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Adenosine Signaling in Anxiety

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1. Introduction

Adenosine is a ubiquitous nucleoside that acts as a neuromodulator in the central nervous system (CNS), controlling neuronal excitability, modulating neurotransmitter release, and regulating ion channel function through four subtypes of G-protein-coupled receptors (GPCRs), A_1, A_{2A}, A_{2B}, and A_3. Adenosine receptor agonists are anxiolytic while adenosine A_1 and A_{2A} receptor antagonists such as caffeine can cause anxiety. Pharmacological and genetic manipulation of A_1 and A_{2A} receptors suggests that each contributes separately to the regulation of anxious states. However, a growing body of evidence argues for a particularly important role of the A_{2A} receptor. Single nucleotide polymorphisms (SNPs) in the A_{2A} receptor gene (ADORA2A) are associated with anxiety in psychiatric disorders and in response to stimulants. Additionally, genetic knockout of the type 1 equilibrative nucleoside transporter (ENT1), which plays an essential role in controlling adenosine levels in the brain, reduces anxiety in rodents, while inhibition of ENT1 may mediate the anxiolytic effects of benzodiazepines and alcohol. In this chapter, we discuss the emerging role of adenosine signaling in anxiety, with special focus on the A_1 and A_{2A} receptors and ENT1. This chapter also includes how caffeine and alcohol regulate anxiety through adenosine signaling.

2. Adenosine in the CNS

Adenosine has several roles in the CNS that are critical to proper brain function. As a nucleoside, adenosine is the precursor to adenine nucleotides in DNA and RNA. It can also be phosphorylated to produce ATP, the main form of cellular metabolic energy. Conversely, it is a product of ATP hydrolysis and as such, represents an indicator of metabolic activity. As a neuromodulator, adenosine can inhibit or excite neurons based upon physiological conditions at the time. Thus, adenosine signaling is best conceptualized as a gating mechanism for signaling by other neurotransmitters, modulating both excitatory and inhibitory neurotransmission. It is in this capacity that adenosine regulates a wide range of behaviors, moods, and emotions (Cunha et al., 2008; Ruby et al., 2010; Asatryan et al., 2011).

Because adenosinergic signaling impacts most neurotransmitter systems in the brain, extracellular adenosine levels must be tightly regulated to support proper neuronal function. Unlike classical neurotransmitters that are synthesized, stored, and released into the synapse in response to electrochemical stimulation, adenosine concentrations are

regulated to a much greater extent by production and transport (Burnstock, 1972, 2006, 2008). This pattern of control allows adenosine levels to change rapidly, which is essential to fine-tune the activity of neighboring neurons. Adenosine reaches extracellular space in two ways: 1) it is produced extracellularly from ATP released by neurons or by astrocytes, and 2) it is released through equilibrative nucleoside transporters (ENTs; **Fig. 1**). Interestingly, astrocytes appear to be significant sources of extracellular adenosine and ATP (Haydon et al., 2009).
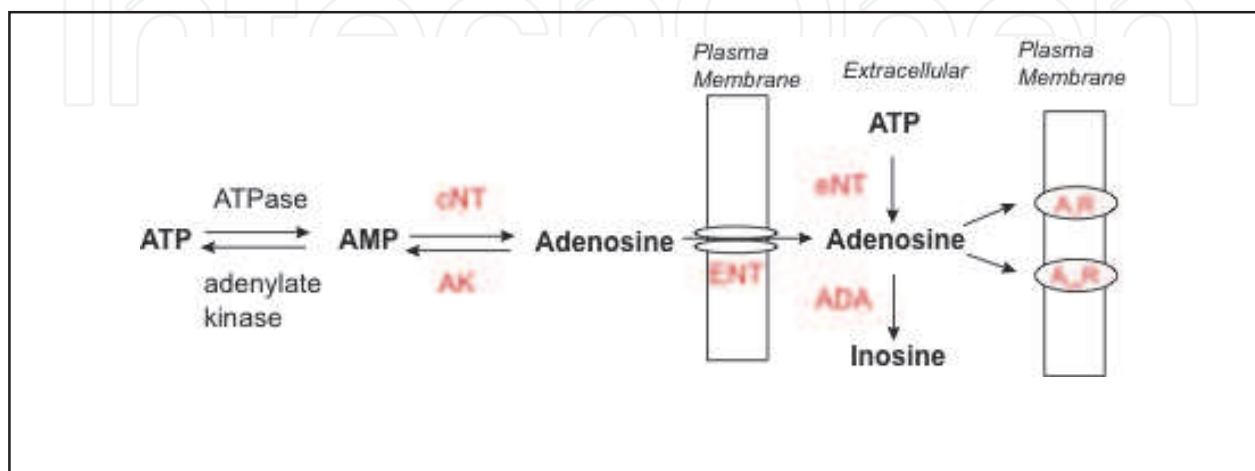

Fig. 1. Schematic showing adenosine production in the central nervous system. Abbreviations: cNT: cytosolic endo-nucleotidase, AK: adenosine kinase, ENT, equilibrative nucleoside transporters, eNT: exo-nucleotidase, ADA: adenosine deaminase, A_1R and $A_{2A}R$: adeonsine A_1 and A_{2A} receptors.

