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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.

Keywords

Schizophrenia; Pre-pulse inhibition; Glutamate; Pregabalin; Startle; Sensorimotor gating

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

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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 "hyper-excited" 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 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.

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 broadband 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 the ISI, although as expected PPI performance was increased with longer ISIs across all groups (data not shown) [Main effect of ISI $F(2,24) = 16.56$, $p < 0.001$].

Both doses of pregabalin increased PPI in healthy humans with low baseline gating level. While visual inspection of Fig. 1A appears to show pregabalin decreasing PPI in the group with high baseline gating level, this difference did not reach statistical significance in the post-hoc tests. This finding is the first known demonstration of a pregabalin effect on PPI. To confirm and extend these results, we attempted to corroborate the effect in a mouse model of high and low PPI performance.

3.Experiment 2

3.1. Methods

3.1.1. Subjects—Twenty four male C57BL/6J mice obtained from Jackson Laboratories (JAX®; Bar Harbor, ME), aged 6–8 weeks on arrival. Mice were housed 4 per cage in a temperature-controlled (21–22 °C) room under a reverse 12 h light/dark cycle (lights off at 8:00 A.M.) with free access to food and water. Mice began behavioral testing one week after arrival to the vivarium. All procedures were approved by the UCSD Institutional Animal Care and Use Committee. The UCSD animal facility meets all federal and state requirements for animal care, and has been approved by the American Association for Accreditation of Laboratory Animal Care.

3.1.2. Treatment—Pregabalin (Tocris Bioscience Ellisville, Missouri) was dissolved in saline vehicle and administered 2 h before testing. On each testing day, mice received either

vehicle, 30 or 100 mg/kg via interperitoneal injection. These doses were based on previous studies demonstrating anxiolytic effects in C57BL/6 mice (e.g. Lotarski et al., 2011). Order of dose was counterbalanced across mice and tests were separated by a 7 day washout period.

3.1.3. Stimuli and apparatus—Startle chambers (SR-LAB; San Diego Instruments, San Diego, CA) consisted of non-restrictive Plexiglas cylinders 5 cm in diameter resting on a Plexiglas platform in a ventilated chamber. High-frequency speakers mounted 33 cm above the cylinders produced all acoustic stimuli, which were controlled by SR-LAB software. Piezoelectric accelerometers mounted under the cylinders transduced movements of the animal, which were digitized and stored by an interface and computer assembly. Beginning at startling stimulus onset, 65 consecutive 1 ms readings were recorded to obtain the peak amplitude of the animal's startle response. A dynamic calibration system was used to ensure comparable sensitivities across chambers. Sound levels were measured as described previously using the A weighting scale in units of decibels sound pressure level (Risbrough and Geyer, 2005). The house light remained off throughout all testing sessions.

3.1.4. Experimental procedure—The session was modified from the test used for human subjects to include a greater range of ISIs to be characterized. Broad-band noise was used for all acoustic stimuli and background noise. The background was kept constant at 65 dB. The session began with 5 pulse-alone trials at 120 dB intensity (40 ms) to stabilize startle. The pre-pulse testing block then consisted of 5 pre-pulse trial types in which the 77 dB pre-pulse (20 ms) onset preceded the 120 dB pulse (40 ms) by 20, 70, 120, 360 or 1080 ms. Prepulse trials (5 per ISI type, 25 total) and pulse alone trials (7 total) were presented in pseudorandom order. The session ended with 5 pulse alone trials. The intertrial interval was 7–23 s with average of 15 s.

