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α_2 adrenergic receptor dysregulation in depressive disorders: implications for the neurobiology of depression and antidepressant therapy

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Abstract

Dysfunction in noradrenergic neurotransmission has long been theorized to occur in depressive disorders. The α_2 adrenergic receptor (AR) family, as a group of key players in regulating the noradrenergic system, has been investigated for involvement in the neurobiology of depression and mechanisms of antidepressant therapies. However, a clear picture of the α_2ARs in depressive disorders has not been established due to the existence of apparently conflicting findings in the literature. In this article, we report that a careful accounting of methodological differences within the literature can resolve the present lack of consensus on involvement of α_2ARs in depression. In particular, the pharmacological properties of the radioligand (e.g. agonist versus antagonist) utilized for determining receptor density are crucial in determining study outcome. Upregulation of α_2AR density detected by radiolabeled agonists but not by antagonists in patients with depressive disorders suggests a selective increase in the density of high-affinity conformational state α_2ARs, which is indicative of enhanced G protein coupling to the receptor. Importantly, this high-affinity state α_2AR upregulation can be normalized with antidepressant treatments. Thus, depressive disorders appear to be associated with increased α_2AR sensitivity and responsiveness, which may represent a physiological basis for the putative noradrenergic dysfunction in depressive disorders. In addition, we review changes in some key α_2AR accessory proteins in depressive disorders and discuss their potential contribution to α_2AR dysfunction.

Keywords

α_2 adrenergic receptor; antidepressant; depressive disorder; locus coeruleus

1. Introduction

Nearly half a century ago, the classical monoamine hypothesis for depressive disorders was proposed as an explanation for the therapeutic efficacy of the first antidepressant drugs (Schildkraut, 1965). These compounds, the tricyclic antidepressants (TCAs), which inhibit monoamine reuptake, and monoamine oxidase inhibitors (MAOIs), were known to increase brain levels of the monoamine neurotransmitters norepinephrine (NE) and serotonin (5HT)

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(Baldessarini, 2006). It therefore seemed obvious to hypothesize that a depletion of monoamines was a causative factor in depressive disorders, although in the intervening years, efforts to provide empirical support for the monoamine hypothesis have yielded mixed results (Hindmarch, 2001). It is now generally agreed that the original hypothesis is insufficient as a neurobiological basis for depressive disorders, with the true picture likely to be much more complex and heterogeneous, involving both monoaminergic and non-monoaminergic players (Belmaker and Agam, 2008). Nevertheless, the concept of monoaminergic dysfunction remains a useful and well-regarded component of that neurobiological picture, and has stimulated an extensive and productive line of research into the function of the central noradrenergic system in depressive disorders.

The central noradrenergic system is responsible for noradrenergic neurotransmission in the brain and plays a key role in general cognitive processes (Sara, 2009). The system is anatomically based in the brainstem nucleus known as the locus coeruleus (LC) which is the primary source of central NE synthesis, and its noradrenergic projections reach virtually all areas of the brain (Sara, 2009). The actions of NE are mediated by the family of G protein-coupled receptors (GPCRs) known as the adrenergic receptors (ARs), and levels of extracellular NE are regulated by synaptic clearance via the NE transporter (NET) and modulation of NE metabolism. Almost all of these noradrenergic system components can be direct molecular targets for antidepressant drugs, including the newer 5HT/NE reuptake inhibitors (SNRIs) such as duloxetine, atypical antidepressants like mirtazepine, and the older TCAs and MAOIs mentioned above (Baldessarini, 2006). In addition, many of these noradrenergic system components have been examined for potential dysfunction in the context of depressive disorders.

The ARs, consisting of β, α_1, and α_2ARs, are the cellular mediators of noradrenergic neurotransmission. Arguably, α_2ARs comprise the most important receptor family involved in regulation of noradrenergic transmission, and have consequently been subject to intensive study for potential roles in depressive neurobiology and antidepressant pharmacology. In this article, we will review the broad base of studies investigating α_2ARs in the depressive setting and attempt to construct a summarizing model for α_2AR dysfunction in depressive disorders. We contend that α_2AR alterations make an important contribution to the clinical manifestation of depressive disorders and are a putative mechanistic basis for depression-related NE depletion and LC dysfunction. Additionally, we will review evidence for depression-related dysfunction of some key regulators of α_2ARs, in particular GPCR kinases (GRKs), arrestins, and spinophilin.

2. The α_2 adrenergic receptor family

The various physiological roles of the α_2AR family in central and peripheral systems have been well-reviewed elsewhere by Hein and others (Brede et al., 2004; Kable et al., 2000; Knaus et al., 2007; Philipp et al., 2002; Wang, 2011), and so we will focus on a brief overview of the functions of these receptors in central noradrenergic neurotransmission. α_2ARs impact neuronal function by classically coupling to heterotrimeric G proteins of the $G_{i/o}$ subfamily upon activation by their endogenous agonists epinephrine and NE. In turn, stimulation of α_2ARs leads to inhibition of adenylyl cyclase and voltage-gated Ca^{2+} channels and activation of inwardly rectifying K^+ channels and MAPK signaling cascades (Kobilka, 1992; Limbird, 1988; Richman and Regan, 1998; Wang et al., 2006; Wang et al., 2004). Presynaptic α_2AR autoreceptors are responsible for inhibition of NE synthesis and release from noradrenergic terminals as part of a negative feedback loop (Hein et al., 1999; Knaus et al., 2007), and α_2ARs on non-noradrenergic terminals regulate release of other key neurotransmitters including glutamate (Shields et al., 2009). Meanwhile, activation of postsynaptic α_2ARs modulates neuronal excitability via regulation of ion channels,

including direct modulation of inwardly rectifying K^+ channels and indirect modulation of hyperpolarization-activated channels (Gilsbach et al., 2011). The importance of postsynaptic α_2ARs is increasingly becoming appreciated as their roles in mediating such classical α_2AR agonist effects as sedation, analgesia, and enhancement of working memory are illuminated (Gilsbach and Hein, 2012; Gilsbach et al., 2009; Wang et al., 2007). The generally inhibitory nature of α_2ARs with respect to neuronal function is also indicated by the ability of α_2AR activation to decrease epileptogenesis (Wilson et al., 1998).