Adenosine controls neurotransmitter release, modulates neuronal excitability and regulates ion channel function through four subtypes of GPCRs, A_1, A_{2A}, A_{2B}, and A_3, all with distinct affinity for adenosine. Whether adenosine exerts a dampening or potentiating effect on neurotrasmission is determined by the expression pattern of adenosine receptors and the levels of adenosine in the brain (Fredholm et al., 1999; Fredholm et al., 2005b; Fredholm et al., 2005a; Fredholm, 2010). A_1 and A_{2A} receptors have 10-100 nM binding affinities, whereas A_{2B} and A_3 receptors have 1-5 mM binding affinities. Since normal CNS adenosine levels are 25-250 nM, A_1 and A_{2A} receptors are the main subtypes involved in the regulation of anxiety and other psychiatric disorders. Adenosine A_1 receptors are expressed ubiquitously in the CNS, have high affinity for adenosine, and mediate tonic inhibition of neuronal activity. Activation of presynaptic A_1 receptors inhibits the release of excitatory and inhibitory neurotransmitters by reducing intracellular cAMP and PKA activation, while postsynaptic A_1 receptors regulate potassium channels to reduce both excitability (the probability of firing) as well as action potential duration (Ebersolt et al., 1983; Fredholm, 1985; Linden, 1991; Heurteaux et al., 1995). Adenosine A_{2A} receptors are primarily expressed in the caudate-putamen and nucleus accumbens. In contrast to A_1 receptors, A_{2A} receptors are positively linked to adenylate cyclase, increasing levels of cAMP and exerting excitatory influences on neurons. A_{2A} receptors are also known to associate physically with other neurotransmitter receptors, including the dopamine D2 and glutamate mGluR5 receptors. Such receptor-receptor interactions appear to be essential for striatal function, and evidence suggests that they may be impaired in a number of psychiatric diseases (Ferre et al., 2010).

3. Adenosine receptors and transporters in anxiety

Adenosine and adenosine receptor agonists are anxiolytic as assessed by a number of ethological tests in rodent models, such as the elevated zero maze and elevated plus maze (Kulkarni et al., 2007), the Vogel conflict test (Okuyama et al., 1999), and the light-dark (LD) box (Florio et al., 1998). Conversely, adenosine receptor antagonism is responsible for the anxiogenic responses elicited by moderate to high doses of caffeine, theophylline (Imaizumi et al., 1994; Kulkarni et al., 2007; Pechlivanova et al., 2010), or other adenosine receptor antagonists (Imaizumi et al., 1994; Florio et al., 1998; Koetter et al., 2009; Zhao et al., 2009) in rodents and humans (Lara, 2010). It has also been suggested that the anxiolytic effect of the adenine derivative BWA78U in the LD box involves adenosine receptor activation (Willard et al., 1990), and that adenosine is the active principle in the Longan Arillus extract (Okuyama et al., 1999), a traditional Asian remedy for mild anxiety. Moreover, adenosine may mediate, in part, the anxiolytic activity of benzodiazepine receptor ligands (Snell and Snell, 1984; Stone, 1999). Genetic evidence supports roles for the A_1 and A_{2A} receptors, as well as the transporter ENT1 in the regulation of anxious states.

3.1 The A2A receptor

Of the many studies implicating adenosine signaling in emotional behavior, the strongest evidence favors a central role for the A_{2A} receptor subtype in anxiety-related disorders under many different conditions (Shen and Chen, 2009). The A_{2A} receptor is enriched in the caudate-putamen and nucleus accumbens, where it interacts physically with dopamine D2 receptors to regulate reward, habitual behavior, and locomotor activity (Cunha et al., 2008). As the A_{2A} receptor is expressed in both neurons and astrocytes, it has also been implicated in controlling glial function and brain metabolic adaptation, processes that are dysregulated in several psychiatric disorders (Lee et al., 2007; Rajkowska and Miguel-Hidalgo, 2007).

Persuasive preclinical evidence for the involvement of the A_{2A} receptor in anxiety comes from several studies based on its genetic deletion combined with pharmacological manipulation. Indeed, A_{2A} receptor null mice are considered a valuable model to study anxiety disorders and develop new therapies (Deckert, 1998). These mice display reduced exploratory activity, heightened anxiety and aggression, hypoalgesia, increased blood pressure and heart rate, and aberrant locomotor responses to caffeine (Ledent et al., 1997), including caffeine-induced depression (rather than enhancement) of exploration (Ledent et al., 1997), and the absence of an anxiogenic response to acute or chronic high-dose caffeine in the elevated plus maze (El Yacoubi et al., 2000). This evidence is in line with a pharmacological study showing that the adenosine A_2 receptor agonist CGS21680 reduced the anxiogenic effect of theophylline in the LD box (Imaizumi et al., 1994). Surprisingly, however, A_{2A} receptor overexpression did not alter anxiety-like responses in the elevated plus maze (Gimenez-Llort et al., 2007).

