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The effect of pregabalin on sensorimotor gating in 'low' gating humans and mice

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ABSTRACT

Pregabalin, an anticonvulsant and anxiolytic compound that binds to α2-δ auxiliary subunit Types 1 and 2 of voltage-gated calcium channels, has been shown to reduce excitatory neurotransmission partially through modulation of glutamatergic signaling. Prepulse inhibition (PPI) of startle is an operational measure of sensorimotor gating impacted by disruption of the glutamatergic system and is reduced in schizophrenia patients. Dysregulation of the glutamatergic system has also been implicated in the pathophysiology of schizophrenia. Here we tested the hypothesis that pregabalin may ameliorate PPI in a model of deficient gating in humans and mice. In study 1, 14 healthy human subjects participated in a within subjects, cross-over study with placebo, 50 mg or 200 mg pregabalin treatment prior to undergoing a PPI task. In study 2, 24 C57BL/6 mice underwent a similar procedure with vehicle, 30 and 100 mg/kg dose treatments. In both studies, subjects were assigned to a "Low" or "High" gating group using a median split procedure based on their PPI performance during placebo/vehicle. Drug effects were then examined across these groups. In humans, pregabalin treatment significantly increased PPI performance in the "low gating" group. In mice, pregabalin treatment significantly increased PPI in the low gating group but reduced PPI in the high gating group. Across species, pregabalin treatment improves PPI in subjects with low gating. These data support further exploration of pregabalin as a potential treatment for disorders characterized by sensorimotor gating deficits and glutamatergic hypersignaling, such as schizophrenia.

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1. Introduction

Recent evidence suggests that excessive glutamate transmission may be a core feature of pathology in schizophrenia, supplanting previous 'hypoglutamatergic' theories which were predicated on NMDA receptor dysfunction (Moghaddam and Javitt, 2012; Krystal et al., 2003). For instance, magnetic resonance spectroscopy studies of medication-naive schizophrenia patients have shown increased glutamate and glutamine levels in the prefrontal cortex (Cecil et al., 1999). Consequently, a number of novel therapies targeted toward reducing glutamate neurotransmission are being explored for treatment of schizophrenia (e.g. Chaki and Hikichi, 2011).

Pregabalin ((S)-3-(aminomethyl)-5-methylhexanoic acid) is FDA approved for use in partial seizures (French et al., 2003), neuropathic pain (Dworkin et al., 2003) and fibromyalgia (Straube et al., 2010) and has also shown efficacy in treating generalized anxiety disorder (Rickels et al., 2005) and social anxiety disorder (Pande et al., 2004). Pregabalin binds to α2-δ auxiliary subunit Types 1 and 2 of voltage-gated calcium channels (VGCC; Taylor et al., 2007), with the effect of reducing excitatory neurotransmission in "hyperexcited" neurons (Quitero et al., 2010; Kavoussi, 2006). Pregabalin has been shown to reduce levels of glutamate in the brain and spinal cord (Errante and Petroff, 2003; Fehrenbacher et al., 2003; Maneuf et al., 2001; Dooley et al., 2000). Recently, Englisch and colleagues (2010) reported on a series of 11 case studies using pregabalin as an adjunctive treatment for anxiety in schizophrenia patients. Pregabalin was effective in reducing anxiety in these patients, as well as enabling a dose decrease in antipsychotic medications. These preliminary case studies and the putative reduction of glutamatergic signaling induced by pregabalin treatment supports the further examination of its use in treatment of schizophrenia. One strategy to further examine its potential as a treatment for schizophrenia is in predictive models of antipsychotic efficacy, such as pre-pulse inhibition.