3.1.5. Data analysis—As with experiment 1, low and high baseline PPI groups were defined by median split of PPI performance across the 20–120 ms ISI trials. This grouping showed a similar median split cutoff for PPI performance as experiment 1 in human subjects (38.82%). Data were then analyzed with two separate ANOVAs. First, to best match the human PPI parameters, we examined PPI across the ascending limb of the ISI curve (20–120 ms) trials and conducted a 3 way ANOVA with performance group (low, high) as a between-groups factor and dose (0, 30, 100 mg/kg) and ISI (20–120) as a within-subject factor. Second, we conducted a 3-way repeated measures ANOVA with PPI group as a between-groups factor and dose and all ISIs on both the ascending and descending limbs of the ISI curve (20–1080 ms) as within-subject factors. Habituation effects were analyzed with a 3 way ANOVA with startle block and dose as within subject factors and PPI group as a between subject factor. Bonferroni-corrected post-hoc tests were conducted to clarify significant main effects and interactions.

3.2. Results

3.2.1. Startle reactivity—Means and standard deviations for startle reactivity by PPI group and dose can be seen in Table 2. Pregabalin had no effect on startle magnitude, nor was there an effect across PPI group. Startle habituation was also unaffected by PPI group or pregabalin (data not shown, main effect of Block: $F(1,23) = 68$, $p < 0.0001$ no interaction with Dose or Group).

3.2.2. Prepulse inhibition—Mean changes in PPI across dose by group is shown in Fig. 1B. Pregablin treatment effects on PPI were dependent upon PPI group [Dose × Group interaction $F(2,44) = 6.10$, $p < .005$, partial $\eta^2 = .22$]. In the low PPI group, 100 mg/kg Pregabalin treatment significantly increased PPI compared to vehicle ($p < .03$). Conversely,

the high PPI group exhibited reduced PPI after 30 and 100 mg/kg treatments compared to vehicle (*ps* <.03). The ISI (20–120 ms) did not interact with dose or group. In the second analysis that included the long ISIs in the model (380–1080 ms), pregabalin effects on PPI were dependent on ISI [Drug × Group × ISI $F(8,176) = 2.33$, $p < 0.05$]. When a post-hoc ANOVA was conducted with the long ISI trials only, there were no significant effects or interactions between ISI, dose or group (data collapsed across 360–1080 ms ISI: Low PPI group: 13 ± 6, 11 ± 8, 22 ± 8 across placebo, 30 and 100 mg respectively; High PPI group: 23 ± 4, 24 ± 8, 10 ± 9 across placebo, 30 and 100 mg respectively). These results suggest that pregabalin effects are not present at long ISI trials, likely due to the relatively variable and low PPI typically seen with very long ISI parameters (>300 ms).

4. General discussion

To our knowledge, this report represents the first investigation of pregabalin effects on sensorimotor gating in humans or mice. These experiments demonstrated that pregablin treatment increases PPI in healthy samples of both humans and mice that exhibit low baseline gating performance (lower 50% of median performance during placebo test). This median-split approach in healthy subjects has also been shown to be sensitive to atypical antipsychotics (Holstein et al., 2011; Vollenweider et al., 2006), as has an approach using healthy subjects performing within the lower quartile of normative samples (Swerdlow et al., 2006). Pregabalin effects on PPI were most robust at short ISIs in mice, which is also consistent with findings from atypical antipsychotics in healthy humans (Holstein et al., 2011; Vollenweider et al., 2006). Human subject eyeblink responses were reduced after 200 mg/kg pregabalin treatment suggesting a sedative effect at this dose, but this effect was similar across low and high gaters. Pregabalin had no significant effects on startle in mice, which may be due to differences in startle measures (eye blink vs. whole body response), plasma levels or pharmacokinetics across the human and mouse studies. These data suggest that the pregablin effects on PPI are unlikely to be an artifact of drug effects on startle reactivity overall. Startle reactivity was also not different between high and low PPI groups, consistent with other studies showing startle reactivity does not differ across subjects stratified for gating performance (Csomor et al., 2008; Vollenweider et al., 2006). Taken together, these data support further examination of pregabalin treatment in disorders linked to deficiencies in gating.