Pharmacological and genetic inhibition of the A_{2A} receptor has also revealed its role in the regulation of anxiety in disease states, by other neuromodulators, or by drugs of abuse. One study showed increased content of a-MSH, a pro-opiomelanocortin (POMC)-derived peptide known to influence anxiety, aggressive behavior, and motor activity, in the amygdala and cortex of A_{2A} receptor knockouts (Jegou et al., 2003). The mice also had augmented levels of POMC mRNA and ACTH in the anterior pituitary, indicating hyperactivity of the hypothalamic-pituitary-adrenal axis that mediates responses to stress (Jegou et al., 2003). The A_{2A} receptor has also been implicated in the anxiolytic activity of

prostaglandin D2, as A_{2A} receptor inhibition by SCH58261 prevented the increase in open-arm time produced by prostaglandin D2 in the elevated plus maze. In addition, A_{2A} receptor blockade prior to quinolinic acid-induced striatal excitotoxic lesions (a rat model of Huntington's disease), prevented the usual increase in anxiety-like behavior for 6 months (Scattoni et al., 2007). Moreover, the A_{2A} receptor may be involved in anxiety during morphine withdrawal, as A_{2A} receptor null mice display more severe naloxone-precipitated withdrawal symptoms (Berrendero et al., 2003). Finally, these mice are more sensitive to the anxiolytic properties of alcohol (Houchi et al., 2008). These studies and other research implicating adenosine signaling in the effects of alcohol are discussed later in the chapter.

Disorders	SNPs	References
Panic Disorder	1083C>T	Hamilton et al., 2004
	1976C>T	
	rs5751876	Hohoff et al., 2010
Agoraphobia	1083C>T	Hamilton et al., 2004
	rs5751876	Hohoff et al., 2010
Blood-Injury Phobia	1976C>T	Hohoff et al., 2009
Autism Spectrum Disorder	rs2236624CC	Freitag et al., 2010
	rs3761422	
	rs5751876	
	rs35320474	
Caffeine-Induced Anxiety	1976C>T	Alsene et al., 2003
	2592C>T	
	rs5751876	Childs et al., 2008; Rogers et al., 2010
	rs2298383	Childs et al., 2008
	rs4822492	
Amphetamine-Induced Anxiety	1976C>T	Hohoff et al., 2005
	2592C>T	
Anxiety-Related Personality	rs5751862	Hohoff et al., 2010
	rs2298383	
	rs3761422	

Table 1. Single-nucleotide polymorphisms (SNPs) in ADORA2A, the gene that encodes the adenosine A2A receptor, are involved in a number of anxiety-related psychiatric disorders.

Perhaps most compelling is the large body of clinical evidence demonstrating that a variety of single nucleotide polymorphisms (SNPs) in the A_{2A} receptor gene, ADORA2A, is associated with anxiety in several psychiatric disorders and under drug-challenge conditions (**Table 1**). Panic disorder has been associated in different studies with several of ADORA2A SNPs including 1083C>T (Hamilton et al., 2004), rs5751876 (Hohoff et al., 2010), and 1976C>T (Hamilton et al., 2004). Association of the 1976C>T SNP with panic disorder was not replicated in a Chinese population (Lam et al., 2005), although the sample numbers were relatively low (>300 total individuals). It is noteworthy that the 1976C>T variant was also associated with self-reported anxiety after a moderate dose of orally-administered caffeine (150 mg; Alsene et al., 2003), amphetamine (10-20 mg; Hohoff et al., 2005), and sympathetic nervous system activation in individuals with blood injury phobia (Hohoff et

al., 2009). In addition to panic disorder and agoraphobia, the rs5751876 genetic variant of ADORA2A was also associated with autism spectrum disorders (ASD) (Freitag et al., 2010) and caffeine-induced anxiety (Childs et al., 2008). Interestingly, a recent study found that people with the rs5751876TT genotype, although more susceptible to caffeine-induced anxiety, habitually drank more coffee, concluding that tolerance to the anxiogenic effect of caffeine occurs regardless of susceptibility (Rogers et al., 2010). Two other variants of the A_{2A} receptor gene, rs2298383 and rs3761422, were found to be associated with multiple anxiety-related personality scores (Hohoff et al., 2010), with the former also involved in caffeine-induced anxiety (Childs et al., 2008), and the latter influencing phenotypic variability in ASD symptoms (Freitag et al., 2010). Other variants, rs2236624CC and rs35320474 (Freitag et al., 2010), associated more specifically with ASD, while rs4822492 was related to caffeine-induced anxiety (Childs et al., 2008), and rs5751862 was related more broadly to anxious personality (Hohoff et al., 2010). Although the effect of these SNPs on the expression or function of the A_{2A} receptor is not yet known, it is clear that this receptor is crucial to the regulation of anxiety.

