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Cognitive enhancers for anxiety disorders ☆

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ABSTRACT

Cognitive-behavioral therapy is an effective intervention for anxiety disorders. However, a significant number of people do not respond or only show partial response even after an adequate course of the treatment. Recent research has shown that the efficacy of the intervention can be improved by the use of cognitive enhancers that augment the core learning processes of cognitive-behavior therapy. This manuscript provides a review of the current state of cognitive enhancers for the treatment of anxiety disorders.

1. Introduction

The most effective treatment for anxiety disorders is cognitive-behavioral therapy (CBT), which is typically administered in form of 12 to 15 weekly sessions (e.g., Cape et al., 2010; Gould et al., 1995; Hofmann and Smits, 2008; Stewart and Chambless, 2009). The CBT model posits that dysfunctional cognitions are causally linked to emotional distress, and that correcting these dysfunctional cognitions result in improvement of emotional distress and maladaptive behaviors. CBT is a short-term individual or group treatment that is typically administered over the course of weekly 1-hour treatment sessions. The treatment consists of several distinct but interwoven treatment components. The therapy introduces cognitive restructuring techniques and the exposure rationale. Specifically, patients practice identifying maladaptive cognitions (automatic thoughts), observing the covariation between anxious mood and automatic thoughts, examining the errors of logic, and formulating rational alternatives to their automatic thoughts. Patients are further asked to identify avoidance strategies and to eliminate them while exposing themselves to anxiety-provoking situations that appear to violate their personal social standards. Patients then confront increasingly difficult feared situations while applying cognitive restructuring techniques and eliminating any forms of avoidance strategies. Behavioral experiments are utilized to confront specific reactions to exposure experiences. Alternative therapies include traditional (anxiolytic) pharmacological agents, including include selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants and benzodiazepines (e.g., Baldwin et al., 2005).

Although both treatment modalities are efficacious, there is clearly room for improvement (Hofmann and Smits, 2008). For example, a completer analysis of placebo-controlled CBT trials showed an average treatment effect size of only 0.73. On the other hand, the success of this brief-treatment approach in the face of such chronicity is a testament to the degree to which patients learn in response to the informational, cognitive-restructuring, and exposure (extinction learning) based interventions offered in these protocols. Moreover, this learning occurs despite the presence of memory deficits that can be associated with the anxiety disorders (Airaksinen et al., 2005; Asmundson et al., 1994–1995).

Similar treatment effects have been found for pharmacotherapy trials (Roy-Byrne and Cowley, 2002). In order to enhance the efficacy of these treatments, a number of studies have examined the efficacy of combination strategies. However, a meta-analysis comparing combination strategies (CBT plus anxiolytic medication) with CBT plus placebo only showed modest benefits of combination strategies immediately after treatment (effect size: 0.59) and no added benefit at 6-month follow-up (Hofmann et al., 2009). Furthermore, partial, or non-response, to treatment remains an all-too-common occurrence, with over half of patients failing to respond fully to first-line CBT or pharmacologic interventions (Pollack et al., 2008). Recently, the search for new strategies to augment treatment has turned to a unique model of combination therapy. Rather than using pharmacotherapy as an anxiolytic in its own right, it is used to augment the core learning processes of cognitive-behavior therapy (Davis et al., 2006a, 2006b; Hofmann, 2007). A particularly successful prototype of such an augmentation strategy of CBT is the use of D-cycloserine (DCS; Norberg et al., 2008; Hofmann, 2007). This goal of this manuscript is

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to provide a review of the nature and success of cognitive enhancers for the treatment of anxiety disorders (Table 1).

2. DCS and the augmentation of extinction learning

In a particular success of translational research (Anderson and Insel, 2006), the application of DCS as an augmentation strategy was the product of animal research on the brain circuits underlying extinction learning (for a review, see Davis et al., 2006a, 2006b). Extinction learning appears to be modulated by activity of the glutamatergic N-Methyl-D-Aspartate (NMDA) receptor in the amygdala. Inhibitors of this activity appear to block the retention of extinction learning (Falls et al., 1992), and likewise, a partial agonist, like DCS, enhances this learning (Walker et al., 2002). Specifically, it appears that DCS enhances the consolidation of the new learning that occurs during extinction learning; augmentation effects continue to be present when DCS is administered within several hours after extinction learning (see Richardson et al., 2004). Hence, DCS appears to act as a memory enhancer, aiding the consolidation of what was learned during extinction learning. Indeed, only animals that show effective learning during extinction training display the benefits of memory enhancement in subsequent tests (Bouton et al., 2008).

These exciting findings from the animal laboratory were extended to the clinic in a placebo controlled trial by Ressler et al. (2004). Height phobic patients were given a single dose of study medication prior to each of two exposure sessions. Exposure was conducted using a virtual reality apparatus, and the use of only two exposure sessions mirrored animal study designs; e.g., an enhancement effect is easier to observe when an inadequate number of extinction sessions are given (cf., Walker et al., 2002). Ressler et al. (2004) found that DCS given prior to exposure significantly enhanced extinction learning, and this effect was evident at both 1–2 weeks and 3 months after the treatment sessions. Moreover, patients who received DCS reported more exposure to heights in life, consistent with the notion that DCS may have enhanced the memory of successful exposure experiences in the virtual reality environment and hence influenced the willingness to continue such exposure.

