CHAPTER 8

Genetic Variations of α_2-Adrenergic Receptors Illuminate the Diversity of Receptor Functions

Christopher Cottingham, Huaping Chen, Yunjia Chen, Yin Peng, and Qin Wang

Department of Physiology and Biophysics, University of Alabama at Birmingham, AL, USA

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I. OVERVIEW

With advanced genotyping and sequencing technology, tremendous progress has been made in identification of human genome variations and their association with disease risk over the past 10 to 15 years. These studies represent a useful tool for understanding disease etiology and developing effective therapeutic strategies. Meanwhile, the wealth of information obtained in these studies provides valuable insights into endogenous functions of a gene in human physiology. Genetic variants have been identified in genes encoding all subtypes of the α_2 adrenergic receptor (α_2AR) subfamily, which represent an important group of receptors in normal and dysfunctional physiology as well as a significant class of therapeutic drug targets. The study of receptor polymorphisms and their associations with disease states in human populations provides insight complementary to that gained from experimental models on subtype-selective functions in the human body. For example, within the central nervous system (CNS), α_2AR genetic variants have been strongly linked to attention deficit/hyperactivity disorder (ADHD). α_2AR genetic variants have also been associated with various forms of cardiovascular dysfunction including heart disease. A relatively new line of evidence has implicated polymorphisms of the α_{2A}AR subtype specifically in type 2 diabetes. Additional evidence exists linking α_2AR genetic variants with other peripheral disorders, especially those involving autonomic nervous system dysfunction. This chapter will primarily review current knowledge of α_2AR genetic variants and their myriad associations with human disease states.

II. INTRODUCTION

The α_2 subfamily of adrenergic receptors (α_2ARs) consists of three subtypes, α_{2A}, α_{2B}, and α_{2C}, which are products of three distinct genes (Bylund et al., 1994). In native cells, all α_2AR subtypes signal through cognate heterotrimeric G proteins of the $G_{i/o}$ subfamily. Activation of these receptors inhibits adenylyl cyclase and voltage-gated Ca^{2+} channels, and also activates receptor-operated inwardly rectifying K^+ channels (Limbird, 1988; Kobilka, 1992). It has also been reported that stimulation of α_2ARs induces activation of phospholipase C (Gesek, 1996; Dorn, Oswald, McCluskey, Kuhel, & Liggett, 1997), which appears to be required for α_2AR-evoked inhibition of hyperpolarization-activated and cyclic nucleotide-gated channel (HCN) inward currents (Carr, Andrews, Glen, & Lavin, 2007). In addition, activation of α_2ARs leads to signaling propagation through the MAP kinase pathway (Richman & Regan, 1998; Wang et al., 2006a).

α_2ARs are widely distributed throughout the body and mediate a large variety of physiological and pharmacological responses *in vivo*. When activated by their

endogenous ligands, epinephrine and norepinephrine (NE), α_2ARs couple to decreased epileptogenesis (Wilson et al., 1998) and anxiety (Schramm, McDonald, & Limbird, 2001), as well as reduction in insulin release (Hiyoshi et al., 1995; Natali et al., 1998). In response to pharmacological α_2AR agonists, activation of α_2ARs lowers blood pressure (MacMillan, Hein, Smith, Piascik, & Limbird, 1996; Altman et al., 1999), evokes sedation (Lakhlani et al., 1997), reduces pain perception (Lakhlani et al., 1997; Stone, MacMillan, Kitto, Limbird, & Wilcox, 1997), and improves working memory (Franowicz, Kessler, Borja, Kobilka, Limbird, & Arnsten, 2002; Ma et al., 2001; Marrs, Kuperman, Avedian, Roth, & Jentsch, 2005; Wang et al., 2007). There are no subtype-selective agonists available for α_2ARs to date, and so subtype-selective functionality has been elucidated primarily through the use of transgenic mouse models. Such studies have revealed *in vivo* functions of individual α_2AR subtypes by characterizing genetically targeted mice. For example, most of the central effects elicited by α_2AR-agonists including sedation and blood pressure reduction can be attributed to the α_{2A}AR subtype, because these responses are lost in mice lacking the functional α_{2A}AR (MacMillan et al., 1996; Altman et al., 1999; Lakhlani et al., 1997). On the other hand, α_2AR agonist-induced peripheral vasoconstriction and hypertensive responses in arteries are mediated by the α_{2B}AR subtype (Link et al., 1996). Functions of individual α_2AR subtypes uncovered by studies in transgenic mice have been extensively reviewed previously (Kable, Murrin, & Bylund, 2000; Philipp, Brede, & Hein, 2002; Knaus et al., 2007), and thus will not be discussed in detail in this review.

With remarkable advances in human genome sequencing and genotyping, identification of genetic variations in human populations and their potential associations with diseases and disorders has become a rapidly growing field. Generally, when a genetic variant appears in more than 1% of a population, it is defined as a polymorphism. Put another way, polymorphisms are (relatively) common genetic variants. In many cases, polymorphisms result in alterations in the expression and/or function of gene products, thereby contributing to disease processes and susceptibility. All α_2AR subtypes have been studied in this regard, and a number of polymorphisms have been identified. These polymorphisms have been investigated for their impact on receptor signaling and pharmacology, and for potential involvement in human diseases and disorders. Pharmacogenetic approaches have also investigated roles for these polymorphisms in relevant drug responses. Given the importance of α_2AR functions in multiple physiological processes and as a therapeutic drug target, it is not surprising that variations at these gene loci have been found to be associated with a number of disease states. Collectively, these genetic association studies illuminate diverse functions of the α_2ARs.

III. OVERVIEW OF α_2AR GENETIC VARIANTS

Before embarking on a review of α_2AR genetic studies in human diseases, we will very briefly introduce α_2AR genetics and outline the common receptor polymorphisms. The three α_2AR subtypes are separate gene products, and all are encoded as intronless genes. Human α_{2A}, α_{2B}, and α_{2C}AR genes are located on chromosomes 10, 2, and 4, respectively. Interestingly, very few polymorphisms have been observed within the coding regions, and all of these reported so far are located within the receptor third intracellular loop (3i loop). Much of the seminal work on adrenergic receptor polymorphisms has been undertaken by the laboratory of Stephen Liggett, and this subject has been extensively reviewed by him and colleagues (e.g., Small, McGraw, & Liggett, 2003). Table I presents a summary by receptor subtype of commonly-studied polymorphisms and their disease associations (which will be detailed in subsequent sections).