There are three α_2AR subtypes, the α_{2A}, α_{2B}, and α_{2C}, which are encoded by separate genes (Bylund et al., 1994; Cottingham et al., 2011a; Wang, 2011). Among these, the α_{2A}AR is the predominantly expressed subtype within the central nervous system (De Vos et al., 1992; Sastre and Garcia-Sevilla, 1994; Wang et al., 1996), and is primarily responsible for the central noradrenergic functions described above (Altman et al., 1999; Franowicz et al., 2002; MacMillan et al., 1996; Stone et al., 1997). The α_{2C}AR also has a well-appreciated role in inhibition of neurotransmitter release, although it exhibits differential responsiveness to action potential frequency compared with the α_{2A} subtype (Hein et al., 1999). This phenomenon may be related to the unique localization of the α_{2C} subtype in synaptic terminals of mature neurons (Brum et al., 2006). The α_{2B}AR is mainly expressed in peripheral tissues and its physiological roles in the brain have not been clearly defined. As mentioned above, the importance of α_2ARs as regulators of noradrenergic system function in general and NE levels in particular has resulted in their being the most extensively studied ARs in the context of depressive disorders. Although clinical studies in this area have generally avoided subtype specificity due to the lack of subtype-selective agents for α_2ARs, genetic evidence from both human and experimental animals has clearly implicated involvement of the α_{2A} and α_{2C} subtypes in depressive disorder.

3. Dysregulation of α_2 adrenergic receptor density and activity in depressive disorders

A wide array of different approaches has been utilized over the last few decades to directly assay both α_2AR density and pharmacological properties in patients with depressive disorders. Attempts to ascertain receptor density have most commonly been made using saturation radioligand binding with radiolabeled α_2AR agonists and antagonists, and less commonly using immunolabeling-based techniques and measurements of mRNA levels. These assays have been carried out directly in postmortem brain tissue largely obtained from suicide completers and using peripheral models such as platelets obtained from living depressed patients. In addition, many studies have utilized classic pharmacological methods such as competition radioligand and GTPγS binding along with other readouts to characterize receptor activity in depressed patients. Given the range of methodologies, it is unsurprising that these studies have yielded seemingly inconsistent results. In particular, variable application of radiolabeled agonists versus antagonists in α_2AR binding studies has led to an apparently contradictory body of literature. As will become clear in the following sections, agonist (which leads to G protein coupling and activation) versus antagonist (which does not activate the receptor) is an important distinction in GPCR binding studies. With a careful accounting of methodological differences within the literature, consistent patterns of α_2AR dysregulation in depressive disorders can be appreciated.

3.1 Platelet α_2ARs

Studies on platelet α_2ARs have been the most commonly-used approach to assay receptor density in patients with depressive disorders. This approach has the advantage of allowing investigators to observe receptor levels in patients with active depression and without the influence of suicidality which pervades studies in postmortem tissue. Moreover, receptor

levels can be monitored in real-time during a course of treatment with an antidepressant therapy. Of course, these studies must be interpreted with a certain level of caution given that peripheral blood cell α_2ARs have different physiological roles and potentially different mechanisms of regulation compared with central receptors.

The body of work investigating α_2AR density in platelets obtained from major depressive disorder (MDD) patients provides a prime example of apparently contradictory findings which can be reconciled by accounting for methodological differences. Studies have variously reported increases, decreases, and no alterations in platelet α_2AR density associated with MDD. However, upon closer review, the literature in this area strongly supports a selective increase in high-affinity conformational state α_2AR density, which is indicative of enhanced G protein coupling and activity.

The numerous studies which have found elevated α_2AR density in platelets from unmedicated MDD patients, indicated by saturation radioligand binding, have utilized radiolabeled α_2AR agonists such as clonidine and UK 13,304 to detect α_2ARs (Garcia-Sevilla et al., 1987; García-Sevilla et al., 2004; Gurguis et al., 1999; Healy et al., 1985; Kaneko et al., 1992; Pandey et al., 1989; Piletz et al., 1990; Piletz et al., 1991; Smith et al., 1983; Takeda et al., 1989; Werstiuk et al., 1996). In fact, only a very few studies have observed no changes (Karege et al., 1992; Werstiuk et al., 1992) or decreases (Carstens et al., 1986) in density in MDD patients when utilizing agonists as the radioligand probe, although Karege and colleagues did report a trend toward an increased density in dysthymic patients (Karege et al., 1992). Conversely, studies conducted with a radiolabeled α_2AR antagonist have consistently failed to find increased platelet α_2AR density in MDD patients (Bhatia et al., 1991; Katona et al., 1989; Marazziti et al., 2001; Smith et al., 1983; Stahl et al., 1983; Theodorou et al., 1991; Wolfe et al., 1987; Wolfe et al., 1989). Although Marazziti and colleagues found that platelet α_2AR density overall was unaltered in their MDD patients, they did observe a significant correlation between receptor density and severity of depression symptoms (Marazziti et al., 2001), supporting a link between these two parameters.

The apparent discrepancies in binding data obtained with radiolabeled agonists versus antagonists can be explained by the distinct nature of these two types of ligands in binding to a GPCR. Receptors can exist in both active and inactive conformations, which are in a steady-state balance. Antagonists have equal affinity for both conformational states, and their binding does not alter the steady-state. Therefore, radiolabeled antagonist binding reflects the total density of receptors in any conformational state. By comparison, agonist binding induces a conformational change of the receptor to the active state resulting in G protein coupling to the receptor. The framework of the ternary complex model (scheme shown in Figure 1) and its extended versions describing the ternary complex of agonist, receptor, and G proteins (De Lean et al., 1980; Samama et al., 1993; Weiss et al., 1996) reveals that G protein coupling to the receptor highly impacts receptor affinity for agonists. Specifically, the receptor/G protein complex with the receptor in the high-affinity state has a much stronger interaction with agonists than the receptor alone in its low-affinity state. In a typical saturation binding assay with radiolabeled agonists, the apparent binding density primarily reflects the high-affinity state of receptor given that binding of an agonist to the low-affinity state of receptor is difficult to detect due to fast dissociation time (Limbird, 2005). Therefore, the specific increase in agonist-binding but not antagonist-binding α_2AR sites in the reports outlined above suggests a selective upregulation of high-affinity state receptors with enhanced G protein coupling. Indeed, several studies have specifically identified MDD-associated increases in the density of platelet α_2ARs in the high-affinity conformational state through competition binding and G protein coupling analyses (García-Sevilla et al., 1986; Garcia-Sevilla et al., 1987; García-Sevilla et al., 1981; Gurguis et al.,

1999). Increases in high-affinity state α_2ARs and G protein coupling to α_2ARs in MDD patients are also supported by reports of depression-associated increases in platelet α_2AR activity as measured by increased α_2AR-mediated platelet aggregation responses (García-Sevilla et al., 1986; García-Sevilla et al., 1990; Piletz et al., 1993). Evidence from platelet α_2AR studies is summarized in Table 1.

3.2 Direct assays of central α_2ARs

A number of studies investigating α_2AR status in depression have been carried out using postmortem brain tissue. This tissue has been almost universally obtained from suicide completers, and so it is important to bear in mind that alterations observed in these studies may be more closely related to the pathology of suicide specifically rather than depressive disorders generally. Nevertheless, these studies have largely tended to confirm the findings of increased α_2AR density in the high-affinity state from the platelet studies outlined above. A summary of these direct assays of central α_2ARs can be found in Table 1.