The successful trial by Ressler et al. (2004) was followed by a number of other successful studies, starting with the application of DCS augmentation to social anxiety disorder (Hofmann et al., 2006a, 2006b). In that study, we randomized 27 patients with social phobia to 50 mg DCS or pill placebo. DCS was administered one hour during the final four of a five session protocol of weekly treatment. During these four sessions, patients completed social exposure exercises. Patients who had received DCS achieved significantly more benefit as evaluated at acute and one-month follow-up evaluations. This small study was subsequently replicated by Guastella et al. (2008) with a larger (N = 56) sample size; similar benefit for DCS administration was found. We have reported similar positive findings for the application of DCS to the treatment of panic disorder (Otto et al., 2009a, 2009b). In that trial, DCS or pill placebo was administered to 31 patients with panic disorder during the final 3 of a 5-session protocol. In addition to targeting patients with panic disorder, this trial was unique for relying on exposure to feared internal sensations (interoceptive exposure) as the key extinction procedure. The majority of participants (87%) had failed to respond to previous pharmacologic interventions; nonetheless, strong DCS effects (reflecting a large effect size) were found relative to placebo. Larger scale, federally funded trials are now underway to confirm these results for social anxiety disorder and panic disorder in separate, large, multisite trials. Furthermore, federally funded controlled trials are currently underway to examine the efficacy of DCS as an augmentation strategy of exposure therapy for PTSD.

As compared to augmentation of exposure-based CBT for social anxiety disorder and panic disorder, applications of DCS to obsessive compulsive disorder (OCD) have been less positive (Kushner et al., 2007; Wilhelm et al., 2008; Storch et al., 2010). These studies are marked by more intensive scheduling of exposure sessions (twice weekly) and/or a greater number of doses of DCS across treatment. The studies by Kushner et al. (2007) and Wilhelm et al. (2008) showed an initial DCS augmentation effect that weakened with continuous administration. This suggests that DCS might enhance the speed of recovery when administered acutely during CBT and thereby reduce dropouts. The only trial in which DCS did not show an augmentation effect is the study by Storch et al. (2010). Patients in this trial received 250 mg of DCS 4 h before each of 12 CBT sessions. As discussed in the later part, these differences in the frequency, amount,

Table 1
Clinical applications of the cognitive enhancers.

Authors (year)	Cognitive enhancer	Disorder	Study design	Results
Ressler et al. (2004)	DCS	Height phobia	50 mg or 250 mg DCS or placebo administered prior to each of 2 virtual reality exposure sessions	Greater gains after DCS than placebo-augmented exposure sessions. No dose–response relationship
Hofmann et al. (2006a, 2006b)	DCS	SAD	50 mg DCS or placebo prior to each of 4 exposure sessions.	Greater gains with DCS than placebo-augmented exposure sessions.
Guastella et al. (2008)	DCS	SAD	50 mg DCS or placebo administered 1 h prior to each of 4 social exposure sessions.	Greater gains with DCS than placebo-augmented exposure sessions.
Otto et al. (2009a, 2009b)	DCS	Panic Disorder	50 mg DCS or placebo administered 1 h prior to each of 3 interoceptive exposure sessions	Greater gains with DCS than placebo-augmented exposure sessions.
Kushner et al. (2007)	DCS	OCD	125 mg DCS or placebo administered 2 h prior to each of 10 exposure/ritual prevention sessions	Greater gains with DCS than placebo-augmented exposure sessions by mid-treatment. This effect weakened with continuous drug administration.
Wilhelm et al. (2008)	DCS	OCD	100 mg DCS or placebo administered 1 h prior to each of 10 exposure/ritual prevention sessions.	Greater gains with DCS than placebo-augmented exposure sessions by mid-treatment. This effect weakened with continuous drug administration.
Storch et al. (2010)	DCS	OCD	250 mg DCS or placebo administered 4 h prior to each of 12 exposure/ritual prevention sessions.	No evidence for treatment benefit of DCS versus placebo at post-test.
Powers et al. (2009)	Yohimbine	Claustrophobia	10.8 mg of Yohimbine or placebo administered prior to each of two exposure sessions.	Greater gains with yohimbine hydrochloride than placebo-augmented exposure sessions.
Soravia et al. (2006)	Cortisol	Spider phobia	10 mg of cortisol or placebo administered prior to each of 6 exposure sessions.	Greater fear reduction after cortisol than placebo-augmented exposure sessions.
Mystkowski et al. (2003)	Caffeine	Spider phobia	4 mg/kg of body weight or placebo prior to 1 exposure session and then again at 1 week follow-up point.	Limited evidence for significant fear reduction versus placebo.

Note: DCS = D-cycloserine; SAD = Social Anxiety Disorder; OCD = Obsessive–Compulsive Disorder.

and dosing schedule of DCS may be one source of the inconsistent results in some of the studies.

2.1. Limits of DCS augmentation: dosing and learning issues

Dose response studies have not been conducted for determining the optimal dose of DCS for the enhancement of extinction learning. Ressler et al. (2004) applied single doses of either 50 mg or 500 mg DCS, and found no differences between them. Subsequent studies have applied single doses of 50, 100, and 125 mg DCS, and have found this dose adequate for enhancement of exposure therapy (Guastella et al., 2008; Kushner et al., 2007; Hofmann et al., 2006a, 2006b; Otto et al., 2009a, 2009b; Wilhelm et al., 2008). In our own studies, we in part chose 50 mg because of a desire to avoid side effects, as well as concerns about the rapid tolerance to DCS. Concerning side effects, we have observed few across our clinical and nonclinical trials, suggesting to us that patients are unlikely to be able to discriminate DCS from placebo when 50 mg doses are used. Concerning tolerance, animal research suggests that tolerance to DCS may be reached rapidly with repeated dosing (for review see Hofmann et al., 2006a, 2006b). For that reason, we have sought to use DCS sparingly, applying it in single doses before therapy sessions arranged one week apart. Weaker results have been found when DCS has been applied twice a week for more extended periods and using larger doses (cf. Kushner et al., 2007; Storch et al., 2010; Wilhelm et al., 2008), but there are enough design differences between studies that attribution of these effects to dosing cannot be made reliably.