A. α_{2A}AR

Although numerous α_{2A}AR genetic variants have been identified, only one nonsynonymous polymorphism has been found within the coding region of the gene. This is the C-to-G substitution at position 753 of the gene which results in an Asn-to-Lys change at residue 251 (N251K), located in the 3i loop (Small, Forbes, Brown, & Liggett, 2000a). The N251K mutant receptor has been shown, at the molecular level, to be a gain-of-function mutant resulting in increased agonist-stimulated G protein coupling to the receptor (Small et al., 2000a). This polymorphism appears to be quite infrequent in the human population (allele frequencies well below 1%), and consequently it has been difficult to study. A number of other polymorphisms have been described in noncoding regions of the gene, including the promoter and 5′-UTR and 3′-UTR regions. Of these, the most-studied is the C-1291G polymorphism in the promoter region, first identified as a restriction fragment length polymorphism (RFLP) creating an Msp1 cleavage site (Lario, Calls, Cases, Oriola, Torras, & Rivera, 1997). The particular effect of this single polymorphism on the receptor itself has not been elucidated. Another well-studied α_{2A}AR polymorphism is the DraI RFLP, originally discovered by Lockette et al. (1995). Subsequent work reported this variant as a G-to-A substitution at position 1780 within the 3′-UTR in combination with a deletion at position 1781 (Finley et al., 2004). This polymorphism (also referred to as rs553668) has since been shown to confer overexpression of the α_{2A}AR in pancreatic islets of carriers of the A allele (Rosengren et al., 2010).

Work from the Liggett laboratory has identified other noncoding polymorphisms and grouped them into 17 haplotypes along with synonymous and

TABLE I

Summary of commonly studied α_2AR polymorphisms and their disease associations arranged by receptor subtype

Receptor	Polymorphism	Association	Reference(s)
α_{2A}AR	C-1291G (MspI RFLP)	ADHD	Roman et al. (2003); Schmitz et al. (2006); Deupree et al. (2006)
		Methylphenidate response	Polanczyk et al. (2007); da Silva et al. (2008)
		Weight gain w/mirtazepine	Lee et al. (2009)
		Weight gain w/olanzapine	Park et al. (2006)
		Suicide	Fukutake et al. (2008)
		Abdominal fat accumulation	Garenc et al. (2002)
		Irritable bowel syndrome	Kim et al. (2004)
	G1780A (DraI RFLP)	ADHD	Park et al. (2005)
		Hypertension	Lockette et al. (1995), Svetkey et al. (1996)
		Type 2 diabetes (risk)	Rosengren et al. (2010)
		Autonomic stress response	Finley et al. (2004)
	C753G (N251K)	Suicide	Sequeira et al. (2004)
α_{2B}AR	Del301-303	Enhanced emotional memory	de Quervain et al. (2007); Rasch et al. (2009); Cousjin et al. (2010)
		Hypertension	von Wowern et al. (2004); Vasudevan et al. (2008)
		Myocardial infarction	Snapir et al. (2001); Laukkanen et al. (2009)
		Sudden cardiac death	Snapir et al. (2003b); Laukkanen et al. (2009)
		Type 2 diabetes (risk)	Siitonen et al. (2004)
		Type 2 diabetes (onset age)	Papazoglou et al. (2006)
		Metabolic rate in obesity	Heinonen et al. (1999)
		Autonomic tone in obesity	Sivenius et al. (2003); Ueno et al. (2006)
α_{2C}AR	Del322-325	Depression	Neumeister et al. (2006)
		Heart failure (risk, in combination w/β1Arg389)	Small et al. (2002)
		Cardiomyopathy (event-free survival)	Regitz-Zagrosek et al. (2006)
		Irritable bowel syndrome	Kim et al. (2004)

nonsynonymous polymorphisms in the coding region (Small, Brown, Seman, Theiss, & Liggett, 2006). Some of these haplotypes were found to affect receptor expression levels in a heterologous system, raising the possibility that combinations of noncoding polymorphisms may affect receptor density endogenously. It should be noted that the position 1781 deletion associated with the DraI RFLP was not observed by the Liggett group in their sample populations (Small et al., 2006).

B. α_{2B}*AR*

The most well-studied polymorphic α_{2B}AR variant is the deletion of nine base pairs beginning at position 901 in the coding region – this results in a loss of three Glu residues (301–303) in the receptor 3i loop (Small, Brown, Forbes, & Liggett 2001). The deleted residues are part of an acidic stretch in the receptor 3i loop (EDEAEEEEEEEEEEE) which is known to be necessary for phosphorylation by G protein-coupled receptor kinases (GRKs) (Jewell-Motz & Liggett, 1995). Not surprisingly, then, this variant has been characterized at the molecular level and found to undergo diminished GRK phosphorylation and desensitization in response to agonist (Small et al., 2001). This variant has also been shown to be resistant to chronic agonist-promoted downregulation (Salim, Desai, Taneja, & Eikenburg, 2009). The Del301-303 polymorphism is relatively common, with allele frequencies of 0.31 for Caucasians and 0.12 for African-Americans (Small et al., 2001).

Other relatively common polymorphisms are found in noncoding regions, and include a 12 nucleotide deletion beginning at position -4825 in the 5′-UTR (Crassous et al., 2010), a G-98C SNP in the 5′-UTR (Cayla et al., 2004), a synonymous coding region mutation at position 1182 (Etzel et al., 2005), and a C1776A SNP in the 3′-UTR. Interestingly, these five polymorphisms listed above have been found to be in linkage with each other, especially in the Caucasian population (Cayla et al., 2004; Etzel et al., 2005; Crassous et al., 2010). At the molecular level, the noncoding region polymorphisms may have effects on transcriptional activity at the α_{2B}AR gene, thereby affecting receptor expression levels (Cayla et al., 2004).

