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Central α_1-adrenergic system in behavioral activity and depression

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ABSTRACT

Central α_1-adrenoceptors are activated by norepinephrine (NE), epinephrine (EPI) and possibly dopamine (DA), and function in two fundamental and opposed types of behavior: (1) positively motivated exploratory and approach activities, and (2) stress reactions and behavioral inhibition. Brain microinjection studies have revealed that the positive-linked receptors are located in eight to nine brain regions spanning the neuraxis including the secondary motor cortex, piriform cortex, nucleus accumbens, preoptic area, lateral hypothalamic area, vermis cerebellum, locus coeruleus, dorsal raphe and possibly the C1 nucleus of the ventrolateral medulla, whereas the stress-linked receptors are present in at least three areas including the paraventricular nucleus of the hypothalamus, central nucleus of the amygdala and bed nucleus of the stria terminalis. Recent studies utilizing c-fos expression and mitogen-activated protein kinase activation have shown that various diverse models of depression in mice produce decreases in positive region-neural activity elicited by motivating stimuli along with increases in neural activity of stress areas. Both types of change are attenuated by various antidepressant agents. This has suggested that the balance of the two networks determines whether an animal displays depressive behavior. A central unresolved question concerns how the α_1-receptors in the positive-activity and stress systems are differentially activated during the appropriate behavioral conditions and to what extent this is related to differences in endogenous ligands or receptor subtype distributions.

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1. Introduction

It is currently thought that central α_1-adrenoceptors are key neuroexcitatory receptors in two different neural networks that underlie the two fundamental and opposed types of behavior: (1) positively motivated exploratory and approach behaviors; and (2) stress reactions and behavioral inhibition. The balance between these two systems is likely to be a critical factor in determining whether an individual copes successfully with stress or becomes depressed.

1.1. Positively motivated approach behaviors

Positively motivated behaviors, which are behaviors that are associated with or conditioned to positive reinforcers and rewards, are of relevance to depressive illness because of their

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stark absence in this disorder [1–4]. One of the cardinal symptoms of major depressive illness is a loss of interest or pleasure in virtually all activities both at home and at work. Studies of these patients in the field by the experience sampling method have indicated that they suffer a profound loss of ''active leisure'' [5,6], which refers to rewarding activities of a sustained and effortful nature such as hobbies, sports, entertainment, social interaction and the like. When contacted at random times by telephone these patients report either ''doing nothing'' or engaged in passive activities such as watching television. The loss of positively motivated behavior appears to be relatively selective since negatively motivated emotions and behaviors such as avoiding aversive stimuli remain intact in depression.

Positively motivated behaviors are known to be elaborated by a hierarchical network of structures that extends throughout the neuraxis and includes prefrontal and motor cortical, lateral hypothalamic and thalamic areas that bidirectionally modulate basal ganglia, midbrain, brainstem and spinal motor control systems [7,8]. This network is subserved by several different neurotransmitter systems including monoamines, excitatory amino acids, opioid peptides and other peptide neurotransmitters and hormones.

The monoamines are the neurotransmitters most closely related to depressive illness. Most previous work on their function in positively motivated activity has involved the dopaminergic system in the nucleus accumbens. Recently, it has been found that a subgroup of α_1-adrenoceptors located in a number of the above brain regions is also a key component in this system and broadly regulates the positive network (and the stress network as well).

2. Role of brain α_1-adrenoceptor activity in exploratory activity

Brain α_1-adrenoceptors have long been known to influence motor and exploratory activity (reviewed in [9,10]). The degree of this influence, however, was not fully appreciated until systematic studies were undertaken on the effects of selective adrenergic receptor antagonists on exploratory behavior of mice and rats in a novel (fresh) cage. Fresh cages of the same type as the home cage are relatively non-threatening environments that elicit sustained exploration (45–90 min) in rodents and are positively reinforcing in that animals will work to gain access to and preferentially visit novel chambers [11]. Although fresh cages can also induce anxiety [12], the exploration that they induce is very vigorous and is not significantly altered by prior treatment with an anxiolytic, chlordiazepoxide (0.5–2 mg/kg, i.p.) (Stone, EA and Quartermain, D, unpublished results) suggesting that it is primarily positively motivated.

Using this measure it was found that blockade of brain α_1-receptors in mice and rats with an intraventricular (ivt.) α_1-antagonist, terazosin, produced a total dose-dependent abolition of all active behavior and movement [9]. Blockade of central α_2-, β_1-, or β_2-adrenoceptors did not produce this effect. Furthermore, there was a near perfect correlation ($r = 0.96$) between the number of central α_1-receptors blocked by terazosin, as measured by the ex vivo binding of [^{3}H]prazosin in brain tissue, and the loss of behavioral activity in the fresh cage [13]. In addition, the terazosin-induced inactivity could be completely reversed by coinjection of an α_1-agonist (either phenylephrine or 6-fluoronorepinephrine). Since α_1-agonists given alone centrally had long been known to stimulate locomotion and exploratory behavior [14], these findings indicated that CNS α_1-receptor activity is both necessary and sufficient to produce activation of these behaviors in rodents.

The inactivity following central blockade of α_1-receptors is most likely due to unopposed stimulation of hyperpolarizing α_2-adrenoceptors as it was shown that exploratory activity could be restored by the additional administration of a selective α_2-antagonist, atipamezole [15]. Therefore, the degree of behavioral activation appears to be dependent on the balance between these two opposing α receptor classes. Interestingly, behavioral activity could also be restored by low (but not high) doses of an α_2-agonist, dexmedetomidine (DMT), suggesting that inhibition of NE release onto unopposed α_2-receptors could reduce the inhibition of behavior.