Evidence for a potential dose effect comes from a study of DCS enhancement outside of an extinction paradigm. First, we found no beneficial effects for augmentation of the learning of verbal and nonverbal stimuli. Specifically, we found that single dose applications of 50 mg DCS vs. placebo prior to weekly trials of learning complex verbal (a detailed narrative) and nonverbal (complex figures) stimuli had no effects on immediate or delayed recall in healthy participants (Otto et al., 2009a, 2009b). Furthermore, only limited and inconsistent positive findings of a single-dose application of 50 mg DCS was found for memory tasks in individuals with schizophrenia (Goff et al., 2008). In contrast, Onur et al. (2010) found that 250 mg DCS did offer augmentation for declarative learning (specifically, item category associative learning), reducing the number of trial repetitions needed to attain improved learning. Onur and associates linked this DCS effect to enhanced activity in the hippocampus. Accordingly, given the failure to achieve a similar effect with 50 mg by Otto et al. (2009a, 2009b), Onur et al. proposed that whereas 50 mg DCS may be sufficient for amygdala-dependent learning such as extinction, a higher dose may be necessary for learning more specific to hippocampal processes. Further research is needed to confirm this hypothesis. Given concerns regarding tolerance to DCS (see Hofmann et al., 2006a, 2006b), it is important to consider in this work the possibility that the dose–response relationship may take on a quadratic function.

Another concern about the clinical application of DCS augmentation concerns the potential for sensitization of negative memories, for example should a patient have a sensitizing experience (e.g., a car accident or a poor exposure session) after taking DCS. It would be preferable to administer DCS after completion of the exposure session, so that the memory enhancing effects of DCS could be targeted toward only the sessions judged to be successful by the clinician, but the time course of orally given DCS is such that peak doses are achieved 4 to 6 h after ingestion. For this reason, even though the targeted activity for DCS is to be after the session, DCS is typically given 1 h prior to the session, so that it is likely to be active during the hours after the session (e.g., with a 90 min session, starting 150 min after the pill was taken). Despite potential limitations of this time course, testing of post-session oral administration of DCS is underway. Nonetheless, sensitizing experiences could occur after the session. In response to this issue, Davis et al. (2006a, 2006b) have reasoned that under fear conditioning experiences, the NMDA receptors may already be saturated, and that because DCS is a partial agonist, it may have relative inhibitory effects at times of fear. Specifically, Davis et al. (2006a, 2006b, p. 272) argue, "if the site on the NMDA receptors involved in fear conditioning is fully saturated, DCS might actually reduce the activity of the receptors by displacing the more effective endogenous chemicals. This could explain why DCS seems to actually inhibit fear conditioning in some situations." Recent evidence that DCS facilitation of extinction learning can be disrupted by the occurrence of a stressor (e.g., footshock) prior to DCS administration (Langton and Richardson, 2010) provides support for this hypothesis. In humans, testing of the relative effects of DCS vs. placebo on positive and negative emotional stimuli is currently underway, allowing the evaluation of aspects of this hypothesis. Similarly, a number of studies are underway to examine the optimal timing of administration of DCS, providing data that has important clinical and theoretical implications.

In summary, clinical studies provide strong evidence for a role of DCS in augmenting exposure therapy for the anxiety disorders, with evidence of a medium effect size ($d = .60$) for clinical populations (Norberg et al., 2008). Additional and ongoing examination of DCS will provide more information of the limits of this strategy and whether the very promising effects can be replicated across large samples. If so, DCS may emerge as a clinical strategy for three purposes. First, it can be applied as a strategy for reducing the number of sessions needed for treatment, a strategy of particular value in practice settings where access to CBT providers may be limited. For example, in primary care settings where limited numbers of sessions have been offered (Roy-Byrne et al., 2005), DCS augmentation may help more patients enter remission from treatment. Second, it can be applied to patients who have failed to respond adequately to standard CBT strategies, to see if additional retention of session material can aid outcome. Third, it can be applied in a targeted way to patients who are likely to have difficulty retaining the benefits of exposure therapy. For example, deficits in extinction retention have been found in schizophrenia (Holt et al., 2009), and animal studies suggests that DCS may help overcome specific extinction retention deficits, at least those that occur developmentally (e.g., McCallum et al., 2010). All of these applications hold promise for decreasing the burden of anxiety disorders on affected patients. Finally, one value that successful studies of DCS augmentation offer is encouragement for further study of memory enhancement strategies to empirically-supported psychosocial treatments for anxiety. In the following sections, we review a number of candidates for these additional augmentation efforts.

3. Cortisol for the augmentation of extinction consolidation

In recent years, there has been a re-conceptualization of the role of cortisol in memory. Specifically, even though chronic elevations in glucocorticoids may impair memory functioning, there is evidence, from studies of both humans and laboratory animals, that acute increases in glucocorticoids can enhance emotional consolidation and extinction-based learning (for review see Lupien et al., 2005; Otto et al., 2010).

In animal studies, cortisol activation is linked to enhanced consolidation of memory and, specifically, enhanced extinction learning (e.g., Barreto et al., 2006; Yang et al., 2007). While promoting new learning, acute corticosterone increases may impair reconsolidation of existing memories (Cai et al., 2006; Pakdel and Rashidy-Pour, 2007) providing an additional mechanism for the creation of adaptive memories for clinical interventions.