C. α_{2C}*AR*

For the α_{2C}AR, the primary polymorphism that has been identified is a 12 nucleotide deletion beginning at position 964 of the gene. This mutant receptor has a deletion of four residues (Gly–Ala–Gly–Pro) in the receptor 3i loop, and was shown to exhibit deficient coupling to heterotrimeric G proteins and

downstream effectors including MAP kinase (Small, Forbes, Rahman, Bridges, & Liggett, 2000b). The Del322-325 variant is infrequent in the Caucasian population (frequency of well below 1%), but is quite common in African-Americans (allele frequency of 0.381). Subsequent work demonstrated that α_{2C}AR polymorphisms (including Del322-325) exist in as many as nine different haplotypes (Small, Mialet-Perez, Seman, Theiss, Brown, & Liggett, 2004). Interestingly, a more recent study indicated that the α_{2C}AR Del322-325 variant does not exhibit any alteration in inhibition of cAMP production compared with wild-type receptor when expressed in HEK293 cells (Montgomery & Bylund, 2010). Thus, the effects of this deletion on α_{2C}AR function may be more complex than initially thought.

IV. α_2ARs IN CENTRAL NERVOUS SYSTEM DYSFUNCTION AND DISEASE

α_2ARs have been well studied with regard to their roles in CNS functions. In particular, α_2ARs are strongly linked with CNS dysfunction involving the noradrenergic system, as has been linked to disorders such as attention deficit/hyperactivity disorder (ADHD) and depression. As well, α_2AR genotypes could potentially serve as predictors of treatment outcomes to therapeutics modulating the brain noradrenergic system. In this section, we will examine available evidence on α_2AR polymorphisms and their roles in various CNS disorders and diseases, including ADHD, mood disorders such as depressive disorders and schizophrenia, Alzheimer's disease (AD), and emotional memory dysfunction.

A. Attention Deficit/Hyperactivity Disorder

Dysfunction of the brain noradrenergic system in general has long been implicated in ADHD; this subject has been well-reviewed by others (Biederman, 2005; Brennan & Arnsten, 2008; Prince, 2008). Additionally, genes involved in noradrenergic neurotransmission, including α_2ARs, have often been considered as candidates in genetic studies of ADHD (Banaschewski, Becker, Scherag, Franke, & Coghill, 2010).

Studies of human patients have been carried out to investigate a possible link between α_2AR genetics and ADHD. While some studies have found no link between α_{2A}AR (Xu et al., 2001; Wang, Lu, Zhao, & Limbird, 2006a) and α_{2C}AR (Barr et al., 2001; De Luca, Muglia, Vincent, Lanktree, Jain, & Kennedy, 2004) genetic variants and ADHD, several others have suggested a possible role for α_{2A}AR polymorphisms in ADHD. A pair of studies in an

adolescent Brazilian population identified a small contribution of the C-1291G polymorphism to ADHD susceptibility and disorder severity (Roman, Schmitz, Polanczyk, Eizirik, Rohde, & Hutz, 2003), and specifically to susceptibility to the primarily inattentive type of ADHD (Schmitz et al., 2006). Another study in a population of American children found that the DraI RFLP was positively correlated with both the inattentive and hyperactive-impulsive symptoms of ADHD (Park et al., 2005). More recently, Deupree et al. (2006) studied three different polymorphisms (C-1291G and DraI and HhaI RFLPs) and found that certain haplotypes were associated with ADHD. Intriguingly, this study also examined binding characteristics of platelet α_2ARs and found that altered receptor affinity for ligand was correlated with the C-1291G and DraI polymorphisms, thereby providing evidence from human patients that genetic variability can affect α_2AR pharmacological properties. Although not dealing with ADHD specifically, it was recently reported that C-1291G may contribute to inattention and hyperactivity symptoms in adolescents who have experienced maltreatment (Kiive, Kurrikoff, Maestu, & Harro, 2010).

Treatment of ADHD classically relies largely on stimulants, which are thought to work by modulating catecholaminergic neurotransmission (Arnsten, 2006), and, more recently, on α_2AR agonists such as clonidine (Banaschewski, Roessner, Dittmann, Santosh, & Rothenberger, 2004). A pair of studies utilizing a pharmacogenetic approach found a positive association between the C-1291G polymorphism and methylphenidate-induced improvement in inattentive symptoms in cases of ADHD (Polanczyk et al., 2007; da Silva et al., 2008). Collectively, this evidence provides strong support for the general hypothesis that the α_{2A}AR is involved in ADHD, and suggests that continued efforts to target α_{2A}ARs for treatment of this disorder may prove fruitful. Future studies investigating a link between α_2AR genetics and response to clonidine treatment may also be of value.

B. Neuropsychiatric Disorders

α_2ARs, particularly α_{2A}ARs, have been implicated in a number of neuropsychiatric disorders. These receptors may likely be involved in the pathogenesis of these disorders, although details of this are yet to be worked out. Additionally, α_2ARs are valid molecular targets in the therapeutic treatment of these disorders.

1. Depression and Suicide

α_2ARs have been linked quite strongly with mood disorders, in particular depressive disorders including major depressive disorder (MDD), and suicide. A role for α_2ARs was originally suggested by the classical monoamine

hypothesis of depression (Belmaker & Agam, 2008). While this hypothesis has proven inadequate to explain the neurobiology of depression, it has nevertheless stimulated a productive line of research into α_2ARs and depressive disorders. In particular, studies on post mortem brain tissue from depressed suicides have consistently yielded results showing upregulation of α_2ARs (Meana, Barturen, & Garcia-Sevilla, 1992; Callado, Meana, Grijalba, Pazos, Sastre, & Garcia-Sevilla, 1998; Garcia-Sevilla et al., 1999; Ordway, Schenk, Stockmeier, May, & Klimek, 2003; Escriba, Ozaita, & Garcia-Sevilla, 2004). Conversely, it has been reported that chronic antidepressant treatment lowers brain α_2AR density in human patients (De Paermentier, Mauger, Lowther, Crompton, Katona, & Horton, 1997) and alters receptor density in experimental models (Barturen & Garcia-Sevilla, 1992; Mateo, Fernandez-Pastor, & Meana, 2001; Subhash, Nagaraja, Sharada, & Vinod, 2003).