The activating effect of central α_1-receptors on motor activity is not simply the result of awakening the animals since terazosin-treated (ivt.) animals were not found to be sedated or hypotensive, but to be cataleptic [9]. Although central administration of prazosin has been found to block the arousing effect of central α_1-agonists, the antagonist by itself does not produce an increase in slow-wave high-voltage EEG [16,17]. Furthermore, others have shown that it is possible to separate the arousing versus motor activity stimulating effects of central α_1-receptors in that their activation in basal forebrain regions in rats produces EEG and behavioral arousal but does not elicit motor activity [18] whereas α_1 stimulation in brainstem regions produces vigorous exploratory behavior of familiar surroundings.

The subtype of α_1-receptor that mediates behavioral activation appears to be the 1B. Using several different α_1-receptor antagonists, it was shown that the ability of these drugs, given ivt., to block behavioral activity in the fresh cage was highly correlated with their binding affinities for the cloned α_{1B}-receptor ($r = 0.89$) but not the cloned α_{1A}- ($r = 0.30$) or α_{1D}-receptors ($r = 0.13$) [19]. Other workers have shown that the α_{1B}-receptor is also the subtype involved in the reversal of narcolepsy in dogs by stimulants [20]. In addition, α_{1B}-deficient mice have marked reductions in motor activity responses to stimulant drugs (see below).

However, the α_{1A}- and α_{1D}-receptors are probably also involved since knockout of the α_{1B}-receptor in mice has not usually been found to reduce behavioral activity in novel surroundings [21] (but see [22]). This resistance may be due to compensation by the remaining two α_1-receptor subtypes since mice with combined knockout of both the α_{1B}- and α_{1A}-receptor have a markedly diminished nocturnal activity compared to wild type mice [23]. Furthermore, an α_{1D}-deficient mouse has been found to show reduced rearing (but not ambulation) in a novel chamber and reduced wheel running in the home cage [24] suggesting that the latter receptor subtype is also involved in behavioral activation and possibly in compensatory mechanisms. It should be noted however that these conclusions are tentative in view of recent discoveries that α_{1B}- and α_{1D}-receptors form heterodimers that have different affinities and efficacies for catecholamines [25].

The stimulation of active behavior by α_1-agonists has several characteristics that are reminiscent of rate-dependency. For example, these agonists will stimulate active behavior if animals are tested under conditions that make for low activity and low stress (e.g., the home cage during the light period) or after depletion of brain catecholamines or blockade of receptors but will reduce activity under high-active, high-stress or non-depleted or non-blocked conditions (e.g., the fresh cage, swimming tank) [15,26,27]. Furthermore, whereas low to moderate doses of α_1-agonists produce a dose-dependent increase in motor activity, high doses produce a fall-off or actual depression of activity even in the low-active condition. In addition, low doses of α_2-adrenoceptor agonists, which induce an opposing hyperpolarization, can enhance the behavioral stimulation produced by α_1-agonists [15]. Since, α_1-receptors produce depolarization in their host neurons in many brain regions via calcium modulated potassium conductance [28,29], this rate-dependency could be the result of a depolarization block occurring at high doses coupled with high endogenous catecholamine release [30]. However, it may also be the result of the diffusion of high doses of α_1-agonists to brain regions involved in stress reactions that lead to the inhibition of ongoing behavioral activity.

3. Brain localization of behaviourally activating α_1-receptors

Where in the brain these receptors act to stimulate behavior has been studied in mice and rats [31] by determining where terazosin microinjection induces immobility in the fresh cage test and where α_1-agonists stimulate exploratory activity in a low activity environment (home cage). Eight to nine brain regions have been found in the mouse brain including the locus coeruleus, periaqueductal gray in the vicinity of the dorsal raphe, vermis lobe of the cerebellum, nucleus accumbens (NAC), medial or lateral preoptic area (POA), lateral hypothalamic area, secondary motor cortex, piriform cortex and possibly the C1 nucleus of the ventrolateral medulla (Fig. 1).

The most marked effects were found in the locus coeruleus, dorsal raphe, piriform cortex and cerebellum with mice that