The most consistent line of evidence demonstrating upregulated α_2AR density is a series of studies from the Garcia-Sevilla group using tissue obtained from depressed suicide completers. Using radioligand-based approaches, they have shown significantly increased density of α_2ARs generally (Gonzalez et al., 1994) and of the α_{2A}AR subtype specifically (Callado et al., 1998; Meana et al., 1992; Meana and Garcia-Sevilla, 1987) in the frontal cortex, hippocampus, and hypothalamus. These findings are supported by separate studies reporting increased α_2AR density by radioligand binding in temporal cortex and locus coeruleus tissue from depressed suicide completers (De Paermentier et al., 1997; Ordway et al., 2003; Ordway et al., 1994b). Given the use of radiolabeled agonists for their binding assays, these studies tend to further support an increase in the density of high-affinity state α_2ARs in depressed suicide completers. In addition, the Garcia-Sevilla group has reported increased α_{2A}AR receptor protein levels using an immunolabeling method (Garcia-Sevilla et al., 1999) and increased α_{2A}AR mRNA levels using RT-PCR (Escriba et al., 2004) in the prefrontal cortex of depressed suicide completers.

Studies reporting no change in α_2AR density associated with suicide tend to differ from those above in either lacking a requirement for depression diagnosis in their suicide subject population (Arango et al., 1993; Gross-Isseroff et al., 2000) or using an antagonist instead of an agonist as the radiolabeled probe (Sastre and Garcia-Sevilla, 1997). The first difference is supportive of increased α_2AR density as an association with depressive disorders rather than suicide in general. The second provides additional support for a selective increase in high-affinity state α_2AR as found with platelet α_2ARs; indeed, Ordway and colleagues found increased locus coeruleus α_2AR density using a radiolabeled agonist but not an antagonist in the same patient samples (Ordway et al., 1994b). Only a single study utilizing a radiolabeled agonist found no alterations in prefrontal cortical or hippocampal α_2AR density in postmortem tissue from MDD patients specifically (Klimek et al., 1999). However, as the authors rightly point out, there are important differences between this study and those from the Garcia-Sevilla group. In particular, differences in the precise prefrontal cortex subregions assayed and the length of postmortem delay could most likely account for the discrepancy. Thus, these findings collectively suggest that regulation of receptors in depressive disorders is likely to vary considerably among different brain regions and even highly localized subregions.

The selective increases in the density of high-affinity state α_2ARs in brain regions of depressed suicide completers are indicative of enhanced G protein coupling and receptor activity. Indeed, an investigation utilizing a GTPγS binding technique in postmortem tissue demonstrated enhanced G protein coupling to prefrontal cortex α_2ARs, but not to other GPCRs including $5HT_{1A}$, μ-opioid, $GABA_B$, and muscarinic receptors previously shown to

be upregulated in depressed suicide completers (Gonzalez-Maeso et al., 2002). This finding has been characterized by the authors as "selective supersensitivity of α_2ARs" (Gonzalez-Maeso et al., 2002), and has been more recently supported by a separate study through assays of α_2AR-mediated G protein coupling and adenylyl cyclase inhibition in whole frontal cortex tissue (Valdizán et al., 2010).

Enhanced G protein coupling to α_2ARs in depressive disorders could result from alterations in the heterotrimeric G proteins themselves. Indeed, an elevated density of $G\alpha_{i2}/G\alpha_o$ (members of the G protein subfamily to which the α_2AR classically couples) subunits has been found in platelets from MDD patients; this was subsequently normalized by antidepressant drug treatment (García-Sevilla et al., 1997). An upregulation of $G\alpha_{i2}$ proteins has also been observed in postmortem prefrontal cortex tissue from untreated depressed suicide completers, while this alteration was not observed in patients subjected antidepressant treatment (Garcia-Sevilla et al., 1999).

Elevated G protein coupling to α_2ARs in depressive disorders may also be due to changes in non-G protein interacting partners (details in section 7). It is well-appreciated that GPCR kinases (GRKs) and arrestins play a key role in terminating G protein coupling to receptors (Premont and Gainetdinov, 2007; Shenoy and Lefkowitz, 2011). Reductions in expression of both GRK2/3 (Garcia-Sevilla et al., 2010; García-Sevilla et al., 2004; Matuzany-Ruban et al., 2010) and arrestin2 (Avissar et al., 2004; Matuzany-Ruban et al., 2005) have been reported in MDD patients. Such alterations may contribute to enhanced G protein coupling to α_2ARs in these patients. In addition, we have identified that binding of the scaffolding protein spinophilin to α_2ARs reduces G protein coupling to the receptor (Lu et al., 2010). A downregulation of spinophilin, as reported previously in brain tissue from MDD patients (Law et al., 2004), would also result in enhanced G protein coupling to α_2ARs.

3.3 Modeling α_2AR activity through physiological responses

A final approach to studying α_2ARs in depressed patients has been to assay receptor activity by measuring centrally-mediated α_2AR physiological responses to the classical agonist clonidine. A selective increase of high-affinity state α_2ARs in patients with depression, as discussed above, would be expected to result in enhanced sensitivity and responsiveness to α_2AR agonist administration in these patients. Indeed, several studies have found enhanced physiological α_2AR responses to clonidine (Coote et al., 1998; Paparrigopoulos et al., 2001), and this enhancement was normalized following antidepressant treatments (Balldin et al., 1992; Charney et al., 1981; Coote et al., 1998; Corn et al., 1984; Glass et al., 1982; Schittecatte et al., 2002). However, conflicting results of diminished (Schatzberg and Schildkraut, 1995; Schittecatte et al., 2002), and no changes to (Heninger et al., 1988; Trestman et al., 1992) α_2AR activity in depressed patients have also been reported. These discrepant results are most likely explained by the diverse array of methodologies used to assay α_2AR activity, which include assessment of classic α_2AR agonist effects such as sedation and hypotension, measurement of peripheral NE and NE metabolite levels, measurement of hormone levels modulated by clonidine administration, and the novel clonidine REM sleep suppression test developed by Schittecatte and colleagues (Schittecatte et al., 2002). A complete understanding of the neuronal loci and signaling pathways responsible for these various responses is currently lacking and will be necessary to properly interpret these kinds of studies.

3.4 Clinical genetic studies

Not surprisingly, given the evidence outlined in the preceding sections, a number of studies have been undertaken to investigate possible genetic links between the α_2AR subtypes and depressive disorders. We have recently reviewed genetic evidence for α_2AR involvement in

depressive disorders (Cottingham et al., 2011a), and so here we will simply emphasize a few of the most intriguing of these studies. The first comes from Sequeira and colleagues, who uncovered a possible link between the N251K variant of the α_{2A}AR and suicide, with the mutant allele found only in the suicide group and not in matched controls (Sequeira et al., 2004). Given that the N251K variant is a gain-of-function mutant (Small et al., 2000a), this association would provide a potential genetic basis for at least some of the cases of α_2AR supersensitivity reported in studies of postmortem tissue as reviewed above. Another intriguing study by Neumeister and colleagues has provided the first clinical evidence to-date for involvement of the α_{2C}AR subtype in depressive disorders. The authors utilized a positron emission tomography (PET) imaging approach to measure neuronal activity in response to viewing of happy and sad facial expressions, finding that the Del322-325 variant of the α_{2C}AR, a loss-of-function mutant (Small et al., 2000b), was associated with enhanced neuronal responsiveness to sad facial expressions in subjects with a history of MDD (Neumeister et al., 2006). Further investigation is necessary to elucidate the specific roles and contributions of specific α_2AR subtypes in the context of depressive disorders.