3.2 The A1 receptor

In contrast to the A_{2A} receptor, a role for the A_1 receptor has been more difficult to establish. Genetic knockout of the A_1 receptor appears to argue for this receptor mediating the anxiolytic activity of adenosine, while approaches relying solely on pharmacological methods have been less clear. Moreover, no studies to date have implicated genetic variants of the A_1 receptor in anxiety disorders in humans.

Pharmacological regulation of the A_1 receptor has borne mixed results, with some studies demonstrating anxiolytic properties of its activation, others showing anxiolysis produced by its inhibition, and still others showing no effect of A_1 ligands on anxiety measures at all. Moreover, the differences in these studies are difficult to reconcile on the basis of drug selectivity or dose. For example, one study showed that A_1 receptor agonist CCPA was anxiolytic in the elevated plus maze and LD box, while A_1 receptor antagonists CPT and IBMX were anxiogenic in these tests (Florio et al., 1998). Another study showed that the anxiogenic effect of A_1-selective antagonist DPCPX was unaffected by A_1 agonist CPA. Yet another study showed the both CPA and CPX (A_1 antagonist) decreased the anxiolytic activity of ifenprodil (a glutamate NMDA antagonist; Fraser et al., 1996). Likewise, antagonism of A_1 receptors has been implicated in the actions of magnolia and ziziphus extracts, traditional Eastern treatment of mild anxiety and nervousness (Koetter et al., 2009).

Where pharmacology has failed to illustrate a consistent role for the A_1 receptor in anxiety-like behavior, genetic methods have yielded a much clearer picture. Deletion of the A_1 receptor gene in mice results in increased measures of anxiety in several different behavioral assays, including decreased exploration in the open-field and hole board, reduced open arm entries and time in the elevated plus maze, less time in the light portion of the LD box (Gimenez-Llort et al., 2002), and increased wall-hugging in the water maze (Lang et al., 2003). A_1 receptor knockouts also show a reduction in adenosine-mediated inhibition of glutamate neurotransmission and abolishment of theophylline-induced enhancement of glutamatergic signaling (Johansson et al., 2001). Other changes in these mice include reduced activity during some phases of the LD cycle, and reduced muscle strength and survival (Gimenez-Llort et al., 2002), indicating a possible role for the A_1 receptor in aging-related deficits, despite the normal spacial performance by the mice (Lang et al., 2003). Additionally, mice lacking the preproenkephalin gene, that show decreased locomotor activity, hyperalgesia, increased

anxiety and aggression, have enhanced central A_1 receptor-specific DPCPX binding, presumably reflecting an attempt to counteract or balance the loss of endogenous opioids (Bailey et al., 2004). These lines of evidence support the notion that the A_1 receptor does indeed regulate anxiety, and that its activation produces an anxiolytic behavioral response.

There is also preclinical evidence that the A_1 receptor may be involved in anxiety-like behavior in stressed animals and rodent models of hyperthyroidism. Rats subjected to a 3-day stress procedure showed a 15% increase in A_1 receptor binding in hypothalamic membrane preparations, as well as higher plasma corticosterone (Anderson et al., 1987). Thyroid hormones affect the development, function, and expression of A_1 receptors and regulate the transport of adenosine in the brain (Fideu et al., 1994), a hallmark of hyperthyroidism is anxiety. Hyperthyroidism induction was shown to have lasting effects on nucleotide hydrolysis (and thus, the availability of adenosine) in the rat brain, with young rats showing decreases of 14-52% in the hippocampus and cortex, while older rats had increased AMP hydrolysis in the cortex, but lasting decreases in the hippocampus (Bruno et al., 2003). Because CPA reduced anxiety-like behavior in hyperthyroid rats (Bruno et al., 2006), reduced A_1 receptor activation may underlie anxiety in hyperthyroidism.