Memory enhancing effects of cortisol have been documented in humans (e.g., Beckner et al., 2006; Cahill et al., 2003), particularly for emotional stimuli (Abercrombie et al., 2006; Buchanan and Lovallo, 2001; Putman et al., 2004). Moreover, cortisol has been linked to

facilitated extinction learning in humans. Specifically, Soravia et al. (2006) examined the influence of oral cortisol (10 mg) relative to placebo on exposure to photos of a spider. Study pills were administered 1 h before exposure, and this procedure was repeated six times over two weeks, with greater fear reduction in patients who had received cortisol. Furthermore, in exposure protocols, cortisol levels have been linked to clinical outcomes in patient samples. For example, Junghanns et al. (2005) found that greater cortisol reactivity during 60 min cue exposure sessions predicted lower relapse at 6 weeks post-treatment in alcohol dependent participants. Likewise, levels of cortisol (but not specifically cortisol reactivity) predicted clinical outcomes in patients with panic disorder and agoraphobia undergoing in vivo exposure sessions (Siegmund et al., 2011). Finally, salivary cortisol levels decreased in rape victims with post-traumatic stress disorder following successful exposure-based treatments for PTSD (Gerardi et al., 2010). These findings are tentative and in need of replication, but they do draw attention to a potentially important role for cortisol in aiding extinction learning.

In contrast to strategies to enhance cortisol levels, many anxiolytic (benzodiazepine or antidepressant) medications suppress cortisol or hinder cortisol reactivity (e.g., Curtis et al., 1997; Fries et al., 2006; Pomara et al., 2005; Rohrer et al., 1994). In reviewing these data, and the above findings on cortisol levels and the facilitation of extinction memory, Otto et al. (2010) hypothesized that attenuation of glucocorticoid activity by anxiolytic medications may interfere with extinction learning in exposure-based CBT, reducing some of the benefits of traditional combination therapy when CBT and these medications are applied simultaneously. Accordingly, attention to these potential interfering effects may lead to more judicious application of combination treatments, relative to the efficacy of either strategy alone.

4. Catecholamines

4.1. Potential role for dopamine and norepinephrine

Studies of nonhuman primates suggest that catecholamine modulation, especially prefrontal cortex dopamine, is implicated in higher cognition, such as working memory. For example, the D1 receptor in the dorsolateral prefrontal cortex appears to be critical to spatial working memory performance in monkeys (Sawaguchi and Goldman-Rakic, 1991). D1 receptors in the PFC primarily exist on the distal dendritic spines of pyramidal cells. D1 activation not only directly excites pyramidal neurons, but enhances the responsiveness of the post-synaptic NMDA receptor on those cells as well (Seamans and Yang, 2004). D1 receptor activation appears to attenuate the recurrent excitation, probably by presynaptic inhibition of glutamate release (Seamans and Yang, 2004). This may have the effect of constraining the extent of local activation during cognitive processes. Therefore, D1 receptor-mediated action in the PFC appears to potentiate intense focal activity, whereas dampening the responsiveness of the local surrounding circuitry that would otherwise compete with the presently active circuit (Goldman-Rakic et al., 2004). It appears that the D1 receptor activation adjusts the gain (i.e., the strength of the representation) of the glutamate-encoded information in the PFC (Seamans and Yang, 2004), which includes a depression of background PFC activity. This then serves to make the self-sustained activity robust to noise and distractors (Durstewitz and Seamans, 2002).

In addition to working memory and cognition, dopamine has demonstrated a clear implication of its role in other various important brain processes such as motivation and reward seeking. In the anxiety disorders, there appears to be an inhibitory effect on dopaminergic activity in response to activity of two other neurotransmitters, GABA and serotonin. Therefore, it may be possible that there is an overactivity of dopamine in brain regions implicated in the maintenance of anxiety pathology when there is a deficiency of serotonin or GABA (Nikolaus et al., 2010). Specifically, neuroimaging and lesion studies reveal that a higher binding potential at dopamine receptors in brain areas such as the mesolimbic and striatal regions seem to be related to a greater frequency of anxiety and compulsion-related disorders (de la Mora et al., 2010; Olver et al., 2009; Stein and Ludik, 2000). Similar patterns in dopaminergic receptors have been observed in these brain regions in individuals reporting symptoms of generalized social anxiety disorder (van der Wee et al., 2008; Sareen et al., 2007; Furmark, 2009).

Given this observed relationship between dopamine transmission and anxiety symptoms, investigators have turned their attention to either directly or indirectly manipulating dopamine availability in relevant brain areas. Indirect methods have included use of serotonin-reuptake inhibitors for disorders such as OCD, in order to increase synaptic serotonin which would in turn inhibit dopamine release, but these drugs have not been found to be satisfactorily effective when used alone (Koo et al., 2010). Given the observation of higher binding potential of dopamine to its receptors in the striatal regions of the brain, direct methods that target the blockade of these dopamine receptors by dopamine antagonists to ideally produce anxiolytic effects would be a promising area to explore further, particularly for reduction in symptoms of OCD and generalized social anxiety. Indeed, preclinical studies indicate that such antagonists may be helpful in reducing dopamine activity, but this still warrants attention in clinical samples to see whether this translates to a reduction in anxiety symptoms.

Norepinephrine is implicated in PFC-dependent cognitive functions. For example, α_2 receptors modulate working memory performance in monkeys and rodents. These effects probably occur at post-synaptic sites (Arnsten and Goldman-Rakic, 1985). It has been suggested that phasic locus coeruleus activity is driven by the outcome of task-related decision processes that are signaled by descending projections from the ACC and orbitofrontal cortex (Aston-Jones and Cohen, 2005). This then adjusts the gain in target neurons via ascending projections back to the PFC. One implication of the inverse relationship between phasic and tonic activity is that α_2 agonists could act either at the cell-body autoreceptor to adjust the balance of phasic to tonic LC activity in a manner to optimize decision-making performance or at the post-synaptic α_2 receptor to enhance sustained PFC activity (Arnsten, 2004).

4.2. Yohimbine and extinction learning

One other potential candidate for stimulating mPFC activity is yohimbine hydrochloride, a selective competitive alpha2-adrenergic receptor antagonist. Yohimbine increases extacellular levels of norepinephrine in this region by blocking autoreceptor inhibition of norepinephrine release (see Holmes and Quirk, 2010). Initial studies examining the effect of yohimbine hydrochloride on extinction learning have yielded mixed results. On the positive side, in an early rodent study, systemic administration of yohimbine hydrochloride resulted in a speeding up of extinction learning during massed exposure and successful fear extinction with spaced extinction trials, which usually yield minimal extinction learning relative to massed trials (Cain et al., 2004).

