metabolite, metanephrine, have been found to be markedly elevated in the accumbens during stimulant-induced hyperactivity (Espejo and Miñano, 2001).

These findings led us to propose that there is a central EPI-innervated α_1-adrenergic system in the foregoing brain regions that activates motor behavior by producing either a parallel stimulation of three central monoaminergic systems, the noradrenergic, serotonergic, and dopaminergic, and/or an enhancement of their postsynaptic signaling (Figure 1). Serotonergic stimulation may predominate in this effect, since 5HT given without an α_1-agonist was found in the above study to be capable of reversing the PNMT-inhibitor-induced inactivity (but not the home-cage light-phase-induced inactivity), whereas DA was not. Dopaminergic stimulation of active behavior may require the coactivation of postsynaptic α_1- and DA-receptors to elicit the powerful synergy known to exist between the two on motor activity (Anden *et al*, 1973; Eshel *et al*, 1990). Noradrenergic activation may play a contributory role in behavioral activation or may be necessary to maintain arousal necessary for the latter to occur. As noted above, it
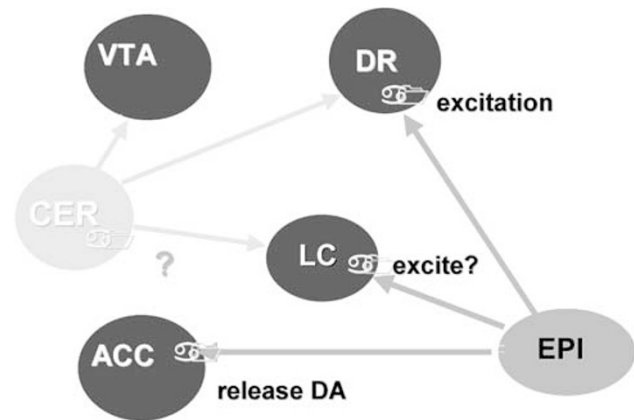

Figure 1 Cartoon showing relations between EPI innervation of α_1-adrenoceptors in DR, dorsal pons–LC, nucleus accumbens (ACC), and cerebellum (CER). EPI is believed to either excite output neurons in these structures or facilitate the release of DA in the ACC via its actions on local α_1-receptors. Also shown are efferent pathways from CER to the ventral tegmental area (VTA), DR, and LC. ? Indicates uncertainty that EPI is a neurotransmitter in CER which has a very low EPI tissue level.

cannot be decided from the present and previous findings whether NE itself contributes to the innervation of motoric α_1-receptors in these regions and therefore this possibility remains open.

As it currently stands, however, there are several problems with the foregoing hypothesis. First, the identity and properties of the neurons supplying EPI to the above brain regions is not yet clearly established. Second, excitation of EPI-containing neurons in the C1 area of the medulla has been found to inhibit rather than excite neuronal activity in the LC (Aston-Jones *et al*, 1992). Third, in the PNMT-inhibitor-treated mice ivt. EPI failed to restore rearing responses, a major component of exploratory behavior in rodents. Fourth, although EPI abolished immobility induced by PNMT-inhibition, it actually had a biphasic action reducing the latter behavior in doses up to about 10 nmol and then reinstating it at 30–100 nmol. Animals given the high doses showed alternating bouts of activity and immobility, and fifth, blockade of β_1-adrenoceptors enhanced the reversal effect of EPI in the PNMT-inhibited mice and restored their rearing responses.

With respect to the identity of the EPI-supplying neurons, there appear to be at least two types of neurons that serve this function in the brain (see reviews by Mefford, 1988, 1987 and Fuller, 1982). The first, which is similar to classical monoaminergic neurons, contains all the catecholamine-synthesizing enzymes, including PNMT, and is capable of storing small but measurable amounts of EPI. These neurons predominate in the C1, C2, and C3 regions of the medulla and send axons to a variety of brainstem and forebrain structures including the LC, DR and, nucleus accumbens (Hokfelt *et al*, 1984). The second type of neuron is capable of synthesizing NE but does not contain PNMT. The latter enzyme is present in adjacent brain neurons and glia, which apparently synthesize EPI from released NE and transport it back to the NE-containing neurons, which store and utilize it as a cotransmitter of NE. This neuronal type predominates in the hypothalamus. It is presently not clear what the proportions are of these two neuronal types in the brain regions containing the motoric α_1-receptors. It is also

not established whether either or both of these EPI neurons possesses high-affinity uptake for EPI and to what extent they are sensitive to various uptake blocking drugs or to destruction by 6-OHDA or DSP4 which require uptake for their neurotoxicity (Fuller, 1982; Routledge and Marsden, 1987b). Blockade of monoamine oxidase A leads to a greater proportional rise in EPI compared to NE, however, the only pharmacological method presently available for selectively manipulating CNS EPI release independent of NE release is the inhibition of PNMT.