4. Effects of antidepressant therapy on α_2 adrenergic receptors

Given the copious evidence for altered α_2AR density associated with depressive disorders, investigations into the impact of effective antidepressant therapies on α_2AR density have also been undertaken within the field. Antidepressant therapies, including pharmacotherapy with antidepressants possessing noradrenergic activity (e.g. TCAs, 5HT/NE reuptake inhibitors, mirtazepine, etc.) and other treatments such as electroconvulsive therapy (ECT), have been generally associated with a normalizing effect on α_2AR density (i.e. downregulation). Evidence in support of this point comes from both clinical and experimental models, and is summarized in Table 2.

4.1 Clinical evidence

Clinically, many studies have found that chronic, symptom-alleviating antidepressant therapies cause reductions in platelet α_2AR density, often returning to control levels. Specifically, such an α_2AR downregulation response has been associated with chronic TCA (García-Sevilla et al., 1986; Garcia-Sevilla et al., 1987; García-Sevilla et al., 1981; Gurguis et al., 1999; Healy et al., 1985; Karege et al., 1992; Piletz et al., 1991; Smith et al., 1983) and mirtazepine (García-Sevilla et al., 2004) treatment and ECT (Cooper et al., 1985; Smith et al., 1983; Werstiuk et al., 1996), including reductions in both overall receptor density and high-affinity conformational state density. Studies utilizing postmortem brain tissue have also found antidepressant treatment to be associated with a normalizing trend of decreased α_2AR density in their patient populations (De Paermentier et al., 1997; Garcia-Sevilla et al., 1999), paralleling the findings on platelet α_2ARs. Collectively, these findings indicate that MDD-associated increases in α_2AR density are corrected over the course of therapeutically successful antidepressant treatment.

4.2 Experimental evidence

Given the clinical evidence, it is possible to draw a fairly clear connection between experimental studies investigating the phenomenon of antidepressant-induced adaptive alterations in α_2AR density and the therapeutic mechanism. Indeed, several studies have reported downregulation of cortical and hippocampal α_2ARs through direct assays of receptor expression levels following chronic exposure of rodents to antidepressant drugs (Barturen and Garcia-Sevilla, 1992; Cottingham et al., 2011b; Giaroni et al., 2008; Giralt and Garcia-Sevilla, 1989; Smith et al., 1981; Subhash et al., 2003). Further, studies have reported functional α_2AR downregulation in the form of decreased α_2AR-mediated responses following chronic exposure of rodents to antidepressant drugs (Esteban et al.,

1999; Mateo et al., 2001; Menargues et al., 1990; Nomura et al., 1987). Among those studies, downregulation of both presynaptic autoreceptors (Esteban et al., 1999; Mateo et al., 2001) and postsynaptic α_2ARs (Menargues et al., 1990) has been reported. Furthermore, the decreases in α_2AR density are likely due to an increased turnover rate for cortical α_2ARs (Barturen and Garcia-Sevilla, 1992) rather than regulation of expression at the transcriptional level (Canciani et al., 2006; Giaroni et al., 2008). This is consistent with findings that antidepressant treatment leads to increased expression of GRKs and arrestin (see sections 7.1 and 7.2), which would in turn promote α_2AR turnover from the cell surface. Collectively, these findings support the notion that downregulation of central α_2AR density is at least a significant component of the therapeutic antidepressant mechanism. It should be noted that of the above studies, only two (Giaroni et al., 2008; Cottingham et al., 2011b) have attempted subtype specificity, showing downregulation of the α_{2A}AR specifically.

Mechanistically, this α_2AR downregulation response has been traditionally conceived of as resulting from chronic repetitive receptor stimulation by increased levels of NE. However, our own recent work has provided new insight into the mechanism of antidepressant-induced α_2AR downregulation (Cottingham et al., 2011b). We have shown that a physiologically-relevant concentration of NE, corresponding to extracellular levels reached with chronic reuptake inhibition, is in fact unable to sustain any α_{2A}AR downregulation response. Instead, the TCA desipramine, which we identified as an arrestin-biased ligand at the receptor, directly drives reductions in α_{2A}AR density both *in vitro* and *in vivo* through recruitment of arrestin to the α_{2A}AR and subsequent arrestin-mediated internalization and downregulation. These findings provide a novel mechanism for therapeutic physiological antidepressant drug action.

It is important to note that antidepressant effects on α_2AR expression levels may be both region- and age-dependent. There has been some variability in whether downregulation is observed in cortex, hippocampus, or both, and it has been reported that chronic NE reuptake inhibition stably downregulates presynaptic α_2AR autoreceptors but not somatodendritic α_2ARs in the LC (Mateo et al., 2001; Parini et al., 2005). In addition, Deupree and colleagues have reported deficits in chronic antidepressant-induced downregulation in juvenile rodents likely owing to developmental immaturity of the α_2AR/noradrenergic system (Deupree et al., 2007).

5. The role of α_2 adrenergic receptors in animal models of depression

Rodent models have been extensively exploited as a means to experimentally explore roles for the α_2ARs in depressive disorders. Mechanistic studies in rodent models can be difficult given the limitations of currently available experimental paradigms, which often suffer from a lack of face and/or construct validity. These issues have been well-discussed by others (Nestler et al., 2002; Nestler and Hyman, 2010; Petit-Demouliere et al., 2005). For our purposes, it seems best to conceptualize the rodent studies as modeling different mechanistic aspects of depression-related neurobiology and antidepressant pharmacology rather than providing definitive answers on α_2 adrenergic mechanisms in depression. Such a conceptualization can help to account for discrepancies in this area, although the relative contribution of these different putative mechanisms to the clinical therapeutic antidepressant mechanism of action remains an open question. Regardless of mechanistic complexity, animal models have provided additional confirmation of the importance of α_2ARs in depressive disorders.