In an important study in humans, Powers et al. (2009) showed evidence in support of the use of yohimbine hydrochloride for augmenting exposure-based treatment. They randomly assigned 24 adults with claustrophobic fears to receive two sessions of exposure treatment after administration of yohimbine hydrochloride (10.8 mg) or two sessions of exposure treatment after administration of a pill placebo. Consistent with hypothesis, participants who received yohimbine-augmented exposure showed better outcomes relative to those who received pill placebo-augmented exposure. Importantly, yohimbine hydrochloride was well tolerated. However, as reviewed by Holmes and Quirk (2010), a number of other animal studies have

not replicated the yohimbine augmentation effect, and some have even shown impairment in extinction learning.

In their detailed accounting of both the potential benefits and limitations of yohimbine augmentation, Holmes and Quirk (2010) draw attention to differential results that may be due to mouse strain-related differences in the alacrity of extinction learning, the paradigm (e.g., bar pressing vs. freezing behaviors) used to assess extinction learning, as well as the possibility that yohimbine augmentation may be especially sensitive to the context dependence as compared to cue-focused aspects of fear stimuli (see Morris and Bouton, 2007). Holmes and Quirk raised questions whether the potential beneficial effects of yohimbine augmentation occur through the assumed noradrenergic (alpha2 adrenoreceptor) stimulation as compared to alternative (5-HT1a or D2) mechanisms. Another potential limitation of yohimbine is its tolerability. That is, although Powers et al. (2009) did not observe any adverse events in their study, there is work suggesting that yohimbine can be panicogenic when administered at doses over 10.8 mg, especially among individuals who fear somatic arousal (Charney et al., 1984, 1987). At the same time, it is possible that such side effect profile (e.g., somatic arousal, panic) in fact aids the therapeutic effects of yohimbine. Specifically, interoceptive exposure, or the repeated confrontation to feared bodily sensations (e.g., racing heart, rapid breathing, and dizziness), has been shown to be efficacious for treating panic and related disorders (Hofmann and Smits, 2008), presumably because it results in the extinction of fears of somatic arousal. In summary, yohimbine has shown early promise in a clinical trial in phobic humans (Powers et al., 2009), but much work needs to be done to clarify the reliability as well as the mechanism of these effects.

4.3. Modafinil

Modafinil (2-[(Diphenylmethyl) sulfinyl] acetamide; brand name Provigil in the United States) exhibits effects on catecholamines, serotonin, glutamate, gamma amino-butyric acid, orexin, and histamine systems in the brain. Many of these effects may be secondary to catecholamine effects, with some selectivity for cortical over subcortical sites of action (Minzenberg and Carter, 2008). Modafinil is a wakefulness promoting agent. It is currently approved by the FDA for treating excessive sleepiness as part of narcolepsy, shift work sleep disorder and obstructive sleep apnea/hypopnea syndrome. In addition to its application for sleep disorders, it has been used off-label as a psychostimulant for the treatment of cognitive dysfunction in some psychiatric conditions, such as schizophrenia, attention-deficit/hyperactivity disorder (Minzenberg and Carter, 2008), and a general cognitive enhancer in normals (Volkow et al., 2009).

Preclinical data suggest that modafinil can improve working memory performance in a dose- and delay-dependent manner, that the processing of contextual cues is enhanced with modafinil, and that these effects may be augmented with sustained dosing regimens (for a review, see Minzenberg and Carter, 2008). Human studies have shown that modafinil enhances working memory, recognition memory, sustained attention, and other tasks dependent on cognitive control in healthy subjects (with or without undergoing sleep deprivation). Among psychiatric populations, there is some evidence that modafinil improves attention and response inhibition in children and adolescents with ADHD. Other studies suggest that, as mentioned previously, modafinil improves several prefrontal-dependent cognitive functions in schizophrenia, major depression, and adult ADHD.

Modafinil appears to be associated with greater anxiety in both animal and humans, but the evidence is mixed and might be dose-dependent. Whereas amphetamine increased measures of anxiety in mice (increased latency of exploration of a white compartment, increased open-field thigmotaxis, and decreased time in the open arms of an elevated-plus maze), modafinil did not show these effects at doses that induce comparable effects on locomotor activity (Simon et al., 1994). A study in monkeys found no effect of modafinil on anxiety after single or repeated doses that increased nocturnal activity (Hermant et al., 1991). A pharmacokinetic study of modafinil in healthy humans reported heightened anxiety at doses from 200 to 800 mg (Wong et al., 1999). Another study of mood and cognitive function in healthy young adults found that a single 100 mg dose of modafinil was associated with greater subjective and physical symptoms of anxiety than placebo, but a higher dose (200 mg) did not show these effects (Randall et al., 2003). In contrast, healthy adults who received modafinil 400 mg daily for 3 days reported being less calm than those receiving a placebo (Taneja et al., 2007). Similarly, placebo-controlled studies found that repeated administration of modafinil was associated with greater anxiety in myotonic dystrophy patients (MacDonald et al., 2002), obstructive sleep apnea (Schwartz et al., 2003), and multiple sclerosis patients (Zifko et al., 2002). In sum, the literature suggests that that modafinil is associated with increased anxiety in healthy individuals and clinical populations. Its potential role in augmenting extinction learning (and the potential role of enhanced anxiety in this process) remains to be studied.

5. Nutrients and botanicals

Another area warranting investigation is the use of natural compounds as adjunct enhancers of traditional anxiety treatments. Indeed, several studies have tested naturally occurring compounds such as omega-3 fatty acids, caffeine, and nicotine for their effects on the fear system and anxiety disorder symptoms. A brief overview of the findings for each of these substances is given below.