The present study also found that pregabalin treatment reduced PPI in mice and humans with high baseline gating levels. Though this decrease only reached statistical significance in mice, the same pattern is evident in humans as well, suggesting that the human subject sample may have been underpowered to detect this difference ($n = 7$ and 12/group for human and mouse study respectively). The pregabalin-induced decreases in PPI in high gaters are similar to the reductions in PPI observed after antipsychotic treatment in high gaters (Holstein et al., 2011; Gogos and van den Buuse, 2007). This opposing effect on PPI across low and high gaters may suggest that pregabalin is affecting a neural mechanism that modulates PPI via an inverted-U shaped curve. An analogous finding is the effects of COMT (catechol-o-methyltransferase) inhibition on PPI across individuals carrying the high or low efficiency COMT alleles (Giakoumaki et al., 2008). Subjects carrying the high efficiency alleles for the COMT gene, which presumably have lower dopamine levels in the prefrontal cortex showed low baseline PPI that was increased with treatment with the COMT inhibitor tolcapone. The opposite effect was found in individuals carrying the low efficiency COMT allele, exhibiting high baseline PPI that was reduced by tolcapone treatment. These effects were suggested to be due to the inverted U-shaped curve of cortical dopamine effects on PPI, with subjects with low dopamine tone showing increases after COMT inhibition while subjects that had higher tone were pushed into the “descending limb” of the response curve resulting in lower PPI. These effects were also mirrored in a

working memory task. Thus pregabalin effects may be via a similar “inverted U” response mechanism, although the neurotransmitter and neural circuit mediating these effects is unknown.

One candidate mechanism underlying the present study effects is regulation of glutamatergic signaling in the forebrain. PPI has been shown to be disrupted by infusion of glutamate and glutamate agonists into the nucleus accumbens, ventral striatum, and ventral hippocampus (Klarner et al., 1998; Wan et al., 1996; Swerdlow et al., 1992). Further, NMDAR antagonists MK-801, ketamine and phencyclidine disrupt PPI in rodents (Martinez et al., 2000; Mansbach and Geyer, 1991). These effects can be mimicked by direct infusion of MK-801 into the dorsal hippocampus, amygdala, or medial prefrontal cortex, but not striatum (Bakshi and Geyer, 1998). $mGlu_{2/3}R$ agonists reduce both glutamate release and schizophrenia-like behaviors in animal models, although the effects on NMDA antagonist-induced disruptions in PPI is inconsistent (Imre et al., 2006; Galici et al., 2005; Henry et al., 2002). Further, *N*-acetylaspartylglutamate peptidase inhibitors ZJ43 and 2-PMPA suppress glutamate release but failed to reverse phencyclidine-induced PPI deficits (Profaci et al., 2011). These data indicate that modulation of glutamate tone does not consistently affect PPI disruptions induced by NMDA receptor blockade. If the pregabalin-induced increases in PPI are mediated by a reduction in glutamate tone, this would suggest that pregabalin effects on PPI in low gaters would not be via normalization of a putative hypo-NMDA receptor activation state in these subjects. It is also important to note, treatment with the NMDAR antagonist ketamine in humans increases PPI, suggesting that the NMDA-modulation of PPI may not be completely conserved across species (Abel et al., 2003). In the present study, pregabalin effects were mirrored across animals and humans, suggesting that the mechanism by which it acts on PPI is conserved across species.