The finding that activation of EPI-containing neurons in the C1 area depresses LC unit activity appears to argue against a role of EPI in the activation of the LC-noradrenergic system. However, it should be noted that this finding was made in anesthetized rats and has not yet been shown in unanesthetized animals. Furthermore, there does not appear to be a tonic inhibition of LC neurons by EPI as blockade of PNMT with DCMB does not increase LC unit firing rate in rats (Engberg *et al*, 1981). Finally, the ability to elicit an α₁-receptor-stimulated excitatory response from these neurons may also depend on the age of the animals and their hormonal status since LC excitation is readily observed in young animals (Williams and Marshall, 1987), and the expression of both α₁B-receptors and PNMT are highly sensitive to induction by circulating levels of corticosterone (Sakaue and Hoffman, 1991; Stone and Kramer, 2001a; Wurtman, 2002).

With regard to the inability of EPI to restore rearing responses in PNMT-inhibited animals, this may have been due in part to the possibility that the exogenous catecholamine does not stimulate *all* or *only* the α₁-receptors to which the endogenous amine has access as has been observed previously (Yang and Chiba, 2002). A second likely factor may be related to the fact, mentioned above, that in addition to their motor activating functions, brain α₁- (and β₁-)adrenoceptors in other regions play major roles in vigilance, fear and anxiety, behavioral processes that are frequently associated with inhibition of motor activity, particularly rearing behavior (van Dijken *et al*, 1992). Global brain activation of these receptors by high doses of ivt. EPI may therefore trigger both behavioral activation and inhibition, which was observed in the above experiments at high doses. The findings that α₁-receptors in the hippocampus and septum suppress rather than stimulate active behavior together with the finding that coinfusion of the β₁-receptor blocker, betaxolol, with ivt. EPI restored rearing in PNMT-inhibited animals strongly support this explanation. Therefore in order to evaluate these factors future research will need to study the behavioral actions of endogenous brain EPI release in the absence and presence of β-receptor antagonists at brain sites containing motoric α₁-receptors *vs* sites containing other α₁-receptors.

An additional problem for this hypothesis stems from the fact that deficiencies of dopamine-β-hydroxylase in humans and mice that totally deplete NE and EPI from the organism produce relatively subtle changes in behavior. Patients with this disorder have been reported to be apathetic and incapable of sustained exercise, but otherwise normal (Man in 't Veld *et al*, 1987). DBH-deficient mice show an impairment of motor activity in swimming and rotarod tests, but no impairment of home-cage activity (Thomas and Palmiter, 1997). However, since these deficiencies exist throughout development, the high plasticity of the developing nervous system may compensate for impaired behavioral activity.

How the putative EPI-α₁ system would be related to other adrenergic receptors and to the brain noradrenergic systems remains to be clarified. As discussed above, EPI is also an established neurotransmitter at central α₂-adrenoceptors. The activation of CNS α₂-receptors is well known to inhibit active behavior (Niittykoski *et al*, 1998), suggesting that brain EPI may have bidirectional control of activity via its effects on the two types of α-receptors. In this regard, it is of interest that a recent study has shown that α₁- and α₂-receptors are located on different cholinergic pontomesencephalic neurons suggesting that their afferent inputs may be separable (Hou *et al*, 2002). Also as noted above, the noradrenergic system may innervate those α₁- and β₁-adrenoceptors in forebrain regions related to arousal, vigilance, and anxiety based on the finding that selective destruction of noradrenergic neurons produces an upregulation of these two receptors in the hippocampus and neocortex (Reader and Briere, 1983). As noted above, since some degree of arousal is necessary for behavioral activation to occur, some degree of noradrenergic stimulation of these other α₁-receptors would be necessary to permit behavioral activation by the putative EPI-α₁-system. High noradrenergic activity in these areas, however, which occurs during severe anxiety, may suppress behavioral activation (Weiss *et al*, 1996; Weiss *et al*, 1998).