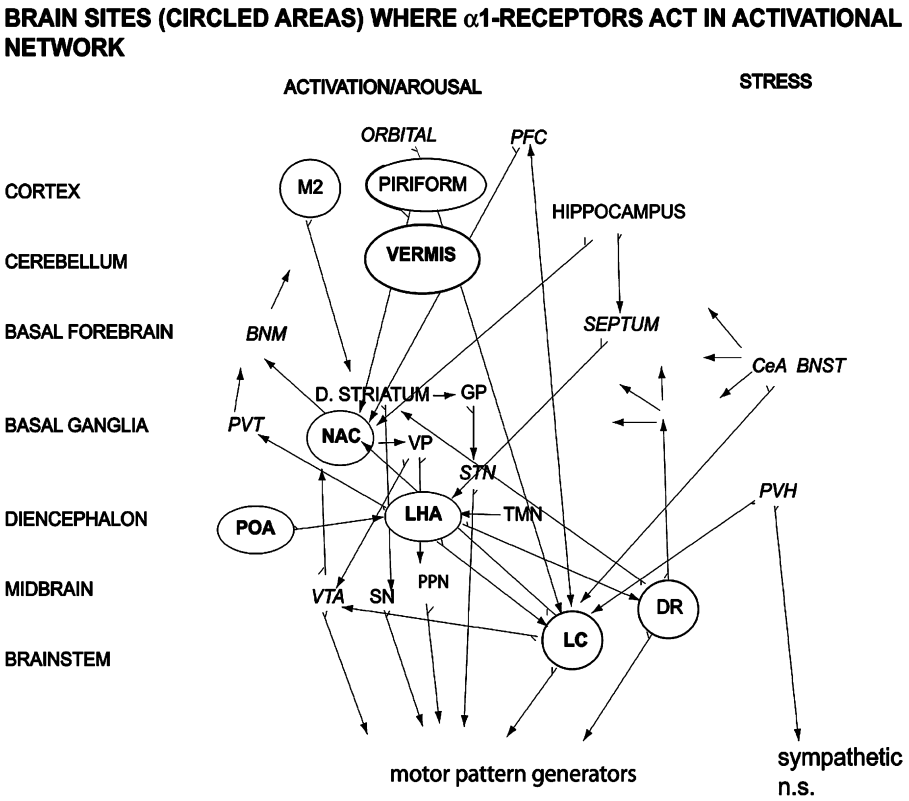

Fig. 1 – Localization of mouse brain α_1-adrenoceptors mediating fresh cage exploration (circled areas) found in mapping studies. These areas are shown as part of the larger complex network of all structures that are involved in positively motivated behavior and stress responses. Note the wide distribution of the positive α_1-receptor regions across all major subdivisions of the CNS. Italized regions with asterisks are known to contain significant α_1-receptor populations that failed to influence fresh-cage behavioral activation. Abbreviations: secondary motor cortex (M2); piriform cortex (PIR); nucleus accumbens (NAC); preoptic area (POA); lateral hypothalamic area (LHA); vermis cerebellum (VERMIS); locus coeruleus (LC); dorsal raphe (DR); globus pallidus (GP); paraventricular n. of thalamus (PVT); pedunculopontine n. (PPN); subthalamic n. (STN); tuberomamillary n. (TMN.); ventral pallidum (VP); substantia nigra (SN); ventral tegmental area (VTA); basal nucleus of Meynert (BNM); prefrontal cortex (PFC); bed n. of the stria terminalis (BNST); central n. of the amygdala (CeA); orbital (orbital cortex).

were injected in these areas spending 51, 58, 60 and 44%, respectively, of a 10 min test in the fresh cage completely immobile as compared to 28% for the nucleus accumbens, 33% for the medial preoptic area and 17% for the motor cortex. Injection of terazosin in the 4th ventricle produced the greatest degree of immobility (80% of test) in both mice and rats probably by acting simultaneously on the locus coeruleus, dorsal raphe and cerebellum or because of the denser localization of brainstem as opposed to forebrain motor circuits. The immobility induced by terazosin in each of these regions was reversed by coinjection of the α_1-agonists, 6-fluoronorepinephrine (6FNE) and phenylephrine (PE), and injection of these agonists alone in the locus coeruleus stimulated behavioral activation (including wheel running) in the home cage test in the mouse and rat [32].

The location of motoric α_1-receptors in the locus coeruleus was confirmed in rats by a mapping study using terazosin and by the use of the noradrenergic neurotoxin, DSP4, pretreatment with which abolished the behavioral inhibitory effect of terazosin and the behavioral excitatory effect of PE in this nucleus [33]. DSP4, however, did not reduce the ability of the fresh cage stimulus to induce behavioral activation indicating that the organism can compensate for the loss of noradrenergic inputs. In mice (Swiss Webster), however, DSP4, did not affect the inhibitory effect of LC-injected terazosin possibly due to the lower potency of the neurotoxin in this strain [34].

The above brain regions represent or project to motor, motivational and arousal systems and extend throughout the neuraxis (Fig. 1). Location in the lateral hypothalamus, locus coeruleus, dorsal raphe and nucleus accumbens indicate that α_1-receptors may excite three major monoaminergic systems and the orexinergic system, which underlie motivation, initiation of movement and reinforcement. Location in the secondary motor cortex suggest that these receptors may play a role in the selection of specific motor acts [35] while presence in the piriform cortex is consistent with a role in sniffing behavior which is a central component of rodent exploratory activity [36]. Location in the preoptic area is suggestive of a role in the circadian and sexual motivation regulation of behavioral activation.

The excitatory role of α_1-receptors in the above regions is in agreement with the finding that these areas exhibit increases in fos expression and mitogen-activated protein kinase (MAPK) activation in conditions that produce increased behavioral activity such as arousal [37], exposure to a fresh cage [38], injection of stimulants [39], forced swimming [40] and wheel running [41]. Expression of fos and activation of MAPK in these brain areas to the fresh cage can be blocked by α_1-antagonists and can be mimicked by peripheral injection of α_1-agonists given in a 15% DMSO vehicle to aid penetration of the blood brain barrier (Lehmann M, Carr K, Stone E, unpublished results).

It is likely that the widespread distribution of motoric α_1-receptors makes for a partially redundant system [42] since, as noted above, DSP4 lesion of the dorsal noradrenergic bundle abolishes the behavioral responses to injection of α_1-selective drugs in the locus coeruleus but does not significantly affect behavioral activation to sensory input (i.e., fresh cage) that acts through broader sensory channels. Thus, remaining intact sites may subsume the function of lesioned areas in this system.