Prepulse Inhibition (PPI), or the unlearned suppression of the startle reflex to an intense acoustic stimulus when immediately preceded by a weaker acoustic pre-pulse, has been characterized as

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a measure of pre-attentive information processing or sensorimotor gating (Geyer et al., 1990). Specifically, PPI is thought to reflect the ability of an organism to gate out extraneous sensory information and subsequent motor response in order to allow for processing of the pre-pulse. PPI is observed across all mammals tested (Braff et al., 2001; Dulawa and Geyer, 1996; Swerdlow et al., 1986). PPI has been widely used as a model of sensorimotor gating deficits and screening tool for novel therapeutics for schizophrenia (Swerdlow et al., 2008). PPI is disrupted by infusion of glutamate into the nucleus accumbens and the ventral striatum (Klarner et al., 1998; Swerdlow et al., 1992), and infusion of the glutamate agonist NMDA into the ventral hippocampus (Wan et al., 1996), suggesting that excessive glutamate signaling in some forebrain regions can induce sensorimotor gating deficits.

Pregabalin has effects in areas of the brain implicated in the regulation of PPI, including the hippocampus, prefrontal cortex, basolateral amygdala, and striatum (Li et al., 2011; Taylor et al., 2007; Swerdlow et al., 2001). Thus, pregabalin may have the effect of regulating glutamate function in areas where excess glutamate has been shown to disrupt PPI including the prefrontal cortex, where dysregulated glutamate signaling has also been implicated in the pathophysiology of schizophrenia (Moghaddam and Javitt, 2012).

The current studies investigated the effect of pregabalin on PPI in healthy controls (experiment 1) and a sample of C57BL/6J mice (experiment 2). A median split procedure was conducted on baseline PPI in order to isolate treatment effects on subjects with low baseline gating performance. This data analytic strategy has been increasingly used in PPI research with healthy samples as a measure of gating normalization by antipsychotic medications (Holstein et al., 2011; Csomor et al., 2008; Gogos and van den Buuse, 2007; Vollenweider et al., 2006; Swerdlow et al., 2006; Bitsios et al., 2005). Such a strategy identifies a subset of healthy subjects who exhibit traits similar to those observed in patient samples, and thus facilitates translation of findings into patient populations.

2. Experiment 1

2.1. Methods

2.1.1. Subjects

Subjects were recruited by flyers placed around the UCSD campus and advertisements in local newspapers. 17 subjects underwent the written informed consenting process and were screened for study eligibility. Exclusionary criteria included meeting criteria for a DSM-IV Axis I disorder, current substance abuse, neurological disorders, current medication, smoking, excessive caffeine consumption (>4 cups per day), hearing threshold > 45 dB at a 500–6000 Hz range and head trauma with loss of consciousness > 5 min. Three subjects were excluded from analysis due to a lack of startle response during the procedure (mean baseline startle trials/mean no stimulus trials < 1.5). Subject characteristics are described in Table 1. All subjects gave written, informed consent and were treated in accordance with the Declaration of Helsinki. The study was approved by the University of California, San Diego Human Research Protection Program.

2.1.2. Treatment

The study consisted of a randomized double blind cross-over design with 3 testing days and a 7–10 day washout period between each test. On each testing day, subjects received either a Placebo dose, a "Low" dose (50 mg), or a "High" dose (200 mg) of pregabalin (purchased from Pfizer, Inc). This dose range covered both a sub-therapeutic dose and a dose demonstrated as therapeutic for generalized anxiety disorder (Bech, 2007). The therapeutic dose was intended to be in the low range to limit interference from sedative effects. Order of dose was randomized across subjects. Pregabalin was dissolved in a soft drink for administration, and was delivered ~150 min prior to testing. Pregabalin reaches peak plasma concentration in ~1.3 h following oral dose and has a half-life of 4.6–6.8 h in healthy subjects (Busch et al., 1998). Startle testing was part of a larger battery of tests that included psychosocial surveys and fMRI that preceded the startle study presented here (Aupperle et al., 2011).

2.1.3. Stimuli and apparatus

Startle pulses were delivered using a San Diego Instruments (SDI, San Diego, CA, USA) SR-HRLAB EMG system as previously described (Braff et al., 1992). Sound levels were measured using continuous tones and a calibrated Quest Sound Level Meter on the A scale, coupled to the headphones by an artificial ear. EMG responses were band-pass filtered (1–1000 Hz) and 60 Hz notch filtered, digitized, and recorded (1 kHz sampling frequency) using the SDI SR-HLAB EMG system coupled with a standard Dell desktop computer.