5.1 Rodent behavioral studies

Some rodent behavioral studies have confirmed a detrimental role for α_2ARs in the context of depressive disorders. It has been recently demonstrated that α_2AR antagonist treatment causes an enhancement of chronic antidepressant-induced hippocampal neurogenesis and hastens the appearance of antidepressant behavioral effects in the novelty-suppressed feeding paradigm (Yanpallewar et al., 2010). These effects have been postulated to occur through blockade of postsynaptic α_2ARs. Meanwhile, in Porsolt's forced swim test (FST) (Porsolt et al., 1977), administration of the subtype-selective α_{2A}AR antagonist BRL44408 has been reported to exert an acute antidepressant effect (Dwyer et al., 2010). However, reports that α_2AR antagonists lacking subtype-specificity do not exert antidepressant effects in the FST (Reneric et al., 2001; Zhang et al., 2009) raise the possibility that blockade of different α_2AR subtypes may have opposing effects in this assay. This possibility is supported by the phenotypes of the α_{2A}AR and α_{2C}AR knockout models (see section 5.2 below).

Contrastingly, other studies have indicated that α_2AR activation can have antidepressant efficacy in rodents. For example, α_2ARs have been consistently implicated in mediating the antidepressant behavioral effects of TCAs in the rodent FST (Cervo et al., 1990; Reneric et al., 2001; Zhang et al., 2009), with some studies demonstrating α_{2A}AR subtype specificity (Cottingham et al., 2012; Schramm et al., 2001). Antidepressant effects of the TCA desipramine in a rodent chronic stress model were also found to be α_2AR-dependent (Yalcin et al., 2005). In addition, direct α_2AR activation by agonists has been shown to have antidepressant effects on behavior in the FST (Cervo and Samanin, 1991; Cottingham et al., 2012; Stone et al., 2011). These studies are consistent with a mechanism relying on a decrease in locus coeruleus firing activity mediated by somatodendritic α_2ARs. Such a phenomenon has been consistently reported with antidepressant administration (Grant and Weiss, 2001; West et al., 2009) and shown to occur in an α_2AR-dependent fashion (Berrocoso and Mico, 2007; Grandoso et al., 2005; Linner et al., 1999; Mateo et al., 1998). Therefore, these studies are supportive of an MDD-related increase in LC firing activity which is normalized by antidepressant treatment.

Indeed, there is evidence to directly support dysfunction of the LC in depressive disorders. In LC tissue from MDD patients, both decreased expression of NET (Klimek et al., 1997) and increased expression of tyrosine hydroxylase (Ordway et al., 1994a; Zhu et al., 1999) have been reported. Collectively, these findings are suggestive of secondary adaptive alterations in the LC compensating for a depletion of NE levels in MDD (i.e. decreased NE reuptake activity, increased NE synthesis, and increased neuronal firing activity to enhance noradrenergic transmission).

It is important to note that the above rodent studies have largely reported on acute antidepressant drug effects, and so do not directly model the full clinical therapeutic actions of these treatments. As mentioned above, these studies should be interpreted as modeling different mechanistic aspects, and are supportive of a complex and variable role for α_2ARs in the neurobiology of depression and in antidepressant pharmacology. Put another way, these findings suggest that there may be more than one way to obtain an antidepressant effect by modulating noradrenergic neurotransmission.

5.2 α_2AR knockout models

Studies using knockout models for the α_{2A} and α_{2C} subtypes have suggested opposing roles for these receptors in the FST. α_{2A}AR-deficient mice were found to have enhanced swim stress-induced behavioral despair (Schramm et al., 2001), while the opposite was true for α_{2C}AR-deficient mice (Sallinen et al., 1999). Although the phenotype of the α_{2C}AR-

deficient mice corresponds nicely with the aforementioned clinical genetic study of Neumeister and colleagues (see section 3.4), the phenotype of the α_{2A}AR-deficient mice seems contradictory to the clinical findings. However, it is important to bear in mind that the FST is a pharmacological screening model and is not intended as an etiological model for depressive disorders, and so these mouse models have yet to be truly evaluated for their depressive phenotypes in behavioral paradigms with better face and/or construct validity. As well, it seems likely that global loss of either receptor subtype may have drastically different effects on behavior than the more localized alterations associated with clinical depressive disorders.

6. A working model for α_2 adrenergic receptor dysfunction in depressive disorders

A schematic representation of our overall working model for α_2AR dysfunction in depressive disorders is presented in Figure 2. Based upon the available evidence, it can be stated that there is clearly involvement of α_2ARs in depressive disorders, and their roles certainly appear to be complex and variable. To summarize, it seems reasonable to conclude that depressive disorders are, in at least a significant proportion of cases, accompanied by a physiological upregulation of high affinity state platelet α_2ARs, and so techniques geared toward detecting such receptors may have utility as both experimental and potential diagnostic tools. Further, depressive disorders seem to be accompanied by an increase in α_2AR density and/or a supersensitivity of α_2ARs in the central nervous system. Collectively, these alterations can be presumed to increase α_2AR signaling drive in a region-specific fashion, leading to decreases in neurotransmitter release and overall neuronal activity and to corresponding compensatory changes in the LC. Accordingly, successful antidepressant therapies, including antidepressant drugs (particularly noradrenergic drugs) and ECT, are generally associated with α_2AR downregulation, an effect which would serve to normalize the elevated α_2AR activity. Overall, the findings reviewed here support a model whereby neuroadaptive changes to α_2AR density and pharmacological properties, which normalize pathophysiological changes to these receptors, are a component of the therapeutic antidepressant mechanism of action.

7. Receptor accessory proteins in depressive disorders

A number of non-G protein interacting partners play important roles in regulating and mediating α_2AR function. These proteins include GRKs, arrestins, and spinophilin. It is important to note, of course, that arrestins and GRKs are involved in the function of almost all GPCRs (Premont and Gainetdinov, 2007; Shenoy and Lefkowitz, 2011), while spinophilin has a number of roles in synaptic function in addition to directly regulating multiple GPCRs (Sarrouilhe et al., 2006; Wang and Limbird, 2007). Therefore, alterations in any of these players may have implications beyond α_2ARs. Nevertheless, alterations in these key accessory proteins may help to provide a mechanistic basis for the α_2AR dysregulation in depressive disorders in addition to potential changes in the G proteins themselves, a topic which has been well-reviewed by Gonzalez-Maeso and Meana (Gonzalez-Maeso and Meana, 2006).

7.1 GRKs

GRKs classically participate in the process of receptor desensitization by phosphorylating conformationally active receptors (Pitcher et al., 1998), which in turn leads to arrestin binding and uncoupling of G proteins, and these kinases have been implicated in a number of disease states (Gurevich et al., 2012). Reductions in GRK2/3 at the protein level (Garcia-Sevilla et al., 2010; García-Sevilla et al., 2004; Matuzany-Ruban et al., 2010) and GRK2 at

the mRNA level (Matuzany-Ruban et al., 2010) have been reported in peripheral blood cells obtained from MDD patients. These levels were correspondingly normalized by antidepressant treatment. Lack of sufficient GRK phosphorylation would lead to reduced receptor desensitization and enhanced signaling responses, which may help to explain the enhanced α_2AR activity in MDD. Conversely, plasma membrane-associated GRK2 (a cytosolic protein which translocates to the plasma membrane upon receptor activation) was found to be increased in PFC tissue from depressed suicide completers but not in tissue from patients subjected to antidepressant treatment (Garcia-Sevilla et al., 1999; Grange-Midroit et al., 2003). This increase in plasma membrane-associated GRK2 was correlated with the elevated level of the α_{2A}AR and $G\alpha_i$ observed in the PFC of the same patients, and may be indicative of cellular efforts to compensate for elevated receptor activity. Taken together, these findings clearly support a role for GRKs both in the neurobiology of depression and in antidepressant pharmacology. However, given the large number of GPCRs that are regulated by GRKs in the central nervous system, the involvement of GRKs in depressive disorders is likely to be complicated and will require further investigation.