5.1. Caffeine

Caffeine is one of the most widely consumed substances in the class of psychostimulants, which are part of the larger family of methylxanthine compounds. The primary site of action for the substance is at adenosine receptors, where caffeine has been shown to modulate brain activity and cerebral blood flow (Chen and Parrish, 2009). Further, there appears to be a dose–response effect with caffeine such that low to moderate consumption patterns are associated with increased alertness and mental focus, while high dosages have been implicated in the exacerbation of negative feelings such as insomnia and anxiety (Yun et al., 2007). In addition, evidence points to a heightened sensitivity and reactivity to caffeine in individuals reporting histories of panic attacks as compared to controls (Boulenger et al., 1984). Specifically, patients with panic disorder or agoraphobia have reported significantly higher ratings of fear and physical symptoms (e.g. trembling, palpitations, nausea, and tremors) when administered equal doses of caffeine as control subjects, and these symptoms were significantly correlated to plasma caffeine levels (Charney et al., 1985). Similar observations have been made in social phobics fearing public performance situations, although with mixed results for generalized social anxiety cases (Nardi et al., 2008; Aouizerate et al., 2004). This, with other studies directly measuring adenosine receptor activity with caffeine administration, have strongly suggested a link between fear of physical symptoms and a particular sensitivity to caffeine-induced neural activity at adenosine receptor sites (DeMet et al, 1989; Nardi et al., 2008).

In order to better parse out how caffeine may impact the fear and alarm circuitry, several studies have used caffeine challenge tasks with individuals meeting criteria for panic disorder. Typically such experimental paradigms have involved administering various dosages of caffeine to subjects (e.g. 200 mg–400 mg), and then measuring performance on another task aimed to mimic the symptoms typically experienced during panic attacks, such as breath holding (BH), CO_2 inhalation, and hyperventilation. Results of such experimental set-ups have primarily revealed a reduced capacity to tolerate the unpleasant

physical symptoms generated by such tasks in individuals with panic disorder histories who have consumed caffeine, but no differences as a result of caffeine intake in those with no such anxiety history (Masdrakis et al., 2009). Others have hypothesized a beneficial application of caffeine in the treatment of anxiety, such as in exposure therapy for spider phobia, where participants were administered either caffeine or placebo at the time of an exposure session and then again at a one-week follow-up visit, where they were assessed for return of fear (Mystkowski et al., 2003). The results indicated that those individuals experiencing congruent drug states (i.e. ingestion of caffeine at both test and follow-up periods) exhibited significantly less return of fear than those in incongruent drug states. However, this was also true of the placebo group, therefore this study provided evidence more generally for state-dependent learning in extinction of fear, and not specifically for an additive benefit of augmentation with caffeine.

5.2. Omega-3 fatty acids

Mammalian brain tissue is primarily comprised of lipids which are themselves composed of combinations of saturated, monosaturated, and polyunsaturated fatty acids. Several key omega-3 fatty acids (i.e. a-linolenic acid or ALA, and linoleic acid) are can be synthesized quite readily from foods such as flaxseed, canola, and soy. Others (particularly docosahexaenoic acid or DHA, which makes up some 10–20% of brain fatty tissue) are not easily synthesized from dietary sources, but are obtained in preformed fashion from sources such as fatty fish (e.g. tuna and salmon) (McNamara and Carlson, 2006). In animal models, deficiencies in these brain matter constituents are associated with neurocognitive deficits, elevated aggression, anxiety, and depression levels, and deficits in primary neurotransmitter transmission such as dopamine and serotonin.

In humans, the effect of this deficiency looks a little different. Specifically, a deficit in fatty acids (as seen most typically in pre-term babies) has been implicated in increased risk for attention-based pathology such as attention deficit/hyperactivity disorder (ADHD), other psychopathology such as schizophrenia, and in deficits in cortical gray matter maturation. On the whole, the work on omega-3 fatty acid levels in human populations has been scant thus far, but preliminary evidence indicates that deficiencies in this particular substance may be associated with higher incidence of depression in human populations, as observed in animal studies (Timonen et al., 2004; Klokk et al., 2010). A handful of studies have investigated the effects of baseline omega-3 levels on responsiveness to traditional SSRIs in treatment of depression, but the results of these studies have not indicated a clear added benefit of taking a supplement of omega-3 (Fiedorowicz et al., 2010). The beneficial use of omega-3 supplements has been even less frequently examined in the anxiety disorders, but given the relatively supported link of omega-3 deficiency to elevated indices of anxiety in animals, this would be a potentially fruitful avenue to explore further.

5.3. Nicotine

Nicotine has been widely understood to be positively linked to psychiatric disorders such as schizophrenia, depression, and certain anxiety disorders. In particular, researchers have noted a higher incidence of smokers in the population of individuals diagnosed with panic disorder (Breslau and Klein, 1999). Others have actually found a lower incidence of nicotine dependence in individuals meeting criteria for OCD, thus creating a mixed picture of the specific effects of nicotine on the fear and alarm system. Pre-clinical studies on the effects of nicotine on non-human species have suggested a dose–response relationship of nicotine to anxiety such that low doses are associated with anxiolytic effects and higher doses are associated with anxiogenic effects (Brioni et al., 1993; File et al., 1998). Others have suggested that the anxiolytic properties of nicotine are more readily linked to other factors such as whether the animal is tested on a task such as the elevated plus maze which more readily models specific phobia, as compared to the anxiogenic effects of the substance on other tasks such as social interaction tasks (File et al., 2000).