Table 1
Subject characteristics by median group.

	Low PPI	High PPI	Total
N	7	7	14
Mean age	22.86	24	23.43
Percent male	71%	43%	57%
Ethnicity	Caucasian = 5 Asian = 1 Other = 1	Caucasian = 2 Asian = 3 Hispanic = 1 Other = 1	Caucasian = 7 Asian = 4 Hispanic = 1 Other = 2
Women in follicular/luteal menstrual phase			
Placebo	1/1	1/3	2/4
50 mg	1/1	2/2	3/3
200 mg	0/2	3/1	3/3

Note. Both a *t*-test for Age and a Fisher's exact test for Percent Male yielded no significant difference between PPI groups.

2.1.4. Experimental procedure

Subjects were seated in a comfortable lounge chair in a dimly lit testing chamber. Once seated, two electrodes (Ag/AgCl) were placed lateral to and below the left eye over the *orbicularis oculi* muscle. A reference electrode was also placed on the left mastoid. Subjects were fitted with standard headphones through which the startle pulses could be presented (all acoustic stimuli are presented as broad-band noise; 70 dB background, 86 dB prepulses of 20 ms duration and 114 dB pulses of 40 ms duration). The session began with 5 114-dB pulses to stabilize startle responding. After this block pre-pulse trials (6 each of 3 trial types) or 114-dB pulse alone trials (10 total) were presented in a pseudorandom order. Prepulse trials consisted of 3 types, with the pre-pulse preceding the pulse at interstimulus intervals (ISI) of 30, 60 or 120 ms. The session then ended with 5 114-dB pulse trials. The intertrial interval ranged between 7 and 23 s (average 15 s) and baseline activity was recorded during each intertrial interval.

2.1.5. Data analysis

EMG responses were visually examined across each trial by a trained technician to identify and remove artifact (e.g. voluntary blinks) that were not associated with the pulse onset (e.g. a response was not counted unless it was within 100 ms of pulse onset). Data from the first and last block of 114-dB pulse-alone trials were analyzed separately from the rest of the session. This first block helps habituate startle to a stable baseline before pre-pulse trials are introduced, and comparing it to the last block at the end of the session measures habituation of the startle response across the session (e.g. Ludewig et al., 2002; Braff et al., 1992). Peak EMG response was averaged across each trial type. To assign subjects to high/low PPI groups, their average pre-pulse inhibition across all pre-pulse types was used, and subjects below and above the median (34%) were assigned to low and high PPI performance groups respectively ($n = 7$/group). Following median split, data were analyzed using a 2×3 repeated measures analysis of variance (ANOVA) with PPI group (low, high) as a between subject factor and dose (placebo, 50 mg, 200 mg) as a within subject factor. Bonferroni-corrected post-hoc tests were conducted to clarify significant main effects and interactions.

2.2. Results

2.2.1. Startle reactivity

Means and standard deviations for startle reactivity by PPI performance group and dose can be seen in Table 2. A 2×3 repeated-measures ANOVA showed a main effect of Dose: $F(2,24) = 3.67$, $p < .04$, partial $\eta^2 = .23$. Post-hoc tests showed that independent of PPI group, startle was significantly reduced after 200 mg treatment compared to both placebo and 50 mg dose groups ($ps < .05$). High and low PPI groups did not differ in startle reactivity. Startle habituation was unaffected by PPI group or pregabalin (data not shown, main effect of Block: $F(1,12) = 10.48$, $p < 0.01$, no interaction with Group or Dose).

2.2.2. Prepulse inhibition

Dose effects were dependent upon PPI group [Fig. 1A; Dose × Group interaction, $F(2,24) = 5.55$, $p < .01$, partial $\eta^2 = .32$]. Post-hoc tests showed that the low PPI group exhibited significant improvements in PPI after treatment with 50 or 200 mg pregabalin compared to placebo ($ps < .02$). There was no significant effect of Dose within the High PPI group. The effect of Dose and Group were not dependent upon