Pregabalin also has the effect of inhibiting the neurotransmitters norepinephrine, Substance P, and serotonin, without demonstrated effects on dopamine (Brawek et al., 2008; Fehrenbacher et al., 2003; Maneuf et al., 2001; Dooley et al., 2000). Thus, these transmitter systems must also be considered as potential pathways through which pregabalin may affect PPI. The possibility of a noradrenergic mechanism is supported by recent research which has shown that stimulation of the locus coeruleus (LC) causes disruption of PPI mediated by downstream norepinephrine (NE) release (Bakshi and Alsene, 2010). In further work, Alsene and colleagues (2011) have identified a candidate thalamocortical network (including the posterior medial prefrontal cortex (mPFC), basolateral amygdala (BLA), and mediodorsal thalamus) through which excess NE activity may disrupt PPI. Thus, pregabalin activity in the mPFC and BLA may have the effect of attenuating NE signaling and facilitating PPI in low gaters. Noradrenergic modulators such as clonidine however do not affect PPI in healthy controls, although possible differential effects were not examined across high and low gating groups (Samuels et al., 2007). Substance P has been shown to elicit excitation in the caudal pontine reticular nucleus (PnC; Kungel et al., 1994). The PnC mediates PPI as the point of convergence between excitatory glutamatergic projections and inhibitory cholinergic projections at the acoustic startle circuit (Koch and Schnitzler, 1997). Thus, excess Substance P may override cholinergic inhibition and reduce PPI. Normalization of Substance P by pregabalin may then facilitate PPI in these individuals. Finally, a substantial body of work supports modulation of PPI by the serotonin system, particularly involving the projections between the median raphe nucleus and dorsal hippocampus and 5-HT1A/1B receptor activation (Adams and van den Buuse, 2011; Geyer and Vollenweider, 2008; van den Buuse et al., 2011). The effect of on the serotonin system also represents a potential pathway through which pregabalin may modulate PPI.

Practically, the ability of pregabalin to facilitate PPI in low gaters suggests that this compound may have clinical utility as a primary or adjunctive therapy for disorders

characterized by impaired sensorimotor gating. Specifically, PPI has been historically used as a screening measure for antipsychotic drugs targeting schizophrenia (Swerdlow et al., 2008; Geyer et al., 1990). The effect of pregabalin on this measure, the emerging research on the role of excess forebrain glutamate in schizophrenia (Moghaddam and Javitt, 2012), and case studies supporting the efficacy of pregabalin as an adjunctive treatment for schizophrenia (Englisch et al., 2010) suggest that this compound may have utility for treatment of this disorder. Beyond schizophrenia, pregabalin may have utility as an adjunctive treatment for other disorders characterized by impaired PPI such as obsessive-compulsive disorder (Ahmari et al., 2012). Indeed, recent research has suggested that pregabalin may be effective for OCD as an adjunct to standard SSRI/atypical antipsychotic treatment, possibly through reduction of glutamatergic neurotransmission (Oulis et al., 2011; Di Nocola et al., 2011). Further studies of pregabalin augmentation for OCD are ongoing.

The current studies contain some limitations. First, the sample size in study 1 was relatively small, however the pattern of results was confirmed in study 2 in mice. Another potential limitation of Study 1 is that menstrual cycle was not controlled for in female subjects. PPI is affected by menstrual phase in humans, with decreased inhibition observed during the luteal phase (Jovanovic et al., 2004; Swerdlow et al., 1997). However, there is no noticeable sex imbalance across median groups or phase imbalance across dose (see Table 1). Additionally, pregabalin had the same pattern of effects across a mixed sex sample of humans and male mice. Thus, it is unlikely that sex or menstrual cycle were significantly influencing the results. One may also be concerned that the median split procedure has to potential to generate a regression to the mean effect. However, we feel that this is unlikely to account for such robust effects given that PPI demonstrates very high test-retest reliability over significant lengths of time in both normal and psychiatric populations (Swerdlow et al., 2009; Talledo et al., 2009; Light et al., 2007). Thus, it is unlikely that PPI would fluctuate so dramatically over the span of 2–3 weeks nor in a dose dependent manner. Overall, this report points to a potentially novel application for gabapentenoid compounds in disorders associated with disruption in gating, including schizophrenia. Future research is needed to elucidate the mechanism and neural substrates of action underlying these effects (e.g. forebrain modulation of glutamate signaling) and to demonstrate facilitation of PPI in patient populations.