No immobility to terazosin was found in 17 other mouse brain regions including the ventral tegmental area, substantia nigra, corpus striatum, amygdala, posterior and anterior hypothalamus, bed nucleus of the stria terminalis, basal nucleus of Meynert, thalamus, prefrontal cortex, olfactory bulb, dorsal hippocampus or septum. The lack of effect in the ventral tegmental area is surprising in view of the presence of excitatory α_1-receptors on DAergic neurons in this region [43] and the synergistic action of α_1-receptor stimulation on the motor response to DA receptor stimulation [44]. In the septum and dentate gyrus terazosin actually produced a small increase in behavioral activation suggesting that α_1-receptors in these brain regions may inhibit behavior or be necessary for habituation to the fresh cage stimulus.

The bed nucleus of the stria terminalis, central nucleus of the amygdala and paraventricular hypothalamus are regions that contain high densities of α_1-receptors but represent key integrative centers for reactions to stress. The α_1-receptors in these regions do not appear to mediate behavioral activation but rather elicit behavioral inhibition and stress responses, and are discussed in a later section.

While it has been assumed in most previous research that the majority of central α_1-receptors are located postsynaptic to noradrenergic terminals, recent studies have documented presynaptic effects of α_1-receptor stimulation on the release of both NE and DA [45]. It will be of interest, therefore, to determine the effects of local lesions of noradrenergic and dopaminergic terminals on the behavioral responses to local infusions of α_1-agonists.

4. Endogenous agonist of central motoric α_1-adrenoceptors

It had been thought that this was norepinephrine (NE) since the latter is the chief α_1-agonist in the mammalian brain. However, there is indirect evidence to suggest that the ''minor'' brain catecholamine, epinephrine (EPI), and brain DA are also agonists for these receptors in vivo.

Although small amounts of EPI are stored in the brain, its extracellular level in the hypothalamus and LC as measured by microdialysis and push–pull cannula is nearly as high as that of NE [46–48], and its metabolite, metanephrine (MN), is present at high concentration in the CSF [49] suggesting that it is a major brain neurotransmitter.

Although EPI was long known to be a neurotransmitter for brainstem α_2-adrenoceptors [50], it had been found that its depletion by synthesis inhibition or genetic factors markedly up-regulated the number of brainstem α_1-receptors as well [50]. This suggested that EPI tonically stimulates brainstem motoric α_1-receptors. In support of this notion it has been found that, there is either a significant degree of innervation by phenylethanolamine-N-methyltransferase (PNMT)-positive nerve endings [51] or evidence of substantial levels of EPI and its metabolite, metanephrine, during heightened behavioral activation [52] in at least four out of the above nine brain regions that contain the motoric α_1-receptors (locus coeruleus, preoptic area, dorsal raphe and n. accumbens). Furthermore, smaller amounts of EPI have been detected in the cerebellum and cerebral cortex [53]. In addition rat strains

with relatively high levels of brainstem PNMT and EPI (Fischer 344 and spontaneous hypertensive) have higher motor activity responses to novelty [54] and to the forced swimming test [55] than strains with lower levels (Buffalo, Wistar-Kyoto).

In further support of a role for EPI as endogenous agonist, it was found that selective blockade of EPI synthesis by the PNMT inhibitor, DCMB (2,3-dichloro-α-methylbenzylamine, which totally depletes extracellular EPI but has no effect on extracellular NE in the brainstem [56]), given i.p., in mice produced a marked dose-dependent reduction in behavioral activity in a fresh cage test. This reduction (which was not the result of sedation [57]) was dose-dependently reversed by EPI injected ivt. [27]. Moreover, EPIs reversal effect was significantly greater than that of NE and was attenuated by blockade of α_1-receptors. (EPI is known to have a greater efficacy than NE at central α_1-adrenoceptors [58–60]). In addition, ivt. EPI, given alone, produced marked behavioral activation of mice in their home cages during their inactive light phase, an effect that was also attenuated with coinjection of terazosin.

With regards to DA as a possible endogenous agonist for α_1-adrenoceptors, this catecholamine is present in a number of brain regions containing motoric α_1-receptors (see Fig. 1 legend for abbreviations: M2, PIR, CG, NAC, MPOA. LH, LC). DA has approximately 1/100th the affinity of NE and EPI for α_1-receptors but can achieve high concentrations in synapses. Wisor and Eriksson [61] have presented intriguing evidence that DA may stimulate motoric α_1-receptors in vivo from studies with the novel stimulant/antidepressant, modafinil. This drug is known to stimulate exploratory behavior by some process that is dependent on the activity of central α_1-receptors [62,63]. The latter authors found that pre-lesioning the dorsal noradrenergic system with DSP4 did not prevent modafinil from stimulating motor activity in C57BL mice however the selective D2 autoreceptor agonist, quinpirole, which blocks the release of brain DA, markedly blocked the effect. Although the ability of DSP4 to lesion the dorsal noradrenergic pathway in certain mouse strains may be limited as noted above, the authors confirmed a total absence of NE transporter sites in their lesioned C57BL/j mice.

5. Central α_1-receptors and positively motivated behavior

Several experiments using peripheral as well as central drug administration have suggested that the behavioral activation seen with stimulation of central α_1-receptors reflects an increase in positive motivation with a smaller contribution from non-specific motor stimulation. Regarding peripheral administration, early studies showed that α_1-antagonists given i.p. [64] reduced lateral hypothalamic self-stimulation behavior without affecting escape responses from aversive brain stimulation [64] suggesting a specific relationship of these receptors to reward efficacy or motivation. The same conclusion was drawn from similar studies on morphine-induced conditioned place preference in mice [65] and from the inhibitory effects of whole organism knockout of the α_{1B} on the motor stimulating effects of a number of positively reinforcing or motivating agents including amphetamine, cocaine, morphine, modafinil [62,66–69].