Such findings could elucidate how nicotine's effects may be best understood as disorder-specific, and explain some of the clinical observations of relative rates of nicotine dependence across the anxiety disorders. Several human studies have adopted paradigms similar to those seen with caffeine whereby non-smoking individuals are administered small doses of nicotine transdermally (via a patch) before they undergo a CO_2 inhalation task. While nicotine increased physiological arousal (e.g. blood pressure and heart rate), it did not induce panic in healthy subjects (Cosci et al., 2006). Yet, other smaller studies with clinical populations have indicated some reduction in the compulsive symptoms of OCD with transdermal administration of nicotine (Salín-Pascual and Basañez-Villa, 2003), Overall, it is clear that more exploration in both normal and clinical populations is required to better parse out whether particular dosages of nicotine may actually be beneficial in tempering the fear response in anxiety patients.

6. Novel treatment approaches and future directions

6.1. Methylene blue

A brain region that appears critical to the consolidation of extinction memory is the medial prefrontal cortex (mPFC; Quirk et al., 2006). Indeed, studies have demonstrated that lesions of the ventral mPFC do not hamper extinction learning per se, but result in impairments of extinction retention (Quirk et al., 2000; Lebrón et al., 2004; Morgan et al., 1993). Both rodent and human studies have further shown that extinction recall is associated with significant activation of the mPFC region (Barrett et al., 2003; Milad and Quirk, 2002; Milad et al., 2004) and that stimulation of the mPFC enhances extinction retention in rodents (Herry and Garcia, 2002; Milad and Quirk, 2002; Milad et al., 2004). Together, these studies support the development of strategies that target mPFC activity.

One approach to enhancing fear extinction through the stimulation of mPFC activity that has received some initial empirical support is the administration of methylene blue (MB; Gonzalez-Lima and Bruchey, 2004). As opposed to DCS, which targets a specific transmitter system, the action of MB is non-specific. MB can activate the mPFC region by its effects on brain cytochrome oxidase activity. Specifically, by increasing brain cytochrome oxidase activity, MB improves oxidative energy metabolism and can thereby supply the energy needs of synapses involved in extinction memory consolidation (Gonzalez-Lima and Bruchey, 2004). In an initial rodent study, Gonzalez-Lima and Bruchey (2004) demonstrated that post-extinction administration of MB (4 mg/kg intraperitoneally) was associated with greater extinction retention as well as increased brain cytochrome oxidase activity, particularly in the prefrontal cortical region. Clinical studies on the efficacy of MB for augmenting exposure-based treatment are currently underway.

6.2. Endocannabinoids

The endogenous cannabinoid (or endocannabinoid) system has become another focus of research investigating novel therapeutic approaches for anxiety and related disorders (Porter and Felder, 2001). This research has largely been done due to the large presence of CB1 receptors in brain regions related to anxiety and emotional learning in general (e.g., amygdala, hippocampus). There are two types of cannabinoid receptors, CB1 and CB2. CB1 is most often in the peripheral and central nervous system, while CB2 receptors are involved more in the immune and enteric nervous system, as well as

in glial cells in the central nervous system. Studies on humans and animals have shown that cannabinoid agonists have an anxiolytic effect that is dose dependent. Lower doses have been shown to produce an anxiolytic effect in animals whereas higher doses result in an anxiogenic effect (Viveros et al., 2005; Pacher et al., 2006). With respect to anxiety and depression, human studies of depression, which is often comorbid with anxiety, have demonstrated involvement of CB1 (Vinod and Hungund, 2006). In fact, CB1 antagonists are being explored as a potential treatment for depression (Stein et al., 2006) due to the interaction of cannabinoids and conditioned fear. The cannabinoid system modulates basal anxiety and appears to be involved in the conditioned fear. Additionally, cannabinoid neurotransmitters effect both acquisition and the expression of fear conditioning (Haller et al., 2002) in that CB1 antagonists decrease acquisition of contextual fear conditioning involving the amygdala and hippocampus (Arenos et al., 2006).

This system has been linked to extinction learning in animal models (e.g., Chhatwal et al., 2009; Marsicano et al., 2002). As discussed previously, extinction learning is the foundation for most empirically supported treatments for anxiety disorders. CB1 antagonists lead to significant deficits in extinction learning, indicating that CB1 activation is necessary for extinction learning to occur, and therefore CB1 agonists serve as an opportune novel augmentation treatment (Chhatwal et al., 2005).

6.3. Genetic modulation

6.3.1. BDNF

Changes or alteration in gene expression have recently provided great insight into the processes of learning in memory. One recent focus has been on brain-derived neurotrophic factor (BDNF), which is part of the neurotrophin family of growth factors. BDNF affects the adult central nervous system and, within this system, plays a role in synaptic plasticity of neurons involved in learning and memory (Egan et al., 2003; Hariri et al., 2003). BDNF is involved in fear and extinction learning and serves a central function in the biological substrates of psychological disorders (Charney and Manji, 2004; Nestler et al., 2002). Fear learning is built off the ability to recognize and remember safety and threat cues to achieve extinction learning. Moreover, this type of learning is impaired in anxiety disorders (e.g., Rauch et al., 2006; Lissek et al., 2005). Animal research has demonstrated that both genetic and pharmacological inhibition of BDNF signaling leads to a significant reduction in long term potentiation, ultimately leading to memory impairments across a variety of memory tasks (see Yu et al., 2009). Regarding fear extinction learning, there is now evidence in animal populations to suggest that BDNF mediates consolidation of extinction memory within the infralimbic medial prefrontal cortex (IL mPFC).