Given the evidence outlined above, it seems reasonable to postulate that α_2AR polymorphisms resulting in altered receptor expression levels may underlie the altered receptor expression patterns associated with depressed/suicidal patients. However, to date, there have been very few studies attempting to link α_2AR polymorphisms with depression and few linking the receptors with suicide. With regard to suicide, a 2004 study suggested preliminarily that the N251K variant of the α_{2A}AR was associated with suicide (Sequeira et al., 2004); however, a follow-up study was unable to replicate this result (Martin-Guerrero, Callado, Saitua, Rivero, Garcia-Orad, & Meana, 2006). A potential confound in these studies is the extremely low allele frequency of this coding region polymorphism; indeed, the 2006 study was unable to find any individuals in either the control or suicide group carrying the variant. Therefore, the possibility remains open that the N251K variant may make a contribution to suicidality. Additionally, it is tempting to speculate that this gain-of-function mutant may account for the α_{2A}AR supersensitivity that has been reported in brain tissue from suicide victims (Gonzalez-Maeso, Rodriguez-Puertas, Meana, Garcia-Sevilla, & Guimon, 2002), although a genetic basis for this receptor supersensitivity has not yet been shown. A more recent study uncovered a possible link between the α_{2A}AR C-1291G polymorphism and susceptibility to suicide in Japanese females (Fukutake et al., 2008). With regard to depression itself, a recent study carried out in a Korean sample population found no significant relationship between the α_{2A}AR C-1291G polymorphism and incidence of MDD or response to the anti-α_2-adrenergic antidepressant drug mirtazepine in MDD patients. A weak association was, however, found between the weight gain side effect commonly observed with mirtazepine and the C/C genotype at position -1291 (Lee et al., 2009). A separate study in a Japanese sample population uncovered a potential link between C-1291G and treatment response to the antidepressant milnacipran, although these results are preliminary (Wakeno et al., 2008). Altogether, currently available data suggest that

α_{2A}AR genetics may influence suicidal behavior, but perhaps not depressive disorders in a more general sense, and may have some use in predicting treatment response to therapeutics.

Interestingly, an fMRI-based study in patients with MDD found a positive association between the α_{2C}AR deletion 322-325 variant and abnormal neural responses to facial expressions in the MDD patients (Neumeister et al., 2006). This study raises the possibility that the α_{2C} subtype is involved in depression and may be a potential therapeutic target.

2. Schizophrenia

Schizophrenia is a complex, multifactorial psychiatric disorder with poorly understood etiology. Although the antipsychotic therapeutics used to treat schizophrenia have been designed to primarily target dopaminergic neurotransmission, they are ''dirty'' drugs with many molecular targets, including α_2ARs (Baldessarini & Tarazi, 2006). Additionally, the enhancement in working memory associated with α_2AR stimulation in the prefrontal cortex has potential therapeutic benefit in schizophrenia (Ramos & Arnsten, 2007). Several pharmacogenetic studies have been carried out investigating a potential role for α_2ARs in the response to antipsychotics. Olanzapine has a well-established side effect of excessive weight gain, which was found to be positively associated with the α_{2A}AR C-1291G polymorphism in a Korean sample population (Park et al., 2006). Other studies have yielded negative results, with no effect of α_{2A}AR C-1291G or a novel 21 bp deletion in the 3′-UTR of the α_{2C}AR on the antipsychotic response (Tsai, Wang, Yu Younger, Lin, Yang, & Hong, 2001a; De Luca et al., 2005). Association studies attempting to link C-1291G (Tsai et al., 2001a; Yamaguchi et al., 2009) and multiple other single α_{2A}AR gene polymorphisms (Clark, Mata, Kerwin, Munro, & Arranz, 2007) with susceptibility to schizophrenia have yielded similarly negative results. Taken together, these results suggest that α_2ARs may be involved in mediating certain clinical effects of antipsychotic drugs, but are perhaps not involved in the underlying disease process. Additionally, these results along with the study from Lee et al. (2009) on the antidepressant mirtazepine indicate that the α_{2A}AR may play a role in mediating the metabolic side effects often associated with psychiatric medications.

3. Other Psychiatric Disorders

Other studies of α_2AR polymorphisms in mood, panic, and personality disorders have yielded largely negative results. A pair of studies by Ohara and colleagues found no association between the C-1291G polymorphism of the α_{2A}AR and a generalized group of mood disorders (Ohara, Nagai, Tani, Tsukamoto, Suzuki, & Ohara, 1998) or panic disorder (Ohara, Suzuki, Ochiai, Terada, & Ohara, 2000). A separate study found no association between the

C-1291G polymorphism and performance on a personality assessment for reward dependence (Tsai, Wang, & Hong, 2001b). It is possible that, as suggested by Small et al. (2006), these and other studies yielding negative results have missed associations by looking at single polymorphisms rather than considering whole haplotypes.

C. Alzheimer's Disease

The loss of noradrenergic input from the locus coeruleus is an early event that often occurs in neurodegenerative diseases, including AD, and this loss has been proposed to play a critical role in the pathogenesis and progression of these diseases (Marien Colpaert, & Rosenquist, 2004). α_2ARs play an essential role in regulating noradrenergic input to the cerebral cortex and the resulting cortical response (Hein, 2006). Although the only study probing for a link between α_2AR polymorphisms and susceptibility to AD yielded a negative result for the α_{2A}AR C-1291G polymorphism (Hong, Wang, Liu, Liu, & Tsai, 2001), the possibility remains that α_2ARs are involved in AD and may be a viable therapeutic target.