7.2 Arrestins

Arrestins bind to GRK-phosphorylated receptors and mediate receptor desensitization and internalization (Premont and Gainetdinov, 2007; Shenoy and Lefkowitz, 2011). The ubiquitously-expressed arrestins, arrestin2 and 3 (also called β-arrestin1 and 2), have also been investigated for possible links to depressive disorders. Much of the support for a role for arrestin in depressive disorders is indirect at this point, as recently reviewed by Golan and colleagues (Golan et al., 2009). However, direct studies have been attempted. Arrestin2 has been reported to be decreased at both the protein and mRNA levels in leukocytes obtained from MDD patients (Avissar et al., 2004; Matuzany-Ruban et al., 2005). Such a reduction may contribute to enhanced G protein coupling to α_2ARs in these patients, given the classical role of arrestin in uncoupling G proteins from receptors. Correspondingly, antidepressant treatment has been shown to increase arrestin2 expression in patient leukocytes (Matuzany-Ruban et al., 2005). Experimental evidence supports antidepressant-induced increases in arrestin2 expression in rodent neural tissue (Avissar et al., 2004; Golan et al., 2011). Intriguingly, the clinical study demonstrated that during the course of antidepressant treatment, the rebound in arrestin2 density preceded the onset of symptom relief (Matuzany-Ruban et al., 2005). Such a biomarker role for arrestin is supported by a recent genome wide expression profiling study in a leukocyte cell model which identified an arrestin gene as a potential marker for the clinical response to paroxetine (Morag et al., 2011).

With regard to arrestin3, a study utilizing postmortem PFC tissue from MDD patients found no alterations in arrestin3 protein levels (Grange-Midroit et al., 2003). Experimentally, a role for arrestin3 in the antidepressant response is strongly suggested by our own recent studies, which identified the TCA desipramine as a direct arrestin3-biased ligand at the α_{2A}AR and demonstrated that chronic desipramine exposure drove arrestin3-dependent downregulation of central α_{2A}ARs *in vivo* (Cottingham et al., 2011b). In addition, we have reported that the acute antidepressant response elicited by desipramine in the FST is both α_{2A}AR- and arrestin3-dependent (Cottingham et al., 2012). Our findings indicate that the involvement of arrestin is variable in nature, as the response to the serotonergic drug fluoxetine does not require α_{2A}ARs and is actually inhibited by arrestin3. Therefore, the arrestins have specific roles in regulating the GPCRs involved in responses to differing antidepressants (i.e. α_2ARs with the noradrenergic drug desipramine versus 5HT receptors with the serotonergic drug fluoxetine).

7.3 Spinophilin

Spinophilin is a dendritic spine-enriched scaffolding protein (Allen et al., 1997; Satoh et al., 1998) which regulates the activity of multiple GPCRs (Sarrouilhe et al., 2006; Wang and Limbird, 2007). We have previously reported that spinophilin interferes with coupling of the α_{2A}AR to cognate G proteins in the mouse brain (Lu et al., 2010). In the context of depressive disorders, reduced spinophilin expression has been reported in hippocampal tissue obtained from MDD patients (Law et al., 2004) and in cortical tissue from animal models of stress-induced depressive behavior (Law et al., 2009; Leussis and Andersen, 2008). Such alterations in spinophilin would result in enhanced G protein coupling to the α_{2A}AR, which may contribute to enhanced high-affinity state α_2AR density in depressive patients. Furthermore, our laboratory has established spinophilin as a functional antagonist of arrestin functions at activated α_2ARs regulating *in vivo* response sensitivity to α_2AR agonists (Wang et al., 2004). Consistent with this finding, we have recently demonstrated that the acute α_{2A}AR- and arrestin3-dependent antidepressant response to desipramine is enhanced in spinophilin-deficient mice (Cottingham et al., 2012), indicating a role for spinophilin and this α_2AR regulatory system in antidepressant pharmacology. In addition, an association between decreased dendritic spine density and depression has been suggested both clinically (Soetanto et al., 2010) and experimentally (Hajszan et al., 2009), further implicating spinophilin given its importance to spine formation and function (Feng et al., 2000). Collectively, these findings strongly suggest that dysregulation of spinophilin may make a contribution to depressive disorders, potentially related to both its α_2AR and synaptic regulatory functions.

8. Conclusions and perspectives

Based upon the evidence presented here, there is clear support for dysfunction of α_2ARs and some key α_2AR regulators in depressive disorders. As summarized in Tables 1 and 2 and Figure 2, available evidence indicates that an upregulation of α_2ARs, either in terms of absolute expression level or overall receptor activity, represents a valid component of the physiological state of depressive disorders. This α_2AR dysregulation would have clear consequences to noradrenergic neurotransmission in the brain, given the important role for α_2ARs in regulating the noradrenergic system. Alterations in other components of the receptor system, including heterotrimeric G proteins, GRKs, arrestin, and spinophilin may contribute to α_2AR dysfunction. In fact, some evidence is suggestive of coordinated changes in both the receptor and its partner proteins in the neurobiology of depression and in response to antidepressant therapy. Future investigations examining the full receptor system may be particularly useful in elucidating the relationship between alterations in the receptor and alterations in its interacting partners.

While our review of the literature has clarified and underscored the importance of α_2AR dysregulation in depressive disorders, this is most likely not the sole causative factor in depressive disorders, given that the neurobiology of depressive disorders is clearly complex and multifactorial. There is almost certainly some etiological heterogeneity in this class of disorders, with α_2AR dysfunction being of great importance in some cases but less so in others. Further, although the alterations in the α_2AR system outlined in this review carry significant consequences for central nervous system function, it is presently unclear if they are symptomatic or in fact causative in the putative noradrenergic pathobiology of depression. In other words, α_2AR alterations could certainly cause LC dysfunction, but they could also be adaptive changes secondary to LC dysfunction with some other root cause. Even as a secondary change, α_2AR alterations could certainly exacerbate the pathobiological changes. These issues remain to be resolved.