3.3 ENT1

As discussed above, nucleoside transport is one of the most important determinants of adenosine levels in the CNS (Dunwiddie, 1985; Burnstock, 2008). Of the several equilibrative and concentrative transporters expressed in the brain, ENT1 appears to be central to the regulation of anxious states. Some of the first evidence in support of this idea came from a study demonstrating that pharmacological inhibition of adenosine uptake by papaverine was anxiolytic in the elevated plus maze test (Zangrossi et al., 1992). This study also suggested that inhibition of adenosine uptake may be a mechanism of the anxiolytic drug carbamazepine, as its actions were inhibited by adenosine receptor antagonist aminophylline (Zangrossi et al., 1992). It is noteworthy that multiple studies have also pointed to inhibition of ENT1 as a mechanism for benzodiazepine-induced anxiolytic activity (discussed later). Recently, we showed that mice lacking ENT1 display decreased baseline anxiety levels in the open-field, elevated plus maze, and LD box tests (Chen et al., 2007). Moreover, decreased anxiety in the open-field and elevated plus maze was replicated in C57BL/6J mice after microinjection of the ENT1 inhibitor NBTI (also called NBMPR) into the amygdala (Chen et al., 2007). NBTI binding was also upregulated in the brain following deletion of the preproenkephalin gene in mice, a manipulation which increases anxiety and aggression (Bailey et al., 2004). Increased ENT1 levels were accompanied by increases in A_1 receptor levels in this study, with these changes presumably an adaptive response to the loss of opioid peptides (Bailey et al., 2004). One clinical study undertaken to test the effect of dipyridamole on anxiety demonstrated no measurable improvement in patients with generalized anxiety disorder or panic disorder (Stein et al., 1993), although the sample size was extremely low (under 20 patients), and dipyridamole is not a very specific drug, acting as an inhibitor of both adenosine uptake and adenosine deaminase. The role of ENT1 and other nucleoside transporters in regulating anxiety clearly warrants future investigation.

4. Adenosine-GABA interactions in anxiety

Another well-known neurotransmitter system involved in the regulation of anxiety is the GABAergic system (Baldwin and File, 1989; Crestani et al., 1999; Kash et al., 1999; Löw et al.,

2000; Hodge et al., 2002). The relationship between GABAergic and adenosinergic signaling is interesting, because there is considerable functional overlap between their actions, such as the reduction of neuronal excitability. However, in contrast to the globally inhibitory actions of GABA upon neurons in the adult brain, adenosine can act as a permissive factor for signaling by other neurotranmitters, excitatory and inhibitory alike. Hence, the actions of adenosine on GABAergic signaling are similar to its actions on glutamatergic signaling, and whether adenosine dampens or potentiates GABA effects depends upon the expression site of adenosine receptors and their differential activation by ever-fluctuating adenosine concentrations. Given the implication of both GABA and adenosine signaling in decreasing anxiety, it is surprising that little research has focused on how these systems interact in anxiety disorders. The benzodiazepine anxiolytics, which potentiate signaling through the GABA$_A$ receptor, also interact with the adenosinergic system at several levels. These interactions represent the main focus of this section.

4.1 Benzodiazepines and adenosine signaling

In addition to their potentiation of GABA$_A$ receptor-mediated signaling, benzodiazepines (BZDs) are known to inhibit adenosine uptake, and several authors have suggested that this action may underlie, at least in part, the anxiolytic effect of these agents (Bruns et al., 1983; Phillis, 1984; Phillis and O'Regan, 1988). Indeed, diazepam and adenosine share a similar physico-chemical structure (Bruns et al., 1983). Inhibition of adenosine uptake by BZDs, including diazepam, lorazepam, and flurazepam, has been demonstrated in different experimental preparations, including rat brain synaptosomes (Phillis et al., 1980) and guinea pig ventricle (Barker and Clanachan, 1982). A study showing that BZDs prevent NBTI binding revealed ENT1 as a specific target of these drugs (Hammond et al., 1981). This is consistent with the reduced anxiety-like behavior in ENT1 knockout mice (Chen et al., 2007) and the anxiolytic action of adenosine uptake inhibitor papaverine (Zangrossi et al., 1992).

Given their structural similarities with adenosine, it is not surprising that BZDs have also been shown to interact with adenosine receptors in some cases. Furthermore, modifications in adenosine signaling have been linked to BZD withdrawal responses in animal models. Both the A$_1$ and A$_2$ subtypes of adenosine receptors appear to be affected by BZD treatment, but most evidence points to the A$_1$ receptor as playing a larger role in BZD action. BZDs did not displace chloroadenosine from A$_1$ receptors, indicating that direct action on these receptors is not likely responsible for BZD-mediated anxiolytic activity (Williams et al., 1981). Chronic treatment with mixed A$_1$/A$_{2A}$ receptor antagonists, caffeine or theophylline, reduced GABA potentiated flunitrazepam binding to the BZD site on the GABA$_A$ receptor (Roca et al., 1988). Since this action was blocked by chloroadenosine (Roca et al., 1988), it appears that A$_1$ receptor activation is required for the full potentiation of GABA$_A$ receptor signaling by BZDs. Studies on BZD withdrawal also indicate that A$_1$ receptor-mediated responses are integral to the effects of these anxiolytics. For example, administration of either caffeine or selective A$_1$ receptor antagonist DPCPX intensified BZD withdrawal in mice (Listos et al., 2006). Additionally, A$_1$ receptor agonist CPA was more efficacious in attenuating BZD withdrawal signs in mice than A$_{2A}$ receptor agonist CGS (Listos et al., 2005). Both studies support at least a minor role of A$_{2A}$ receptors in the actions of BZDs, which is in agreement with an older study showing displacement of adenosine from A$_2$ receptors by BZDs in neuroblastoma x glioma hybrid cells (Snell and Snell, 1984). In this same study, diazepam facilitated A$_2$-mediated cAMP production, but had no effect on this