D. Emotional Memory Dysfunction – Possible Novel Role for α_{2B}ARs?

Noradrenergic neurotransmission has been consistently implicated in the emotional memory function of the amygdala (McGaugh, 2004; Roozendaal, Barsegyan, & Lee, 2008). This knowledge provides the basis for a recent series of intriguing studies that have suggested a possible novel role for the α_{2B}AR in emotional memory, with implications for post-traumatic stress disorder (PTSD) and other forms of emotional memory dysfunction. These investigators set out to investigate a possible link between the α_{2B}AR deletion 301-303 variant and amygdalar function. The first of these studies found enhanced emotional memory in healthy European individuals and enhanced traumatic memory in African war refugees (with and without a diagnosis of PTSD) carrying the deletion (de Quervain et al., 2007). A follow-up study from the same group used a functional MRI (fMRI) approach to demonstrate enhanced amygdala activity during an emotional memory task in healthy individuals carrying the deletion variant (Rasch et al., 2009). Both of these studies collapsed heterozygous and homozygous carriers of the deletion into a single group, suggesting that just one mutant allele can result in a phenotype. An additional independent study, also using an fMRI approach in health volunteers, discovered that deletion carriers exhibited enhanced amygdala activity during an emotional memory task specifically following exposure to acute stress (Cousjin et al., 2010). This last piece

of data provides a further link to the noradrenergic system, which is well-known to be engaged in response to stress, affecting cognition (Sara, 2009).

While these results are indeed interesting, it is important to take some caution in their interpretation. First, these studies have posited that the observed results are due to a loss-of-function effect of the deletion variant (Small et al., 2001), leading to decreased α_{2B}AR presynaptic function and enhanced noradrenergic neurotransmission. However, experimental evidence has suggested that there is little expression of the α_{2B} subtype in the CNS, with no evidence of amygdalar α_{2B} expression (Scheinin et al., 1994; Wang, MacMillan, Fremeau, Magnuson, Lindner, & Limbird 1996), although subtype-specific α_2AR expression is not as well-understood in the human brain. Presynaptic autoreceptor function has been ascribed mainly to the α_{2A} and, to a lesser extent, α_{2C} subtypes (Knaus et al., 2007). Second, the studies rely heavily on fMRI, a technique that relies on changes in blood flow rate to measure neuronal activity, leading to the potential confound of the α_{2B}AR deletion variant affecting fMRI results via direct regulation of vascular function (see Section V) independent of central synaptic transmission. Further studies will be necessary to establish a role for the α_{2B} subtype in noradrenergic neurotransmission in the human brain, and firmly link the α_{2B}AR with the observed abnormalities in amygdalar function. Nevertheless, the studies outlined above have identified the α_{2B}AR as a potential molecular target in emotional memory dysfunction worthy of continued investigation.

E. Summary – α_2ARs in the Central Nervous System

Studies of α_2AR polymorphisms have revealed several potential roles for α_2ARs in the CNS, and have identified α_2ARs as possible molecular targets in therapeutic treatments of CNS diseases and disorders. The α_{2A}AR has been most strongly and consistently linked with ADHD, with the receptor polymorphisms such as C-1291G serving as indicators of disorder severity and/or susceptibility. The receptor may also be a good target for pharmacogenetic studies in ADHD. Within the broad category of neuropsychiatric disorders, α_{2A}ARs have been linked with suicide and metabolic side effects of antidepressant and antipsychotic drugs. Associations with depression and schizophrenia susceptibility have largely not been found; however, the α_{2C}AR deletion 322–325 variant may be linked with MDD. Finally, recent studies have raised the possibility that the α_{2B}AR deletion 301-303 variant may be linked with altered amygdala function in emotional memory, identifying the α_{2B}AR as a possible molecular target in the treatment of disorders such as PTSD. Altogether, the available evidence supports a general role for α_2ARs in cognition and cognitive disorders.

V. α_2ARs IN CARDIOVASCULAR DISEASE

Adrenergic receptors have long been implicated in cardiovascular function and disease. Relevant to our discussion, all three α_2AR subtypes have appreciated roles in the cardiovascular system, through sympathetic regulation and through direct effects in cardiac and vascular tissues. α_2ARs are also known to be targets for a number of sympathomimetic therapeutics utilized in the treatment of cardiovascular dysfunction (Westfall & Westfall, 2006). α_2AR polymorphisms in cardiovascular disease have previously been reviewed (see Flordellis, Manolis, Scheinin, & Paris, 2004). The following sections will briefly discuss roles for α_2AR in cardiovascular regulation, and then focus on α_2AR polymorphisms in hypertension and heart diseases.

A. α_2ARs in Cardiovascular Regulation

Studies from subtype-specific knockout mice have revealed major roles for the α_2ARs in the vascular system with consequences for blood pressure regulation. α_{2A}ARs and α_{2C}ARs have largely been studied in the context of their roles in regulating norepinephrine release from sympathetic terminals. α_{2A}AR-null mice exhibit elevated release of norepinephrine from cardiac sympathetic nerve terminals and higher resting systemic blood pressure and heart rate (Altman et al., 1999). The α_{2A}AR subtype has been demonstrated as the primary presynaptic autoreceptor controlling norepinephrine release from sympathetic terminals, while the α_{2C}AR subtype has been implicated in regulating release specifically at low stimulation frequencies (Hein, Altman, & Kobilka, 1999). Heterozygous and homozygous deletion of the α_{2C}AR resulted in elevated urinary excretion of epinephrine, while heterozygotes were more susceptible to cardiac hypertrophy and heart failure after left-ventricular pressure overload (Gilsbach et al., 2007). Additionally, survival rates of both α_{2A}AR- and α_{2C}AR-null mice have been shown to be decreased following cardiac pressure overload due to heart failure (Brede et al., 2002). In human studies, the α_{2A}AR DraI RFLP has been associated with increased sympathetic drive and elevated blood pressure (Finley et al., 2004), while the α_{2C}AR Del322-325 variant has been associated with elevated basal blood pressure and exaggerated α_2AR antagonist-induced increases in blood pressure/heart rate in healthy volunteer subjects (Neumeister et al., 2005).