Although strongly implicating α_2ARs in depressive disorders, the current body of literature on this subject has several drawbacks. One such drawback is a dearth of subtype-selective studies. Although the α_{2A} subtype seems a likely culprit in most of the reports on α_2ARs given its predominance in the central nervous system, the α_{2C} subtype should certainly not be ignored. Future studies should be aimed at identifying potential subtype-selective roles within the α_2AR family. Another drawback is the extreme methodological variability. Methodology plays an important role in influencing the outcomes of these studies, especially with regard to the identity of the radioligand in the binding assays most commonly used to assay receptor density. Although at first glance there appear to be great contradictions among these studies, accounting for methodological differences reveals a convincing case for upregulation of high-affinity conformational state α_2ARs in depressive disorders. Assaying for this parameter in platelet samples from depressed patients may have use as a diagnostic tool in directing antidepressant therapy. For example, patients with this symptom may benefit more strongly from antidepressant drugs such as desipramine with noradrenergic specificity and which can drive robust α_2AR downregulation.

Finally, it is important to note that our present knowledge on the state of central α_2ARs is limited to studies which have in turn been limited by the almost exclusive use of brain tissue from suicide completers. Suicidality is not a universal feature of depressive disorders, and so it is possible that α_2AR abnormalities observed in these studies apply more specifically to depressive suicidality. At any rate, these findings indicate that depression with suicidality may respond particularly well to strongly noradrenergic antidepressants.

The ability to directly study central α_2ARs in living patients suffering from depressive disorders is currently lacking. However, the advent of PET methodology raises the possibility of being able to do this in the future. PET has already shown promise for assaying central protein levels in living patients, with the Pittsburgh compound B agent for labeling β-amyloid plaques in Alzheimer's disease a conspicuous example (Sweatt, 2010). Indeed, there has been some progress, albeit uneven, in designing labeled α_2AR ligands for PET studies (Jakobsen et al., 2006; Marthi et al., 2004; Prabhakaran et al., 2010). It will be important, of course, to bear in mind the choice of agonist versus antagonist for PET ligands. This methodology would allow investigators to scan depressive patients for central α_2AR density, and then monitor changes to that density over a course of antidepressant treatment. The information that can be obtained from such studies would be invaluable in advancing our understanding of noradrenergic dysfunction in depressive disorders, building upon the existing knowledge base which we have reviewed here.

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Abbreviations

AD	antidepressant drug
AR	adrenergic receptor
ECT	electroconvulsive therapy
GPCR	G protein-coupled receptor
GRK	G protein-coupled receptor kinase
LC	locus coeruleus

MAOI	monoamine oxidase inhibitor
MDD	major depressive disorder
NE	norepinephrine
NET	norepinephrine transporter
PET	positron emission tomography
TCA	tricyclic antidepressant

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Highlights

- Evidence for α_2 adrenergic receptor dysregulation in depression is reviewed.
- The state of key receptor accessory proteins in depression is also appraised.
- Major depression is associated with α_2 adrenergic receptor elevation.
- Antidepressant therapies normalize upregulated α_2 adrenergic receptor levels.
- New insights with clinical and basic science implications are uncovered.

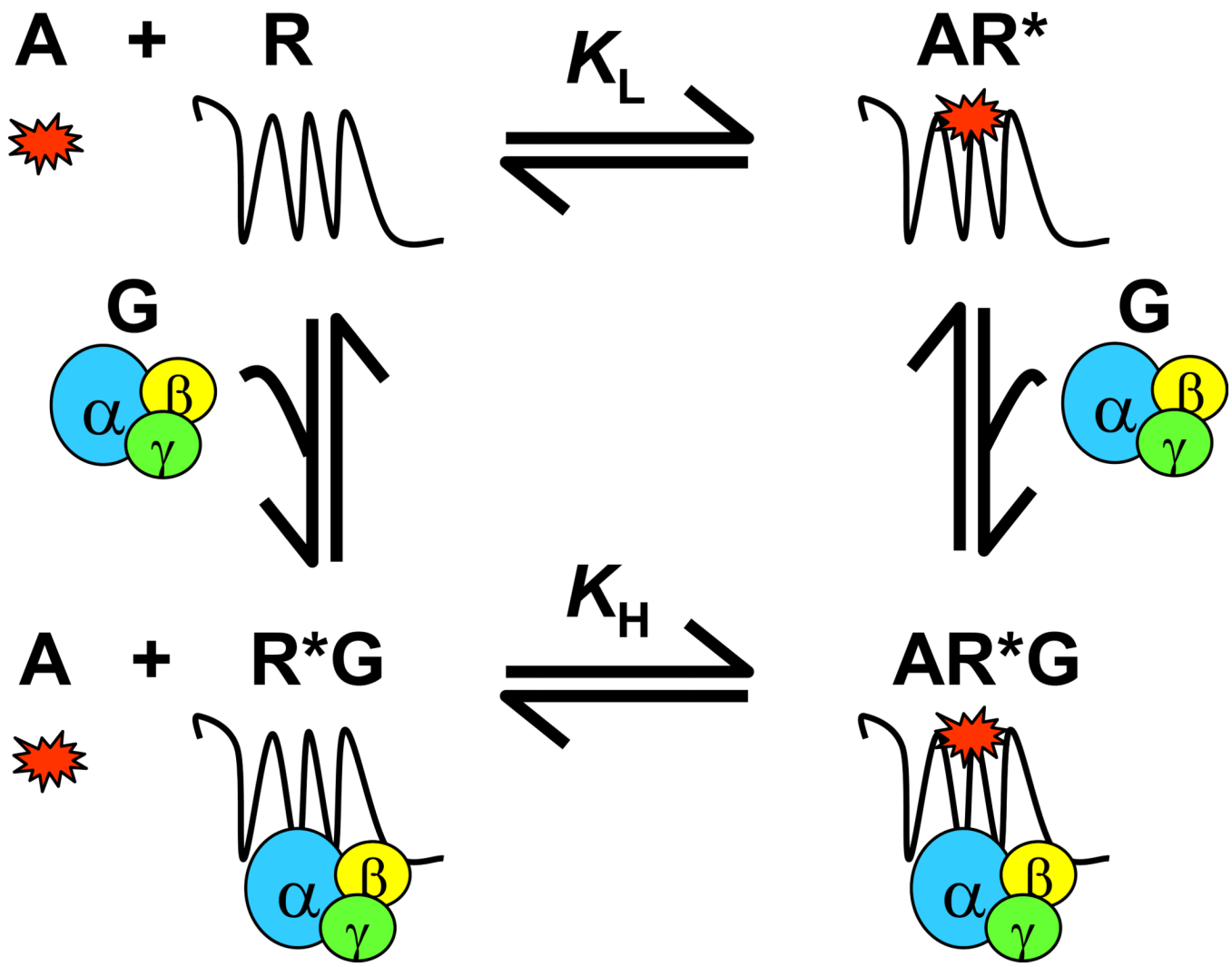

Figure 1.