measure in the absence of adenosine (Snell and Snell, 1984). While the exact contribution of A_1 and A_2 receptors in the effects of BZDs is not known, it appears a role exists for endogenous adenosine in the anxiolytic properties of this class of drug. This is consistent with the elevated availability of adenosine that results from ENT1 blockade by BZDs (discussed previously). Finally, this evidence indicates that BZDs might lose anxiolytic efficacy in habitual caffeine or theophylline consumers, and that people withdrawing from BZDs should avoid coffee, tea, and cola.

4.2 Other adenosine-GABA interactions

Adenosine signaling has also been implicated in the effects of other types of anxiolytic compounds that are known to potentiate $GABA_A$ receptor-mediated neuronal inhibition. Carbamazepine, an anxiolytic and anticonvulsant drug, reduces neuronal excitability in several ways, including stabilization of the inactivated state of sodium channels and $GABA_A$ receptor activation. Evidence for the involvement of adenosine in carbamazepine-mediated anxiolytic activity comes from a study showing that nonselective adenosine receptor antagonist aminophylline blocked the increase in open-arm time in the elevated plus maze in mice (Zangrossi et al., 1992). It is conceivable that adenosine acts as a permissive factor for $GABA_A$ activation, similar to the manner in which adenosine appears to partially mediate BZD action. Another study citing synergism between adenosine and $GABA_A$ signaling in reducing anxiety demonstrated that the anxiolytic activity of prostaglandin D2 in the elevated plus maze test in mice was blocked by both A_{2A} receptor antagonist SCH58261 and $GABA_A$ receptor antagonist bicuculline (Zhao et al., 2009). The synergism between adenosine and GABA in regulating anxiety remains an interesting and potentially important future prospect in the field of anxiety disorders.

5. Regulation of adenosine signaling by caffeine and alcohol

Caffeine and alcohol are the two most commonly used psychoactive substances in the world. Research has revealed that adenosine signaling is central to the anxiety regulating effects of these drugs. While people can benefit from many of the effects of adenosine receptor antagonism by caffeine, such as increased alertness, improved attention or focus, and even amelioration of depressive symptoms (Lara, 2010), sensitivity to caffeine-induced anxiogenesis may preclude certain individuals from enjoying coffee, tea, cola, or chocolate. On the other hand, moderate doses of alcohol are anxiolytic, and sensitivity to this effect may lead a person to abuse alcohol. There is a large body of information indicating that several of the CNS depressant effects of alcohol, including anxiolytic activity, are mediated by adenosine. In this section, the regulation of adenosine signaling by these substances will be discussed, with emphasis on how such action influences anxious behavior.

5.1 Caffeine

Much of what is currently known about adenosine signaling in general is based on studies using caffeine. Caffeine exerts its stimulant effects on the CNS by inhibiting adenosine A_1 and A_{2A} receptors, as does the related compound theophylline, and other synthetic methylxanthine derivatives. Caffeine can also inhibit phosphodiesterases and mobilize intracellular calcium, but the doses required for such actions are enormous, and not physiologically relevant (Nehlig et al., 1992). High (but physiological) doses of caffeine

cause anxiety in most people, low doses go essentially unnoticed, but significant individual differences exist in sensitivity to moderate doses of caffeine. Such individual differences in response to caffeine have been linked specifically to genetic polymorphisms in the A_{2A} receptor gene (ADORA2A), which may affect the expression or function of the receptor. Self-reported anxiety after moderate caffeine intake (150 mg, oral) was associated with ADORA2A variants 1976C>T and 2592C>T (Alsene et al., 2003). Individuals with the ADORA2A SNP rs5751876TT also had greater susceptibility to caffeine-induced anxiogenesis (Rogers et al., 2010). A puzzling observation in this study was that these genetically susceptible people tended to drink more coffee habitually, and that moderate to high habitual consumers of caffeine experienced less caffeine-induced anxiety, irrespective of genotype (Rogers et al., 2010). Thus, it appears that the history of caffeine exposure itself is a better predictor of whether or not someone will feel anxious when consuming caffeine. However, several SNPs in the ADORA2A gene, including those influencing responses to caffeine, are also associated with panic disorder, agoraphobia, autism, and amphetamine-induced anxiety (discussed previously), consistent with an older study showing that the majority of patients with agorophobia and panic disorder find caffeine to be anxiogenic (Charney et al., 1985). The results of these genome association studies underscore the importance of the A_{2A} receptor in several manifestations of anxiety.