The α_{2B}AR subtype has also been extensively studied in this regard. α_{2B}ARs in vascular smooth muscle are known to mediate vasoconstriction contributing to increased blood pressure (Link et al., 1996). The importance of the α_{2B}AR in vascular regulation has since been confirmed in human studies of α_{2B}AR polymorphisms. Work from the laboratory of Mika Scheinin has demonstrated

that the α_{2B}AR Del301-303 variant is associated with altered vascular responses to epinephrine. Specifically, the polymorphism was associated with decreased flow-mediated dilation of the brachial artery and increased blunted coronary blood flow following intravenous epinephrine (Heinonen et al., 2002; Snapir et al., 2003a). More recently, it was shown that the haplotype consisting of Del301-303 along with the G-98C, C1182A, and C1176A polymorphisms was associated with resistance to desensitization of the hand vein response to dexmedetomidine (an α_2AR agonist) in Caucasian and African-American patients (Muszkat et al., 2010), although previous studies by this group had yielded negative results (Muszkat et al., 2005a; Muszkat, Sofowora, Xie, Wood, & Stein, 2005b).

B. Hypertension

Despite the promising evidence presented above, studies probing for a link between α_2AR polymorphisms and hypertension have yielded largely mixed results. Positive associations between hypertension and the α_{2A}AR DraI RFLP have been reported in a number of studies. An early study linked the polymorphism with hypertension in a mixed population of hypertensive and normotensive individuals, specifically in Caucasian but not African-American subjects (Svetkey, Timmons, Emovon, Anderson, Preis, & Chen, 1996). Work by Warren Lockette and colleagues demonstrated that the DraI RFLP conferred increased risk of hypertension, particularly in African-Americans (Lockette et al., 1995). These two pieces of evidence illustrate the variability in conclusions commonly seen among different genetic association studies. The largest association study for α_2ARs and hypertension carried out to date by Li, Canham, Vongpatanasin, Leonard, Auchus, and Victor (2006) revealed negative results for both the α_{2A}AR DraI RFLP and α_{2C}AR Del322-325 variant and associations with hypertension and parameters of hypertensive heart disease. Other α_{2A}AR polymorphisms have been studied in the context of hypertension, with no association found between a novel Bsu361 RFLP and hypertension in a Japanese population (Umemura et al., 1994).

The first study investigating a link between the α_{2B}AR Del301-303 variant and hypertension was carried out by Baldwin et al. (1999), and found no genetic linkage between Del301-303 and essential hypertension. Subsequently, several studies have been unable to find a link between α_{2B}AR Del301-303 and hypertension in Western populations (Snapir et al., 2001; Etzel et al., 2005; Iacoviello et al., 2006). One study also found no association between the synonymous coding region C1182A polymorphism and hypertension (Etzel et al., 2005). A pair of studies carried out in a Chinese population showed no difference in frequency of α_{2B}AR Del301-303 genotype in normotensive

versus hypertensive groups, but did find an association between the nondeletion allele and elevated blood pressure in Chinese men (Zhang et al., 2005; Li, Li, Y., Wen, Y., & Wang, 2008). On the positive side, studies in a Swedish population identified a hypertension susceptibility locus on chromosome 2 which contains the α_{2B}AR gene and subsequently uncovered an association between α_{2B}AR Del301-303 and early-onset primary hypertension as well as a weak association with nondiabetic primary hypertension (von Wowern et al., 2003; von Wowern, Bengtsson, Lindblad, Ratam, & Melander, 2004). Additionally, a study in a Malaysian population determined that α_{2B}AR Del301-303 was associated with essential hypertension in patients regardless of the presence or absence of type 2 diabetes (Vasudevan, Ismail, Stanslas, Shamsudin, & Ali, 2008).

Collectively, the results outlined above suggest a possible role for the α_{2B}AR as a contributing genetic factor to hypertension, although it is likely not the sole or primary causative factor. The impact of α_{2B}AR Del301-303 observed varies based on a number of factors, particularly the ethnic makeup of the sample population. As well, given that the Del301-303 polymorphism is in linkage with other α_{2B}AR polymorphisms in certain populations (Cayla et al., 2004; Etzel et al., 2005; Crassous et al., 2010), it is possible that there are complex effects of the α_{2B}AR genotype. As an example, the Del301-303 polymorphism may result in enhanced receptor signaling while a noncoding polymorphism such as the 5′-UTR deletion beginning at position -4825 may lead to decreased receptor expression. In such a scenario, the combination of polymorphisms would potentially have offsetting effects, thereby leading to a negative result for either with regard to an association with hypertension; such effects would likely differ among disparate human populations. The hypertension phenotype is also likely affected by the genotype status of many other molecular players, the effects of which may obscure contributions of α_{2B}ARs. Even bearing those caveats in mind, it is clear that the α_{2B}AR is a viable therapeutic target in the treatment of hypertension and other disorders of vascular regulation, although pharmacogenetic studies would likely prove difficult.

C. Heart Disease

Regulation of sympathetic activity by α_{2A}ARs and α_{2C}ARs has provided a rationale for studying the genetics of these receptors in the context of heart disease, particularly heart failure. Additionally, a recent experimental study showed that persistent activation of postsynaptic β1 receptors on cardiomyocytes led to a self-accelerating signaling cycle resulting in heart failure (Dorn, 2010), providing direct evidence that dysregulated sympathetic transmission could contribute to heart failure. Most studies to date have focused on the Del322-325 variant of the α_{2C}AR, and such studies have, unsurprisingly,

yielded inconsistent results. An interesting study from Stephen Liggett's group examined the effects of the α_{2C}AR Del322-325 variant in combination with a variant of the β1AR (β1Arg389). The α_{2C}AR variant has decreased function, and the β1AR variant has increased function, and so the rationale was that this combination of variants would lead to both increased norepinephrine release from sympathetic terminals and enhanced adrenergic signaling in the cardiomyocyte, potentially predisposing such individuals to heart failure. Their results demonstrated an increased risk of heart failure for those individuals homozygous for both receptor variants (Small, Wagoner, Levin, Kardia, & Liggett, 2002). However, as pointed out by Dorn, it should be noted that this study had a small number for case-control comparison, and so carries an increased chance of a false-positive association (Dorn, 2010). Indeed, a later study by Savva et al. (2009) was unable to repeat these results, finding no association between α_{2C}AR Del322-325 alone or in combination with β1Arg389 and risk of adverse events in a population of congestive heart failure patients within the MERIT-HF study.