Scheme of the ternary complex model for binding of agonist and G proteins to GPCRs. A receptor exists in both active and inactive conformations, with the active able to form a complex with G proteins. Agonists bind to free receptors (inactive) and receptors coupled to G protein (active) with different affinities; receptors coupled to G protein have a higher affinity than free receptors for agonists. Thus, receptor interactions with agonists as detected by radioligand binding assays are indicative of receptor-G protein coupling efficiency. A, agonist; G, G protein; R, free receptor; AR*, agonist-bound receptor (R* indicates active conformation of the receptor); R*G, G protein-bound receptor; AR*G, agonist/G protein/receptor ternary complex; K_H, K_d value of receptor binding at high-affinity; K_L, K_d value of receptor binding at low-affinity.

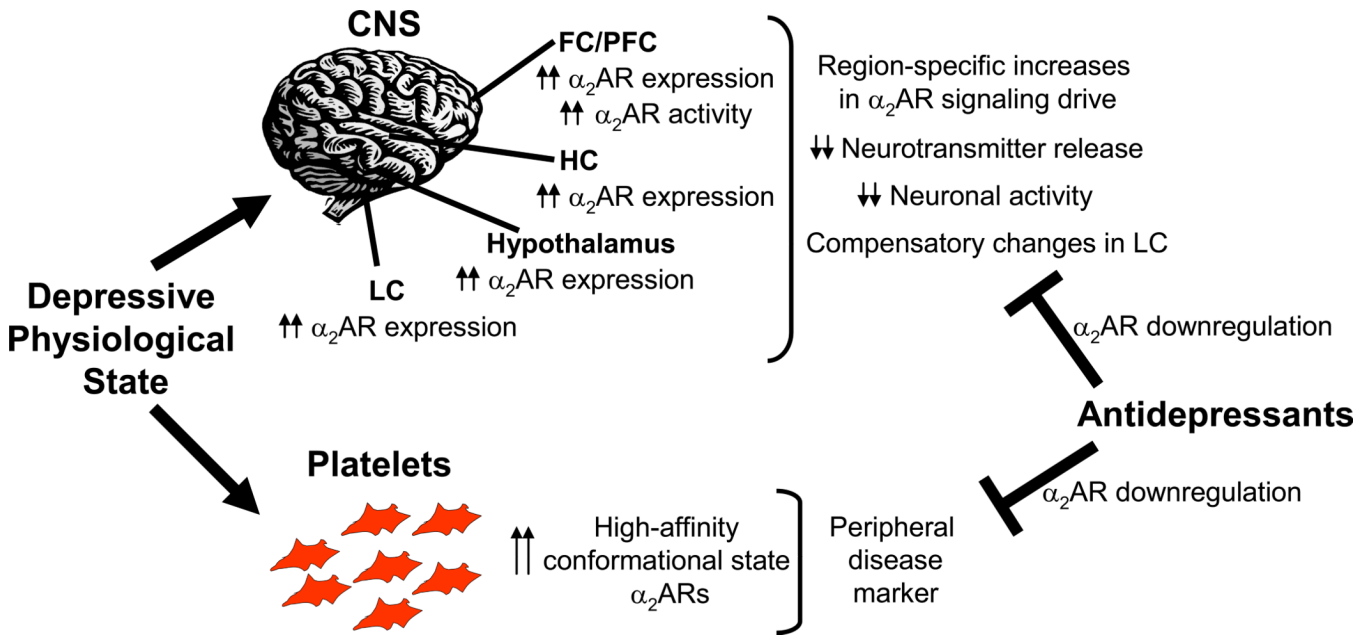

Figure 2.

Working model of α_2AR dysfunction in depressive disorders. The depressive physiological state involves various alterations in α_2AR expression and function, leading to abnormal α_2 noradrenergic signaling activity. Antidepressant therapies (including pharmacological agents and ECT) with noradrenergic effects cause a downregulation of α_2AR expression, normalizing the abnormalities.

Table 1

Summary of clinical evidence supporting upregulation of α_2ARs in depressive disorders.

Finding	Tissue	Method	Reference(s)
Elevated density	Platelet	Radiolabeled agonist binding	Garcia-Sevilla et al., 1987, 2004 Gurguis et al., 1999 Healy et al., 1985 Kaneko et al., 1992 Pandey et al., 1989 Piletz et al., 1990, 1991 Smith et al., 1983 Takeda et al., 1989 Werstiuk et al., 1996
	FC	Autoradiography Radiolabeled agonist binding	Gonzalez et al., 1994 Callado et al., 1998 Meana & Garcia-Sevilla, 1987 Meana et al., 1992
	PFC	Immunolabeling	Garcia-Sevilla et al., 1999
	HC	Autoradiography	Gonzalez et al., 1994
	Hypothalamus	Radioligand agonist binding	Meana et al., 1992
	LC	Radioligand agonist binding	De Paermentier et al., 1997 Ordway et al., 1994b, 2003
Enhanced activity	Platelet	α_2AR-mediated aggregation response	Garcia-Sevilla et al., 1986, 1990 Piletz et al., 1993
Elevated high-affinity conformation	Platelet	Competition radioligand binding	Garcia-Sevilla et al., 1981, 1986, 1987 Gurgius et al., 1999
	Brain	Competition radioligand binding	Callado et al., 1998 Meana et al., 1992 Ordway et al., 1994b
Elevated mRNA	PFC	RT-PCR	Escriba et al., 2004
Enhanced α_2AR-G protein coupling	FC/PFC	GTPγS binding	Gonzalez-Maeso et al., 2002 Valdizan et al., 2010
Density/symptom severity correlation	Platelet	Radiolabeled antagonist binding	Marazziti et al., 2001

Abbreviations: FC, frontal cortex; PFC, prefrontal cortex; HC, hippocampus; LC, locus coeruleus.

Table 2

Summary of clinical and experimental evidence for α_2AR downregulation induced by antidepressant treatments.

Model system	Treatment	References
Patient platelets	TCA	Garcia-Sevilla et al., 1981, 1986, 1987 Gurguis et al., 1999 Healy et al., 1985 Karege et al., 1992 Piletz et al., 1991 Smith et al., 1983
	Mirtazepine	Garcia-Sevilla et al., 2004
	ECT	Cooper et al., 1985 Smith et al., 1983 Werstiuk et al., 1996
Patient brain tissue	TCA	De Paermentier et al., 1997
	Mixed group of AD drugs	Garcia-Sevilla et al., 1999
Rodent brain tissue	TCA	Barturen and Garcia-Sevilla, 1992 Cottingham et al., 2011b Giaroni et al., 2008 Giralt and Garcia-Sevilla, 1989 Esteban et al., 1999 Mateo et al., 2001 Nomura et al., 1987 Smith et al, 1981 Subhash et al., 2003
	MAOI	Giralt and Garcia-Sevilla, 1989 Mateo et al., 2001

Abbreviations: TCA, tricyclic antidepressant; ECT, electroconvulsive therapy; AD, antidepressant; MAOI, monoamine oxidase inhibitor.