Preclinical studies on the effects of caffeine largely support the clinical observations, including the central role of the A_{2A} receptor in caffeine-induced anxiogenesis. Caffeine, theophylline, and DPCPX were anxiogenic in the LD box test, with these effects reduced by A_2 agonist CGS21680, but not by A_1 agonist CPA (Imaizumi et al., 1994). Moreover, high-dose caffeine treatment, both acutely and chronically administered, failed to induce anxiety in A_{2A} receptor knockout mice in the elevated plus maze test (El Yacoubi et al., 2000). Prenatal caffeine exposure in Sprague-Dawley rats reduced anxiety in the elevated plus maze and the LD box, and enhanced responses to A_{2A} receptor agonist CGS21680 (Pan and Chen, 2007). Pretreatment with caffeine or theophylline reversed the anxiolytic effect of adenosine in the elevated plus maze and elevated zero maze (Kulkarni et al., 2007). Interestingly, despite being anxiogenic in Wistar rats in the elevated plus maze, caffeine actually increased open arm time after the rats underwent a chronic, unpredictable stress procedure (Pechlivanova et al., 2010), a method to model depression in rodents. This reduction in anxiety-like behavior by caffeine in the context of depression may be related to other evidence suggesting that moderate caffeine intake (< 6 cups/day) was associated with less depression and a lower risk of suicide (Lara, 2010). This suggests that different mechanisms may underlie the pathogenesis of anxiety and depression, despite their co-occurrence in many psychiatric diseases, and that both may involve changes in adenosine signaling.

5.2 Alcohol

Adenosine is known to contribute to many of the intoxicating effects of alcohol, such as its ataxic and sedative properties (Ruby et al., 2010; Asatryan et al., 2011). In general, sensitivity to the aversive effects of ethanol is inversely correlated with alcohol consumption. Indeed, the importance of adenosine signaling in the subjective effects of alcohol has been illustrated recently by the tragic deaths of several college students who were drinking the caffeinated alcoholic beverage,Four Loko, which has subsequently been taken off the market by the FDA. The incredibly high blood alcohol levels achieved by drinkers of Four Loko (0.4%)

reflected caffeine's ability to decrease sensitivity to the stumbling and tiredness associated with drinking large quantities of alcohol. Importantly, adenosine also appears to mediate some of the reinforcing effects of alcohol, including its well-known ability to reduce feelings of anxiety. Increased sensitivity to rewarding or reinforcing effects of ethanol is associated with greater drinking.

Ethanol reinforcement is in part mediated by A_{2A} receptor activation and associated intracellular signaling cascades in the nucleus accumbens (Adams et al., 2008), but the exact contribution of A_{2A} receptor-mediated signaling to drinking behavior remains unclear. A_{2A} receptor knockout mice show hyposensitivity to the intoxicating effects of ethanol and self-administer more alcohol than do wild-types (Naassila et al., 2002). As discussed previously, these mice also display increased basal anxiety, a potential contributing factor to their drinking behavior. Despite the counterintuitive observation that A_{2A} null mice showed reduced conditioned place preference for ethanol, they demonstrated increased sensitivity to the anxiolytic and locomotor stimulating (ie. pleasant) effects of alcohol, which may explain their greater ethanol self-administration (Houchi et al., 2008). Furthermore, the A_{2A} receptor agonist CGS21680 reduced alcohol consumption and preference in C57BL/6J mice (Houchi et al., 2008). Another study showed that A_{2A} receptor antagonist DMPX dose-dependently decreased lever-pressing for ethanol in an operant chamber, but had no effect on anxiety measures in the elevated plus maze or Vogel conflict assessments (Thorsell et al., 2007). However, yet another study showed that A_{2A} receptor antagonist ZM241385 had no effect on the anxiolytic activity of ethanol, suggesting instead that the A_1 receptor mediates this effect (Prediger et al., 2004). The contradictory results of these studies may reflect differences in specificity of the adenosinergic drugs administered, or general differences in approach between genetic and pharmacological studies. Alternatively, it may reflect a missing factor that affected the balance of adenosine signaling in opposite ways. Whether or not polymorphisms in ADORA2A are associated with alcohol intake patterns in humans is not yet known, so this is an interesting future prospect.