EFFECTS OF STRESS AND DEPRESSION ON EPI-α₁-SYSTEM

At present, most studies point toward a marked impairment or inhibition of this system in depressives or in animal models of stress-induced depression.

With regard to presynaptic neurotransmitter function, a basic study in rats showed that hypothalamic EPI levels are significantly depleted by approximately 35% following an acute severe stress (3 min swim at 4°C) and gradually recover over the following 48 h. In this regard, it is of interest that the learned helplessness model of depression also requires 48 h to recover (Maier, 2001). Whether the latter depletion is severe enough to reduce EPI release in the brain has not yet been determined, although it is known that pharmacological inhibition of PNMT completely depletes extracellular EPI with only a 50% depletion of tissue levels (Routledge and Marsden, 1987b).

Only three small clinical studies have been performed on CSF EPI levels in depressed patients. The first (Berger *et al*, 1984) showed a large 70% reduction in depressed patients (0.017 ± 0.008 nmol/ml) compared to 'nuclear' schizophrenics (those with hebephrenia or catatonia) (0.058 ± 0.019 nmol/ml); however, a second control group consisting of other types of schizophrenics was found to have undetectable levels of the catecholamine. The second and third studies (Christensen *et al*, 1980; Gjerris *et al*, 1981) again showed approximately 75% reductions in EPI compared to neurological control groups. Moreover, there was a greater than four-fold rise in their CSF EPI levels after recovery from depression. If these results can be confirmed

with larger samples, they would indicate a severe impairment or inhibition of central EPI release in depression.

At the level of the postsynaptic receptor most basic research has indicated that repeated stress and stress-related factors such as ACTH, corticosterone, and cytokine release can desensitize brain and peripheral α_1-receptors, although some studies have suggested the reverse effect, that is, sensitization. We originally found that repeated footshock, restraint stress, ACTH, or corticosterone administration to rats reduced the α_1-receptor-stimulated potentiation of cAMP responses in slices of the rat cerebral cortex and hypothalamus (Stone, 1979). These findings were confirmed by three other groups (Duman *et al*, 1985; Gannon and McEwen, 1990; Izumi *et al*, 1996), one of which showed that cotreatment with the antidepressant citalopram (but not imipramine) reversed this desensitization and also reversed the reduced behavioral activity that accompanied it (Izumi *et al*, 1997a, b). However, repeated stress in rats was not found by a different group to reduce the α_1-receptor-elicited phosphatidylinositol hydrolysis response to NE in slices of the cerebral cortex (Morinobu *et al*, 1992). In a more recent preliminary study, stress has been shown to abolish the α_1-receptor-stimulated increase of GABA release in the rat amygdala *in vivo* (Braga *et al*, 2002). The foregoing changes in α_1-responses may involve uncoupling of the receptor from its G-protein since most studies have failed to find a downregulation of α_1-recognition sites in the brains of stressed animals (Lynch *et al*, 1983; Ossowska *et al*, 2001). However, it has been found that repeated restraint in rats markedly depletes the midbrain of α_1-receptor mRNA (Miyahara *et al*, 1999), suggesting that some downregulation of the receptor may eventually occur.

Similar desensitizing effects of stress on α_1-receptors were reported in the peripheral nervous system, where chronic stress reduced the α_1-stimulated contraction of the isolated vas deferens (Singh *et al*, 2001) and downregulated the density of α_1-binding sites in the heart (Torda *et al*, 1985). Furthermore, endotoxin (lipopolysaccharide, LPS) and septic shock markedly desensitized and downregulated vascular α_1-receptors (Suba *et al*, 1992; Wakabayashi *et al*, 1989). Proinflammatory cytokine release is considered a likely etiological factor in depression (Anisman *et al*, 2002; Konsman *et al*, 2002).