Studies on central drug administration have provided more direct support for a role of these brain receptors in positively motivated behavior. First, mice made inactive by ivt. terazosin injection were found to become active when subjected to strong stimuli such as immersion in a room temperature water bath suggesting that the antagonist produces a motivational as opposed to a motor deficit [9]. Second, α_1-agonists injected ivt. or in the LC have been found to produce high levels of locomotion and rearing behavior with no darting or jumping which is similar to the hyperactivity seen after positively reinforcing stimulant drugs or novel cage exposure [9,33,70]. Finally, an early study showed that ivt. administration of EPI or NE enhanced lateral hypothalamic self-stimulation in rats [71] and a more recent one found that terazosin locally injected into the rat LC produced a marked rightward shift in the rate-frequency curve of self-stimulation from the lateral hypothalamus indicating a reduction in reward efficacy or motivation [72]. A smaller reduction in the maximum response rate (16%) also occurred which suggests that LC α_1-receptors may coordinate motor activity with appropriate reinforcement.

6. Central α_1-receptors and negatively motivated behavior

There is abundant evidence that α_1-receptors also mediate *aversively motivated behavior*. Thus activation of both peripheral and central α_1-receptors has been associated with anxiety, stress and CRF secretion [73–76]. Peripheral low dose treatment with the α_1-antagonist, prazosin, has been shown to have anxiolytic effects in the plus-maze and in conflict paradigms [77] and, in higher doses, to successfully reduce nightmares as well as daytime distress in PTSD patients [78,79]. Furthermore, LC neurons are highly sensitive to stress and drug withdrawal [80] and may facilitate behavioral responses to any motivationally salient stimulus [73]. Finally, an early study showed that the turnover of EPI in the LC was elevated by acute footshock stress [81].

To reconcile the latter findings with the foregoing studies on positive motivation, it has been suggested that α_1-receptors mediating aversive stimulation are located in different brain regions than those mediating positively motivated behavior with the former localized in primarily in behaviorally inhibitory stress-associated brain regions such as the bed nucleus of the stria terminalis and central nucleus of the amygdala.

In support of the localization of ''aversive'' α_1-receptors in stress regions, Morilak and colleagues have shown that blockade of α_1-receptors in the bed nucleus of the stria terminalis before restraint stress blocked both the subsequent inhibition in open arm entries in the elevated plus maze and the hypersecretion of ACTH [82] whereas blockade of these receptors in the central nucleus of the amygdala selectively reduced the inhibition of social interaction following the stress [83]. Furthermore, it had been found earlier that α_1-receptors in or near the PVH were activated by ventral noradrenergic bundle nerve endings and mediated CRF release to certain stressors [84,85]. Activation of α_1-receptors in the PVH was also found to produce anorexia and to potentially mediate stress-induced suppression of appetite [86].

How the α_1-receptors in the positive- and stress-associated areas are differentially activated in affectively different situations is a key unresolved question. It has been suggested that the stress area receptors receive significant innervation from the tegmental noradrenergic cell groups (A1 and A2) via the ventral noradrenergic bundle [87–89] while the positive activational regions are innervated primarily by the LC via the dorsal noradrenergic bundle, C1 (EPI) neurons, or VTA dopaminergic fibers [15]. In support, early studies by Kostowski et al. [90] showed that electrolytic lesions of the dorsal and ventral noradrenergic bundles had opposing effects on behavior in the forced swim test with the dorsal bundle lesions producing inactivity and catalepsy while the ventral bundle lesions produced hyperactivity and stereotypy. In contrast, a more recent study by Cryan et al. [91] found that more selective 6-hydroxydopamine lesions of the ventral bundle abolished the anti-immobility effects of the NE selective antidepressant, reboxetine, in the forced swim test, whereas dorsal bundle lesions by DSP4 enhanced the drug's anti-immobility effects. Further studies on this critical question are needed.

Whether the same or different α_1-receptor subtypes mediate neuronal activation in the positive activational as opposed to stress regions has not yet been specifically examined and represents another important avenue of research. A study by Zilles et al. [92] has suggested that the positive areas have a higher density of the α_{1B}-receptor binding sites whereas the stress regions have a higher density of the α_{1A}-subtype sites. Studies on receptor dimerization in these areas might reveal new mechanisms for their differential regulation.

7. α_1-Receptor activity in during experimental depression

7.1. *Measures of α_1-receptor activity in vivo*

Studies on brain α_1-receptor function in behavior have been limited by the lack of ex vivo biochemical measures of the activity of these receptors. To address this problem we undertook several studies to develop such methods. Because α_1-receptors are known to activate fos expression in central neurons in vitro [93–96], we carried out a study to determine if the activation of these receptors by exposure to a fresh cage could be detected from fos responses in the various brain regions shown above to contain these receptors [38], i.e., were the fos responses that are known to occur in these structures in response to novelty dependent on the activity of α_1-receptors? This study showed that exposure to a fresh cage produced marked fos responses in regions containing motoric receptors – M2, CG, PIR and NAC – with a smaller and more variable increase in the LC. Although the stress-sensitive PVH also showed a significant elevation of fos expression (two-fold), this was far weaker than its response to a genuinely stressful stimulus (six-fold increase after 90 min restraint). Pretreatment with peripheral prazosin (at a high dose to penetrate the blood brain barrier of Swiss mice) abolished the fos response of the M2, CG, PIR and NAC to the fresh cage. Furthermore, reverse dialysis of the α_1-agonist, phenylephrine (PE) in the M2 induced a local fos response that was blocked by co-dialysis with terazosin indicating that fos expression in this structure can occur to stimulation of local α_1-receptors. The above results, therefore, indicate that the fos response of activational areas to the fresh cage stimulus is dependent on the functional activity of α1-receptors. (Unlike the other positive areas, the LC showed very marked fos expression in response to the α_1-antagonist itself which may represent a compensatory response to blockade of neurotransmission in projection areas of this nucleus.)