The adenosine transporter ENT1 appears to be involved in many aspects of alcohol-related behaviors (Choi et al., 2004; Chen et al., 2010; Nam et al., 2010; Nam et al., 2011) and anxiety (Chen et al., 2007). Moreover, a recent study showed that a polymorphism in the gene encoding ENT1 is associated with alcoholism and depression in women (Gass et al., 2010) and alcoholics with a history of withdrawal seizures (Kim et al., 2011). Acute ethanol inhibits ENT1, while chronic alcohol treatment leads to decreased ENT1 expression (Short et al., 2006; Sharma et al., 2010). This action of ethanol appears to be related to its ability to produce anxiolysis, as ENT1 null mice display decreased anxiety-like behavior in the open-field, elevated plus maze, and LD box (Chen et al., 2007). Microinjection of ENT1-specific inhibitor NBTI into the amygdala of C57BL/6J mice similarly reduced anxiety in the open-field and elevated plus maze tests (Chen et al., 2007). Interestingly, both manipulations resulted in increased alcohol consumption and preference, indicating that decreasing anxiety (negative reinforcement) does not appear to play a large role in the motivation for alcohol in this model. Since ENT1 null mice also show reduced conditioned place aversion for ethanol (Chen et al., 2010), their high alcohol drinking may be in part related to a lack of "healthy" amounts of anxiety and aversion that would normally prevent them from consuming large amounts of ethanol (ie. a greater degree of impulsivity). The data on ENT1 null mice is consistent with the evidence presented earlier in the chapter suggesting that ENT1 inhibition may be a mechanism by which benzodiazepines exert their anxiolytic

effects. As both high anxiety and low anxiety are associated with increased alcohol drinking behavior in studies of adenosine signaling, perhaps this apparent paradox highlights the importance of appropriate degrees of anxiety (and well-balanced adenosine signaling) in preventing excessive alcohol intake.

Abberrant adenosine signaling is also likely related to anxiety responses during ethanol withdrawal. Adenosine agonist R-PIA decreased open arm time in the elevated plus maze, while antagonist CPT produced partial recovery from ethanol withdrawal-induced anxiety (Gatch et al., 1999). CPT itself was anxiolytic in the LD box in rats, but did not reduce their ethanol consumption or preference (Gatch et al., 1999). A more recent study showed that adenosine and A_1 receptor agonist CCPA, at doses that were not normally anxiolytic, reduced peak-time ethanol hangover-induced anxiety in the elevated plus maze (Prediger et al., 2006). The effect of CCPA was reversed by pretreatment with A_1 receptor antagonist DPCPX, while A_{2A} receptor agonist DPMA had no effect (Prediger et al., 2006). Differences between these studies may reflect the specificity of the adenosine ligands used, or the time and intensity of ethanol exposure.

6. Conclusion

Adenosine is a ubiquitous CNS neuromodulator that regulates the signaling of major neurotransmitter systems involved in mood and emotion. Adenosine and adenosine receptor agonists are anxiolytic, while antagonists such as caffeine, are anxiogenic at high doses in most people, or at moderate doses in susceptible individuals. The availability of adenosine is largely regulated by nucleoside transporters such as ENT1, whose inhibition by benzodiazepines and alcohol may underlie their anxiolytic actions. Research also implies that adenosine-mediated signaling potentiates activation of the $GABA_A$ receptor, another target of anxiolytic drugs. Two types of adenosine receptors, the A_1 and A_{2A} subtypes, appear to contribute differentially to the regulation of anxious states. Both preclinical evidence and genome association studies strongly suggest that the A_{2A} receptor plays a central role in anxiety-related disorders, including panic disorder with agoraphobia, autism spectrum disorder, and anxiogenic responses to stimulants. Multiple lines of evidence support that deviation from a relatively narrow range of adenosinergic signaling balance may contribute to the development of many psychiatric conditions linked with anxiety, including depression and alcoholism.

7. Acknowledgments

8. References

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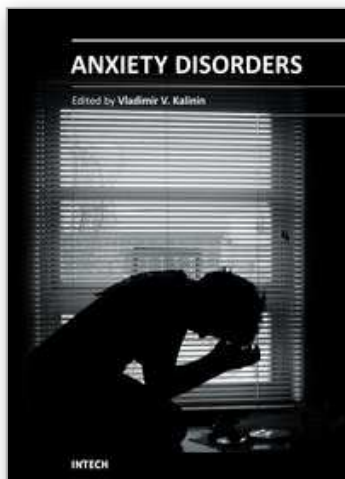
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Anxiety Disorders

Edited by Prof. Vladimir Kalinin

During the last 2-3 decades drastic research progress in anxiety issues has been achieved. It concerns mostly the study of different subtypes of anxiety and their treatment. Nevertheless, the data on anxiety pathogenesis is less elaborated, although here a multidimensional approach exists. It includes neurochemistry, pathophysiology, endocrinology and psychopharmacology. Again, we are able to recognize the multifarious sense of anxiety, and the present collective monograph composed of 16 separate chapters depicting the different aspects of anxiety. Moreover, a great part of book includes chapters on neurochemistry, physiology and pharmacology of anxiety. The novel data on psychopathology and clinical signs of anxiety and its relationship with other psychopathological phenomena is also presented. The current monograph may represent an interest and be of practical use not only for clinicians but for a broad range of specialists, including biochemists, physiologists, pharmacologists and specialists in veterinary.

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