While the above demonstrations of desensitization were intriguing, there were no basic studies on the effects of stress on the behavioral response to brain motoric α_1-receptor stimulation. To investigate this our group examined the behavioral response to the stimulant, modafinil, in mice subjected to acute and repeated restraint stress (Stone *et al*, 2002b). Modafinil, as described above, stimulates prolonged motor activity that can be blocked by peripheral prazosin or ivt. terazosin. It was found that mice given three or more daily sessions of stress showed a reduced motor response to the drug. This change appeared to be selective for α_1-receptors as the motor responses to dopaminergic agonists were not diminished and, in fact, were somewhat increased, in confirmation of previous findings by others (Hahn *et al*, 1986). In a preliminary experiment, we have also found that acute treatment with the cytokine releaser, LPS, transiently blocks the motor activity response to modafinil (Zhang *et al*, 2000).

Whether or not modafinil is an agonist at α_1-receptors is still unclear. The compound does not activate and may inhibit phosphatidylinositol hydrolysis in mouse cortical brain slices yet it does stimulate a prazosin- or terazosin-blockable phosphorylation of MAP kinase (MAPK) both *in vitro* and *in vivo* but only at fairly high concentrations (10^{-4} M) (Stone *et al*, 2001d). Since it was the only (presumed) α_1-agonist used in the above study, the possibility that stress may have acted on other neuronal systems necessary for modafinil action such as DA, orexin, or GABA (Ferraro *et al*, 1997; Scammell *et al*, 2000) cannot yet be excluded.

With regard to clinical findings, several studies are consistent with a reduced responsiveness of brain α_1-receptors in depression. Checkley and Crammer (1977) and Asnis *et al* (1992) provided evidence for desensitized brain α_1-receptors in depressed patients based on reductions in the plasma cortisol responses to amphetamine or DMI challenge, respectively. These responses had been shown to be mediated by α_1-receptor stimulation (Laakman *et al*, 1986). With regard to [3H]prazosin-binding sites, Gross-Isseroff *et al* (1990) reported a significant downregulation in the tail of the corpus striatum in depressed suicides, whereas other brain regions showed no changes. De Paermentier *et al* (1997) also found no difference in the cortex of depressive suicides but Arango *et al* (1993) found increases in cortical α_1-receptor density.

Basic studies on the effects of antidepressants and electroconvulsive shock on brain α_1-receptors indirectly support the notion of an impaired function of α_1-receptors in depression. Many authors have reported that chronic treatment with tricyclic antidepressants or ECS increases either the density (Maj *et al*, 1985; Nowak *et al*, 1988; Vetulani *et al*, 1984), agonist affinity (Maj *et al*, 2000; Menkes *et al*, 1983a), electrophysiological response (Menkes *et al*, 1980), or behavioral response of brain α_1-receptors (Maj *et al*, 1998, 2000; Menkes *et al*, 1983b; Mogilnicka *et al*, 1987; Plaznik *et al*, 1984). As noted above, an antidepressant, citalopram, was also shown to reverse the stress-induced desensitization of the α_1-potentiation of cAMP responses. However, most of these studies examined the cerebral cortex or hippocampus, which may predominantly contain α_1-receptors related to vigilance and anxiety (Arnsten *et al*, 1999). Furthermore, not all investigators have been able to confirm the above findings (Heal, 1984; Stockmeier *et al*, 1987) indicating that the variables involved have not yet been completely isolated.

Not all basic and clinical research on depression, however, is in accord with α_1-receptor desensitization. Harro and Oreland (2001) have recently suggested that catecholamine receptors in depressives may be sensitized by decreases in brain catecholamine release and therefore may show exaggerated responses to stress or drugs. In support of this notion, basic studies in mice and rats have shown that PNMT inhibitors produce a rapid sensitization (1–3 h) of animals to motor activation by i.p. amphetamine and dopa, and by ivt. α_1-agonists (Katz *et al*, 1978, 1980; Stone *et al*, in press). The low CSF EPI levels found in depressives would be expected to sensitize α_1-receptors. In addition, as noted above, corticosterone, which may be elevated during depressive illness, is essential for the expression of α_{1B}-adrenoceptors in cell culture. Moreover, an increased

euphoric effect of amphetamine has been found in depressed patients (Tremblay *et al*, 2002), while increases in the self-administration of amphetamine has been shown in an animal model of depression (Holmes *et al*, 2002). These changes could, of course, reflect sensitized dopaminergic receptors.