One other positive result was found in a study carried out in patients with dilated cardiomyopathy, which found that the α_{2C}AR Del322-325 polymorphism can protect against adverse outcomes such as death or heart transplant (Regitz-Zagrosek et al., 2006). Several other studies in American, European, African, and Asian populations have found no significant association between the α_{2C}AR Del322-325 variant and heart failure risk or heart failure parameters (Nonen et al., 2005; Metra et al., 2006; Canham et al., 2007; Du Preez, Matolweni, Greenberg, Mentla, Adeyemo, & Mayosi, 2008). While available evidence is mixed, the possibility remains that the α_{2C}AR plays a role in heart failure, although it is likely not the primary causative factor. Future studies on this subject, particularly those which account for haplotypes of α_{2C}AR polymorphisms (Small et al., 2004), seem to be in order. The α_{2C}AR should continue to be considered as a therapeutic target in heart failure moving forward.

α_{2B}ARs have also been studied in the context of heart disease. The Del301-303 variant was first established as a genetic risk factor for acute myocardial infarction in a male Finnish sample population, with an approximately doubled risk of acute coronary events (Snapir et al., 2001). Further studies linked α_{2B}AR Del301-303 with increased risk of sudden cardiac death in a Caucasian population, with particular risk for men under age 50 (Snapir, Mikkelsson, Perola, Penttila, Scheinin, & Karhunen, 2003b). More recently, a separate group confirmed the α_{2B}AR Del301-303 variant as a genetic risk factor for myocardial infarction and sudden cardiac death in middle-aged men (Laukkanen, Makikallio, Kauhanen, & Kurl, 2009). Hence, available evidence strongly links the α_{2B}AR genotype with risk of acute heart disease, suggesting the receptor as a useful potential target for screening.

D. Summary – α_2ARs in the Cardiovascular System

Based upon the evidence outlined in the preceding sections, it is clear that α_2AR genotype can impact the functioning of the cardiovascular system, and potentially predispose one to cardiovascular diseases such as hypertension, heart failure, and coronary artery diseases. A particularly strong link has been found between the α_{2B}AR Del301-303 variant and acute heart disease, including myocardial infarction and sudden cardiac death. More equivocal evidence has linked the α_{2A}AR DraI RFLP and α_{2B}AR Del301-303 variants with hypertension and the α_{2C}AR Del322-325 variant with heart failure. Overall, currently available data suggest that continued study of α_2AR genotypes in the cardiovascular system is warranted, although studies looking at broader genotypes encompassing other relevant receptor types in addition to α_2ARs may be especially informative.

VI. α_2ARS IN METABOLISM AND TYPE 2 DIABETES

α_2ARs have been reported to be expressed in tissues including adipose (Lafontan & Berlan, 1995) and pancreas (Lacey et al., 1996). Within pancreatic islets, α_{2A}ARs are predominantly expressed in β-cells (Lacey et al., 1996), while α_{2C}ARs are expressed in α- and δ-cells (Peterhoff, Sieg, Brede, Chao, Hein, & Ullrich, 2003); α_{2B}AR expression has largely not been reported in islets. Based upon this expression pattern, it can be reasonably assumed that α_{2A}ARs play a role in insulin secretion, and indeed this is the case, with stimulation of β-cell α_{2A}ARs leading to a decrease in insulin secretion. Although dysfunction of the insulin system leading to altered glucose handling has long been understood as an essential component of type 2 diabetes, α_2AR genetics have only very recently begun to be studied in the context of this important human disease.

A. Effects on Insulin Secretion and Glucose Handling

The main premise underlying studies of α_2AR polymorphisms in type 2 diabetes is that dysfunctional α_{2A}AR signaling contributes to altered insulin secretion. Early studies demonstrated that overexpression of α_{2A}ARs in pancreatic β-cells as well as treatment with α_2AR agonists resulted in reduced insulin secretion (Rodriguez-Pena et al., 1997; Hirose, Seto, Maruyama, Dan, Nakamura, & Saruta, 1997). α_2AR antagonists have since been shown to enhance both insulin secretion and the proinsulin effects of a sulfonylurea drug in an α_{2A}AR-dependent fashion (Fagerholm, Scheinin, & Haaparanta, 2008). A more recent series of studies have strongly implicated genetically based

alterations in α_{2A}AR expression levels in abnormal insulin secretion and type 2 diabetes. Rosengren et al. (2010) have reported important findings linking the α_{2A}AR DraI RFLP with increased risk of type 2 diabetes in a Scandinavian population. Specifically, the A allele was associated with increased α_{2A}AR expression and diminished insulin secretion in pancreatic islets from human patients. Importantly, the attenuated insulin release in response to glucose was reversed by treatment with α_2AR antagonists, demonstrating dependence on α_2AR signaling.

A separate set of studies have implicated another potential α_{2A}AR polymorphism, referred to as rs10885122, in type 2 diabetes. This polymorphism was identified through a genome-wide association study (GWAS) probing for loci associated with fasting glucose, and is located quite far from the receptor coding region, 202 kilobases downstream of the DraI RFLP in the 5′-UTR (Dupuis et al., 2010; Ingelsson et al., 2010). This polymorphism has been associated with decreased insulin response after oral glucose ingestion in a Danish population (Boesgaard et al., 2010). While this is an interesting finding, given the extreme downstream nature of this polymorphism, it remains to be seen what influence this may have on receptor expression and overall β-cell function.

B. Other Potential Contributions

In addition to direct effects on insulin secretion in pancreatic β-cells, it is possible that α_{2A}AR genetics could influence pancreatic function in a less-direct fashion. Specifically, the α_{2A}AR could regulate insulin secretion via its role in sympathetic neurotransmission impinging on the pancreas (Savoy et al., 2010). α_{2A}AR genetics may also influence metabolism through effects on body fat content, as suggested by data linking the α_{2A}AR C-1291G polymorphism with abdominal fat accumulation in black Canadian subjects (Garenc et al., 2002) and the G1780A polymorphism with BMI and body fat percentage in African Americans (Lima et al., 2007).