The protein fos response requires approximately 1 h to develop in CNS neurons. To determine if it was possible to detect α_1-receptor activity in a shorter interval, we next examined the activation of ERK1/2, an established step in α_1-signaling, in CNS structures, during a 10 min period of stimulation of these receptors. Two procedures of receptor stimulation were used. The first involved peripheral injection of the α_1-agonist, PE and the second, exposure to a fresh cage. Since PE does not penetrate the blood brain barrier, it was injected in a vehicle of 15% dimethylsulfoxide (DMSO), which enables polar molecules entry to the CNS. ERK1/2 phosphorylation was measured by Western analysis of tissue punches from frozen brain sections of mice subjected to each procedure.

The method was found to be successful in detecting increased ERK1/2 activation in a wide range of brain structures after both types of stimulation and also at baseline (Lehmann M, Carr K, Stone E, unpublished results). There was a rough correlation between α_1-receptor density and ERK1/2 response with areas having the highest levels of α_1-binding sites (thalamus, M2, CG, PIR, BNST but not AMYG) showing the highest degree of ERK1/2 activation to PE. That the responses were, in fact, dependent on the stimulation of α_1-receptors was shown by inhibition with an α_1-antagonist (prazosin). These findings indicated that it is possible to measure activation of brain α_1-receptors by exogenous and endogenous catecholamines using activation of ERK1/2.

Having obtained measures of central α_1-receptor activity, we next applied these to the study of depression. For these studies animals were subjected to one of several procedures known to elicit experimental depression and were then challenged with a motivating stimulus prior to measurement of central α_1-receptor-related neuronal activity in positive-activity- and stress-related brain regions. The procedures used to elicit depression were immune activation with lipopolysaccharide (LPS, 100 μg/mouse, i.p.), monoamine depletion with reserpine (5 mg/kg, i.p.), repeated forced swimming (four daily 15 min swims), chronic (21 days) subordination stress and intraventricular injection of galanin (2 nmol/mouse). These procedures were used because they sampled a highly diverse set of physiological and psychological stimuli, which had only one thing in common: the induction of depressive behavior. The motivating stimuli were either exposure to a fresh cage for 90 min or swimming in a large tank of warm water for15 min. As discussed above, both of these stimuli elicit prolonged active and effortful behavior. Fos expression was measured in both positive brain regions (M2, CG, APIR, NAC) and in a stress region (PVH). MAPK activation was measured in a representative positive (CG) and stress region (PVH).