Resolving the above sensitization–desensitization controversy should be a primary goal of future clinical research in this area. A variety of factors may be at work here including the subtype and CNS location of α₁-receptors, the durations of stress, hormone exposure and phase of illness, and possible alterations in the synergistic interactions with dopaminergic receptors. This work would be facilitated by a more definitive characterization of the action of modafinil at brain α₁-receptors as this could potentially provide researchers with a clinical probe for central α₁-receptor function. It would also be greatly aided by the development of clinical imaging techniques for studies of the density, occupancy, and coupling of brain α₁-receptor subtypes in discrete brain regions concerned with the regulation of motor, positive motivation, and anxiety in these patients.

TROPHIC ACTIONS OF α₁-RECEPTORS

Neurotransmission can produce long-term biochemical changes as well as short-term behavioral responses. With respect to the former, adrenergic receptors in the autonomic nervous system are believed to play a major role in long-term adaptation to stress by stimulating trophic, hyperplastic, and other long-term biochemical and morphological changes in end organs that enable adaptive changes in output (Ikeda *et al*, 1991; Stone, 1983). It has been proposed that these receptors trigger similar changes in the CNS during successful adaptation to chronic stress and antidepressant therapy to yield adaptive changes in neural output or plasticity brought about by actions of growth factors (Stone, 1983; Duman *et al*, 1999, 2000). In support of this, α₁-receptor activation has been shown to stimulate both the expression of immediate early genes in the cortex, limbic system and brainstem during stress (Bing *et al*, 1991; Stone and Zhang, 1995) as well as the phosphorylation of cortical MAPK (Williams *et al*, 1998), which is involved in growth factor signaling processes. As noted above, in preliminary experiments, modafinil has been found to activate MAPK in cell culture as well as *in vivo* in the mouse cerebral cortex and to do so via stimulation of α₁-receptors. It has also been found that administration of an α₂-antagonist, yohimbine, which facilitates the release of brain catecholamines, increases the expression of nerve growth factor mRNA in the rat cortex (Stone *et al*, 1994), while catecholamines and/or indoleamines in cell culture (Ohta *et al*, 2002) as well as electroconvulsive shock and antidepressant drugs *in vivo* (Duman *et al*, 2000) can induce the expression of BDNF, GDNF, and/or NT3 as well as elicit functional and neuroanatomical signs of neural plasticity (D'Sa and Duman, 2002).

If the EPI-α₁-system is impaired in depression, as we have proposed, then this may be a factor not only in the reduced behavioral activity of depressives but also in the neuronal atrophy and loss of glial cells in the prefrontal cortex and hippocampus, respectively, that occur in these patients (Drevets, 2000; McEwen, 2000). It should be noted that the human dentate gyrus has a very high concentration of α₁-receptors (Palacios *et al*, 1987). However, it has been found recently that overexpression of constitutively active mutant α₁-receptors causes neuronal degeneration in the mouse brain (Zuscik *et al*, 2000) indicating the need for careful dose–response studies to avoid excessive stimulation. Further research will be necessary to define the mechanism of these changes and to determine how they are related to long-term changes in behavior.

SUMMARY

New behavioral and neuropharmacological evidence has implicated a subgroup of brain α₁ᵦ-adrenoceptors as a key factor in positively motivated behavioral activity. Most of these 'motoric' α₁-receptors are located in or close to monoamine-containing neuron cell bodies (NE and 5HT) or their terminal targets (nucleus accumbens—DA) and appear to receive EPI as their neurotransmitter. It is speculated that this 'EPI-innervated-α₁-system' activates behavior by producing a coordinated excitation of the major monoaminergic systems of the brain. There is evidence that this system is impaired or inhibited in depressive illness from the findings of low levels of EPI in the CSF and of altered responsiveness of brain α₁-receptors in depressed patients. There is also evidence that its impairment may facilitate CNS brain atrophic effects in depression as it is linked to growth factor induction and MAPK activation. As a number of antidepressant agents are capable of restoring or enhancing its function, the EPI-α₁-system would appear to represent a new target for this illness.

Further research is needed on many facets of the above putative system including its relation to aversive as opposed to appetitive behavioral activation, its relation to C1 and C2 medullary EPI-containing neurons as opposed to brain cells containing only PNMT, its status in depression in larger clinical studies, and further basic science studies of the effects of reuptake inhibitors, stress, and immune factors on its function.

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