Although expression of the α_{2B}AR has largely not been reported in pancreatic islets, the α_{2B}AR Del301-303 variant was nevertheless associated with younger age of onset in a study of type 2 diabetes patients (Papazoglou, Papanas, Papatheodorou, K., Kotsiou, S., Christakidis, D., & Maltezos, 2006). A separate study by a Finnish group linked the Del301-303 allele with risk of type 2 diabetes in patients with impaired glucose tolerance, specifically those who did not receive a lifestyle change intervention (Siitonen et al., 2004). Additionally, the Del301-303 variant has been associated with relatively lower resting metabolic rate in obese patients (Heinonen et al., 1999) and risk of weight gain in nondiabetic patients (Sivenius, Lindi, Niskanen, Laakso, & Uusitupa, 2001), providing evidence of a role for the α_{2B}AR in metabolism.

It has been recently shown that dysregulation of glucagon secretion may play a larger role in both the early development of diabetes and the hyperglycemia associated with later stages than previously thought (Gustavsson, Seah, Lao, Radda, Sudhof, & Han, 2010). Given that α_{2C}ARs are known to be expressed on the pancreatic islet cells involved in glucagon release (α- and δ-cells), the possibility arises that dysfunction of α_{2C}ARs may contribute to type 2 diabetes. Although this has not been demonstrated to date, future investigation of the α_{2C}AR Del322-325 variant for possible association with diabetes may prove fruitful.

C. *Summary – α_2ARs as Targets in the Treatment of Type 2 Diabetes*

The recent human genetic studies outlined above strongly suggest a role for the α_{2A}AR in type 2 diabetes, likely through its role in regulating insulin secretion from pancreatic β-cells. In particular, the well-established α_{2A}AR DraI RFLP has been linked with receptor overexpression and diminished insulin release as well as heightened risk of type 2 diabetes in human patients. A novel polymorphism downstream of the receptor coding region may also be linked with altered insulin response and glucose handling. In the future, the α_{2A}AR will likely prove to be an important therapeutic target in the treatment of type 2 diabetes and, potentially, other metabolic dysfunctions.

VII. α_2ARs IN OTHER PERIPHERAL FUNCTIONS

In addition to the prominent associations delineated in the previous sections, α_2ARs have also been studied for associations with other peripheral disorders and diseases. These studies are grounded in the knowledge that α_2ARs are ubiquitously expressed in the human body, and that the sympathetic nervous system (in which α_2ARs play a prominent role) enervates the full range of tissue types. Genetic studies have identified roles for α_2ARs in functional bowel disorders, renal functions relating to hypertension, and a handful of other altered autonomic functions.

A. *Gastrointestinal System*

α_2ARs are increasingly being recognized as important players in the gastrointestinal (GI) system (for review, see Blandizzi, 2007). It is largely appreciated now that enteric α_2ARs are predominantly of the α_{2A}AR subtype, and these receptors are expressed both in sympathetic terminals and postsynaptically

within GI tissues. A role for these α_{2A}ARs in GI pathophysiology, particularly in functional bowel disorders such as irritable bowel syndrome (IBS) was initially suggested by the observation that α_2AR agonists were beneficial in IBS patients, as well as having benefit in improving GI function (Blandizzi, 2007). Subsequently, a genetic association study demonstrated that the α_{2A}AR C-1291G polymorphism was linked to IBS constipation symptoms, while the α_{2C}AR Del322-325 variant was linked with constipation and somatic symptoms (Kim et al., 2004). These results suggest that α_2ARs contribute to the IBS phenotype, and confirm the receptors as viable therapeutic targets in GI dysfunction.

B. Renal Functions

A role for α_{2B}ARs in renal functions, particularly with regard to salt-induced hypertension, was suggested by a pair of studies from the Gavras laboratory. These studies demonstrated that α_{2B}AR-deficient mice ($\alpha_{2B}AR^{+/-}$) do not exhibit an elevation in blood pressure in response to dietary salt loading, and that this occurs despite elevated plasma norepinephrine levels; α_{2A}AR- and α_{2C}AR-deficient mice exhibited normal elevations in blood pressure along with elevated plasma norepinephrine levels (Makaritsis, Handy, Johns, Kobilka, Gavras, & Gavras, 1999; Makaritsis, Johns, Gavras, & Gavras, 2000). This data seems to indicate that the salt-induced hypertensive response is mediated by α_{2B}ARs independent of presynaptic autoreceptor function, suggesting a critical role for renal postsynaptic α_{2B}ARs. This role for the α_{2B}AR may contribute to findings outlined above that this receptor is involved as a risk factor in hypertension, in addition to its role in direct regulation of vascular function, and should be considered in the interpretation of such results going forward.

C. Other Peripheral Nervous System-Mediated Functions

α_2AR genetics have been linked with abnormal peripheral autonomic nervous system functions. Finley and colleagues demonstrated an association between the α_{2A}AR DraI RFLP and susceptibility to stress-induced motion sickness as well as increased exercise-induced sweat sodium concentrations, both used as readouts of the autonomic stress response (Finley et al., 2004). Other studies have linked the α_{2B}AR Del301-303 polymorphism with altered autonomic function, specifically relatively lower autonomic tone, in obese male and female subjects (Sivenius et al., 2003; Ueno et al., 2006). These studies indicate a contribution of α_2AR genotype in both stress response and autonomic tone in relation to metabolism.

VIII. CONCLUSIONS

Polymorphic variations have been identified for all three subtypes of α_2ARs, and genetic association studies suggest that these receptors are important in mediating diverse physiological functions. These functions appear across a variety of human organ systems, and range from cognitive improvement to central and peripheral blood pressure control to regulation of insulin secretion. Cellular studies in heterologous expression systems have demonstrated that the polymorphic alleles of α_2ARs can result in alterations in receptor signaling and/or pharmacology, by changes in either receptor sequences or expression levels. However, precisely how these polymorphisms cause disease phenotypes *in vivo* remains unclear. An effective way to address such questions would be to generate transgenic mouse models expressing polymorphic α_2ARs, especially in a tissue-specific manner. Such humanized mouse models would complement already-established knockout models to fully illustrate α_2AR functions *in vivo*, and could also reveal novel targets for therapeutic interventions targeting α_2ARs.

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