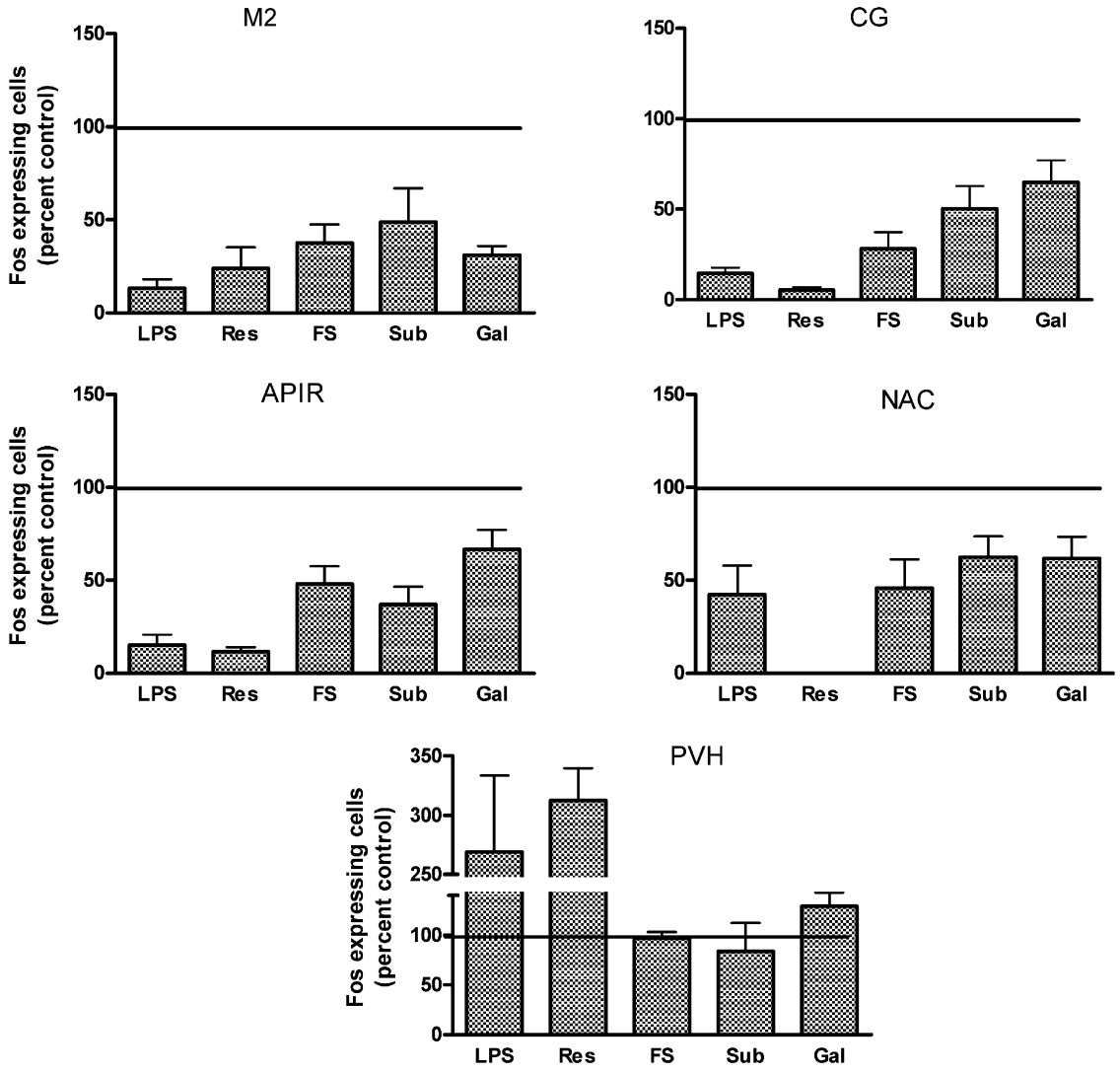

Fig. 2 – Summary of the effects of five different models of depression in mice on c-fos responses of five brain regions to motivating stimuli. Data are combined from [114] and an unpublished study by Stone EA, Lehmann ML, Lin Y and Quartermain D. LPS (lipopolysaccharide, 100 μg/mouse, 2 h), Res (reserpine, 5 mg/kg, 24 h), FS (four daily 15 min forced swims), Sub (subordination stress, 21 days), Gal (intraventricular galanin, 2 nmol/mouse, 2 h). Motivating (challenge) stimuli were 90 min fresh cage exposure for LPS, Res, Sub, Gal models and 15 min swim for FS model. Note that all five models reduced fos expression in the four positive-activity regions but either did not reduce the response or greatly magnified it in the stress region. The data on Res in the NAC were omitted because of the unusually large response in this area caused by local depletion of its DA content. $^{*}p < 0.05$, $^{**}p < 0.01$ by ANOVA in comparison to response of non-depressed control group.

The fos results are summarized in Fig. 2, which shows the responses (number of fos positive cells per unit area) of depressed mice as a percentage of the mean response of the control animals. As can be seen, all of the depression models reduced the responses of the four positive regions while they either left unchanged or increased that of the stress region. The MAPK assays showed the same effects (not shown).

The effect of chronic pretreatment (12–15 days) with a typical tricyclic antidepressant, desmethylimipramine (DMI, 10 mg/(kg day)) on the altered fos responses of one of the depression models (repeated forced swim) is shown in Fig. 3. This antidepressant, which is known to attenuate forced swim-induced immobility, partially restored the fos responses of the four positive regions and blunted that of the stress area. Similar results were obtained with a monoamine oxidase inhibitor (tranylcypromine), a serotonin-selective reuptake inhibitor (escitalopram) and with an environmental procedure (enrichment) that produces many neurochemical effects in common with antidepressants. These results are consistent with the hypothesis that experimental depressions that involve reduced motivated activity are accompanied by both a reduction in neural activity in brain regions involved in positively motivated behavior and an increase in neural activity in region(s) associated with stress. Although we have not demonstrated conclusively that the reductions in the activational regions are related to decreases in the activity of

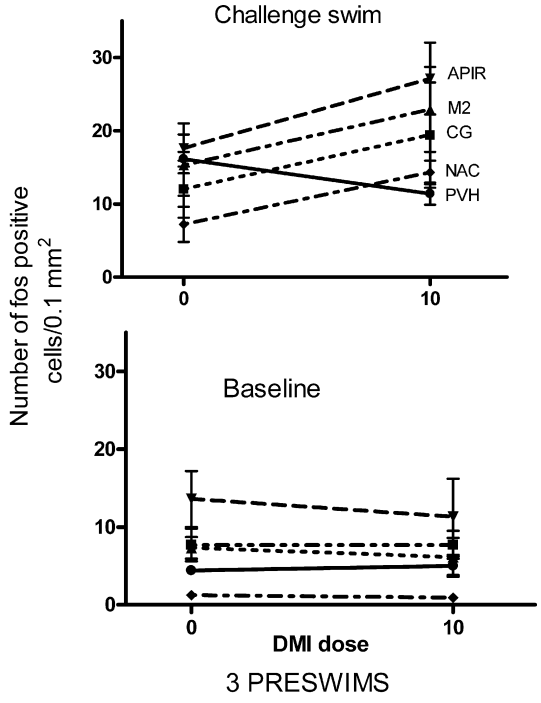

Fig. 3 – Effect of pre- and co-treatment with an antidepressant (DMI, desmethylimipramine, 10 mg/(kg day), 15 days) on regional brain fos baseline values and responses to the motivating stimulus (swim) in the FS model. Data are from an unpublished study by Stone EA, Lehmann ML, Lin Y and Quartermain D. Note that antidepressant treatment increased responses to the challenge of all four positive areas considered as a group ($F_{1,40} = 5.78$, $p < 0.05$) and tended to reduce that of the stress region ($F_{1,40} = 3.48$, $p < 0.07$). Baseline values tended to be affected oppositely.

local α_1-adrenoceptors, it is, however, likely that such a change either in this or a closely related system(s) is a contributory factor in this effect. In this regard, we have found that acute treatment with modafinil, a novel stimulant that acts partially via activation of central α_1-receptors, rapidly stimulates both behavioral activity and fos expression in activation areas in the forced swim model [97]. Furthermore, depression models have been shown to induce central neurochemical changes in these areas that would be expected to oppose or inhibit the excitatory effects of α_1-receptors including reduced brainstem α_1-receptor gene expression [98], increased expression of cortical α_2-adrenoceptors [99], reduced release of glutamate [100], altered serotonergic receptor binding [101], and increased availability of central prostaglandins [102], galanin [103], adenosine [100] and γ-aminobutyric acid (GABA) [104].