The hypothesis that the efficacy of exposure-based treatments can be enhanced with strategies that increase hippocampal BDNF also receives support, albeit indirect, from a study involving human participants. Kobayashi et al. (2005) provided 42 outpatients with panic disorder with manualized cognitive-behavioral treatment (CBT) and found that patients with poor response to CBT had significantly lower serum BDNF levels (25.9 ng/ml [S.D. 8.7]) relative to patients with good response to CBT (33.7 ng/ml [S.D. 7.5]). In addition to pharmacological options to increase hippocampal BDNF, growing evidence supports the use of aerobic exercise for this application (Berchtold et al., 2010; Cotman and Berchtold, 2002). Here, it is noteworthy that Ströhle et al. (2010) found that a 30-minute bout of moderate-intensity exercise ameliorated reduced BDNF concentrations in patients with panic disorder. These findings have formed the basis of ongoing studies testing whether exercise can be a non-pharmacological cognitive enhancer of exposure-based treatment in adults with anxiety disorders.

Given the previously discussed findings, it is not surprising that studies suggest that the $BDNF_{Met}$ polymorphism contributes to impairments in memory extinction (Yu et al., 2009). However, when animals are given a single dose of DCS (as discussed previously), they are able to recover from this deficit across future trials. Such evidence suggests that the impairment caused by $BDNF_{Met}$ and its potential impact on fear-based learning may be reversible.

Research on humans has identified a single nucleotide polymorphism in the BDNF gene (Val66Met) that influences hippocampal volume and hippocampal dependent memory (Egan et al., 2003; Hariri et al., 2003; Bueller et al., 2006). This human specific BDNF nucleotide ($BDNF_{Met}$) has been an area of interest due to the role it plays in vulnerability to psychological disorders, including anxiety and depression (Momose et al., 2002; Sklar et al., 2002; Ventriglia et al., 2002; Sen et al., 2003). The translation of the effect of BDNF polymorphisms from animals to humans supports the idea that extinction learning is impaired in both mice and humans in $BDNF_{Met}$ allele carriers. Imaging research has demonstrated less ventromedial prefrontal cortical activity and greater amygdala activation in $BDNF_{Met}$ allele carriers (Soliman et al., 2010). This research suggests a hypo-responsiveness in $BDNF_{Met}$ allele carriers in brain regions crucial for extinction learning.

In sum, BDNF plays an important role in fear-based learning as demonstrated by BDNF polymorphisms. Understanding the effect of the $BDNF_{Met}$ allele on extinction learning leads to a clearer conceptualization of treatments for anxiety, as well as novel approaches to enhancing treatment. The dysregulation of BDNF found in anxiety disorders, such as PTSD (Kaplan et al., 2010) suggest a key role of BDNF as more research is done on the role of genetic modulation in treatment of these disorders. Moreover, the neuroregenerative effects of BDNF have the potential for reversing cognitive and emotional deficits in not only anxiety disorders like PTSD, but also in other brain related injuries such as a traumatic brain injury.

6.3.2. KIBRA

KIBRA (also known as WWC1) is another biological marker that has recently gained popularity for its potential role in learning and memory. KIBRA was first described by Kremerskothen et al. (2003) and is a molecule that is involved with the postsynaptic protein dendrin. KIBRA has been shown to play a key genetic role in memory and cognition (Papassotiropoulos et al., 2006). In adults it is most commonly expressed in the kidney and brain, and in both rodents and humans it is prominent in memory-related structures, such as the hippocampus, cortex, cerebellum and the hypothalamus (Johannsen et al., 2008). Carriers of certain KIBRA T alleles (e.g., rs17070145, rs6439886) perform significantly better on tasks involving multiple episodic memories compared to individuals that are homozygous for the C allele at either polymorphism (see, Schneider et al., 2010, for a review). Moreover, functional magnetic resonance imaging studies have found greater brain activation in brain areas associated with memory retrieval in WWC1 (rs17070145) T-allele-noncarriers as compared to T-allele carriers on an episodic memory task, suggesting a strong effect of genetic contribution to certain types of memory.

The majority of research on KIBRA has involved healthy controls with and without certain T alleles and individuals with dementia. The use of KIBRA has been investigated as a potential focus for new pharmacological approaches to improve cognition. Although studies to date have not focused on anxiety and depression, KIBRA offers a new genetic link to cognition that may be of benefit beyond diseases such as Alzheimer's. In fact, it may aid in memory impairments that accompany various anxiety disorders that prevent patients from effectively engaging in empirically supported treatments, such as cognitive-behavioral therapy.

7. Summary and conclusion

Our review of cognitive enhancers for CBT of anxiety disorders includes d-cycloserine, methylene blue, catecholamines (dopamine and norepinephine), yohimbine, modafinil, endocannabinoids,

cortisol, and nutrients and botanicals (omega-3 fatty acids, caffeine, and nicotine), as potential cognitive enhancers. Of these substances, d-cylcoserine has demonstrated so far the greatest potential. We further examined BDNF and KIBRA as potentially important biological markers of treatment efficacy and genetic modulators. Our review points to the NMDA receptor complex as the most promising target for future cognitive enhancers of CBT for anxiety disorders.

Traditional treatment strategies combining anxiolytic agents, such as SSRIs, and psychological interventions, such as CBT, have been yielding disappointing results. In general, it has been found that combination treatments are not more effective than monotherapies (Hofmann et al., 2009). Moreover, and more importantly, the traditional combination approach has been conducted without a clear theoretical justification, given that the mechanisms of treatment action are not well understood for either modality. In contrast, combining CBT with cognitive enhancers is a neuroscience-based approach with the goal to translate basic research into clinical practice. This strategy offers considerable advantages over traditional combination strategies, because cognitive enhancers target specific mechanisms of the treatment process. Such strategies may be associated with greater efficacy than traditional combination treatments and monotherapies. Moreover, this may answer important questions about the mechanism of treatment change, which, in turn, can provide new questions for future research. Although the development and maintenance of anxiety disorders in humans are still issues of current controversy (e.g., Poulton and Menzies, 2002), the review of this literature and other evidence (Hofmann, 2008) suggests that cognitive processes are important factors in the treatment of these debilitating conditions.

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