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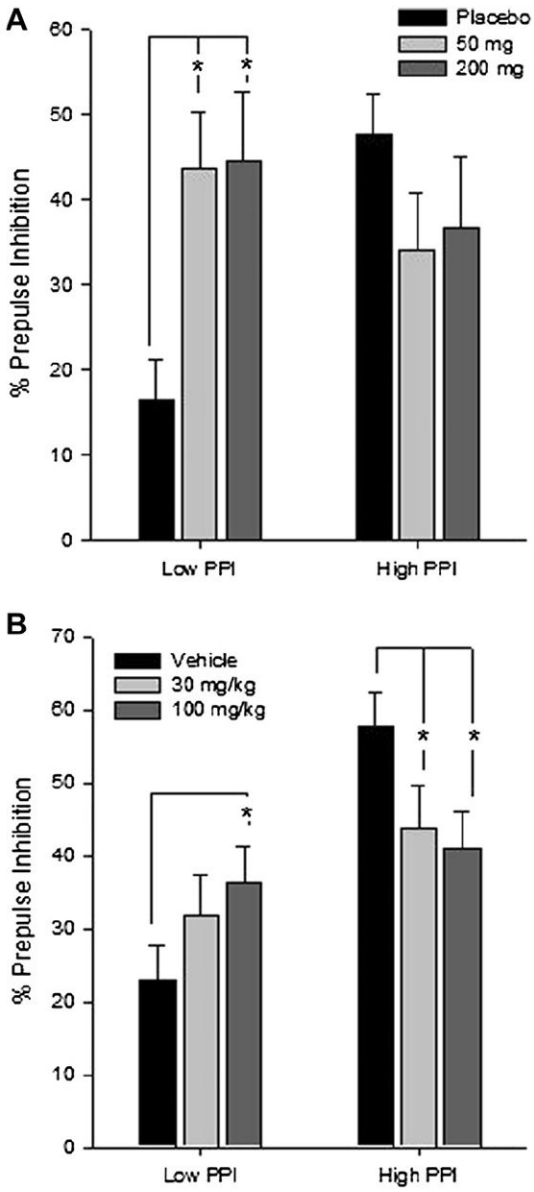

Fig. 1.

Pregabalin modulates PPI differently across high and low gating groups. (A) Healthy human subjects (n = 7/PPI group) were treated with placebo, 50 and 200 mg Pregabalin (oral) in a counterbalanced cross-over design with 1 week washout. (B) C57Bl6J mice (n = 12/PPI group) were treated with 0, 30 and 100 mg/kg (IP) in a counterbalanced cross-over design with 1 week washout. High and low PPI groups were categorized by median split of placebo treatment. Data are depicted as mean +/− SEM percentage PPI. PPI is averaged over 30−120 ms ISIs in humans and 20−120 ms ISIs in mice. *$p < 0.05$, post-hoc simple contrasts after Group × Pregabalin interaction. See results for details.

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	Caucasian = 2	Caucasian = 7
	Asian = 1	Asian = 3	Asian = 4
	Other = 1	Hispanic = 1	Hispanic = 1
		Other = 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.

Table 2

Startle reactivity (in arbitrary units) for both mice and humans by dose and median PPI.

	Humans			
	Low PPI (*n* = 7)		**High PPI (*n* = 7)**	
	M	**SD**	**M**	**SD**
Placebo	226.67	309.9	110.3	55.1
50 mg	202.5	137.58	97.88	54.77
200 mg *	145.63	129.1	83.98	65.4
	C57BL/6J Mice			
	Low PPI (*n* = 12)		High PPI (*n* = 12)	
	M	SD	M	SD
Vehicle	95.38	52.49	110.3	55.1
30 mg/kg	95.98	81.6	97.88	54.77
100 mg/kg	93.67	69.19	83.98	65.4

Note.

* $p < .05$ vs. Placebo post-hoc test after significant main effect of dose. No main effects of Low/High group or interactions with dose were significant.