Whether the change in fos expression and MAPK activation are related to the cause of the behavioral depression or are results of the change in behavior cannot yet be ascertained with certainty. However, in view of the facts that pharmacological manipulation of the activity of brain α_1-receptors produces changes in motivated activity, and that animals that are highly motivated but cannot perform also show marked fos responses in these regions [38,41], it is likely that the brain response is the cause of the behavioral response and probably acts via a motivational variable. The change in behavior, however, probably adds to the brain response since immediate early genes and ERK 1/2 activation are involved in signal processing and memory consolidation [105], and an increased degree of exploratory or swimming behavior would be likely to enhance activation of these pathways.

While the above study was concerned primarily with motivated activity during depression, it should be noted that the widespread reduction in neural activity in activational structures in these models might also be a factor in the impairment of cognitive function during depression. Animal models of depression have been found to produce impaired learning and memory [106] as in the clinical condition.

Whether the above neural changes in depressed mice are homologous to those occurring in human depression is an open question. It is difficult to compare human and animal studies since the subjects are in vastly different behavioral states with the animals engaged in unrestricted active behavior while the humans are lying in scanners, and since it is not known whether fos responses in animal studies are correlated with blood flow and glucose metabolic measures of neural activity in depressed patients. These caveats notwithstanding, some of the effects appear similar. Thus, clinical studies have found widespread reductions in metabolism in the frontal cortex or in dorsal cortical regions [107–110] that may correspond to reductions in the secondary motor cortex found in the animal studies. Also some studies have reported reductions in metabolism in the posterior cingulate gyrus in depressives [111]. Dopamine metabolism in the corpus striatum is reduced in depressives and blood flow in this structure may be similarly affected [112], which may correspond to reduced activity of the NAC in the mouse models. Parallels are also evident in the stress regions of the PVH and CeA, which show elevated activity in both animal and human depressions [113]. Thus, there appears to be at least partial similarity between the central neural activity changes in mouse and human depression, which suggests that the mouse effects can be used as neural targets for studies of neurobiological mechanism, behavioral significance and intervention methods.

Finally, there is the intriguing possibility that the neural outputs of the α1-stress-related and the activational regions are mutually antagonistic such that either can gate excitatory input to the other. This notion has been advanced by several investigators [1,2,103,108,110,114]. Neural pathways that could mediate interactions between the activational and stress regions include cortical regions that have descending inhibitory projections to stress areas [115] and projections from stress areas to brainstem ascending activating nuclei [116–120]. Such an interaction would imply that behavioral depression may arise from either an increase in the activity of stress regions or a decrease in that of activational areas, and that antidepressant action may result from a reversal of either effect or both. As discussed by Mayberg et al. [110] this schema would, therefore, be consistent with the plethora of conditions that can induce depression as well as the variety of agents that can offset it.

8. α_1-Receptors and trophic processes

In an early work, we hypothesized that, in a broad biological view, depression results from inadequate output to meet the demands of stress, and that both successful adaptation to stress and successful antidepressant action raise output level by provoking trophic and hyperplastic changes in peripheral organs and central neurons via the adrenergic and other neural and humoral systems [121]. Early studies showed that antidepressants and stress induce sprouting and degeneration, respectively, of noradrenergic nerve terminals [122,123], and, in the last decade, the neurotrophic and neurogenic nature of antidepressant action has been repeatedly confirmed [124,125]. α_1-Receptors are known to participate in trophic processes in peripheral organs [126] and may also represent an important factor in these processes in the CNS [127] as stimulation of immediate early genes and the MAPK signaling pathway are known to be involved in the latter functions. Moreover, α_1-receptor stimulation has been shown to induce neurogenesis in the hippocampus [128] and synaptogenesis in the visual cortex [129]. The α_1-receptor stimulation of positive activational behavior may, therefore, be linked to a parallel activation of trophic processes in the positive areas to meet new demands, challenges and opportunities. If this is correct, then the prolonged reduction of α_1-receptor activity posited to occur during chronic stress or depression may be a factor in the reduction of neurotrophic support and consequent atrophy of brain structures observed in these conditions. This appears valid for peripheral organs where combined knockout of the α_{1B}- and α_{1A}-receptors in mice subjected to aortic pressure overload leads to apoptosis in cardiac myocytes, impaired cardiac trophic responses and fatal heart failure [130]. Trophic changes, however, are a two-edged sword since α_1-receptor activation in stress regions during adverse conditions may also increase the size and/or output of the PVH [131], AMYG [132] and BNST [133] resulting in the sensitization of stress responses, behavioral inhibition and exacerbated depression. It would, therefore, appear essential at this point to elucidate the differential activation of α_1-adrenoceptors in these two CNS networks.

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