Influence of aripiprazole, risperidone, and amisulpride on PPI and P50-suppression in healthy males with low levels of gating

Csomor PA & Vollenweider FX

Clinic of Affective Disorders and General Psychiatry, Psychiatric University Hospital, Zurich, Switzerland

Introduction

Deficient early information processing has been considered a central feature of schizophrenia spectrum disorders. A fundamental feature of information processing is the ability to gate extraneous stimuli and to attend to salient features of the environment. Two operational measures of gating are prepulse inhibition (PPI) and suppression of the P50 auditory evoked potential (AEP) (P50 suppression). PPI refers to the attenuation of the startle reflex elicited by an intense pulse stimulus when its presentation is preceded by a weak prepulse. Similarly, in P50 suppression the first stimulus (S1) not only produces AEP but also activates gating, resulting in a suppression of the P50 AEP to the second stimulus (S2). It has been shown repeatedly that patients with schizophrenia exhibit deficits in PPI and P50 suppression. Since PPI and P50 gating can be induced in healthy volunteers, patients and rodents, these paradigms represent excellent tools for translational research and might be useful in translational medicine for the discovery of novel pharmacotherapeutic compounds with antipsychotic properties. We have developed a translational model to investigate the possible differential effects of antipsychotic medication on PPI and P50 suppression in healthy human subjects exhibiting low baseline gating rather than in patients[1,2]. In order to validate and extend our model several atypical antipsychotics (aripiprazole, risperidone, amisulpride) have been tested. Furthermore, also CNS-active compounds (lorazepam, modafinil, valproate) without antipsychotic properties serving as a negative control treatment have been tested.

Methods

In a balanced, placebo-controlled within-subjects design, healthy male volunteers received either a single dose of aripiprazole (15 mg p.o., n=27), risperidone (2 mg p.o., n=26), amisulpride (400 mg p.o., n=22), lorazepam (2 mg p.o., n=22), modafinil (200 mg p.o., n=29), valproate (500 mg p.o., n=29), and placebo. At the time of the peak drug effect PPI[I] with stimulus onset asynchronies (SOA) of 30, 60, and 120 ms and P50 suppression[II] of AEP were assessed.

Subjects of each treatment condition were stratified into low and high baseline gating performers. The %PPI values were subjected to a 3 × 2 × 2 (SOA × treatment × group) repeated measures ANOVA, separately for the different medication groups. Analogously, the %P50 suppression data were analyzed by a 2 × 2 (treatment × group) repeated measures ANOVA. P50 AEP amplitudes were analyzed with stimulus number and treatment as within-subject factors and group (low/high P50 gating) as between-subject factors. Post-hoc pair-wise comparisons were conducted using Fisher's Least Significant Difference.

Results

Treatment with aripiprazole ($p<0.005$), risperidone ($p<0.005$), and amisulpride ($p<0.05$) increased P50 suppression in subjects with low baseline P50 gating levels. In contrast, lorazepam, modafinil, and valproate did not influence P50 suppression in low gating volunteers. Furthermore, lorazepam ($p<0.005$) and modafinil ($p<0.05$) exhibited a reducing effect on P50 suppression in the high P50 gating subgroup (Fig. 1).

Analysis of P50 amplitudes revealed that the increase in P50 gating caused by aripiprazole, risperidone, and amisulpride in the low subgroups was due to differences in the amplitudes elicited by the test stimulus (S2) rather than the conditioning stimulus (S1).

Treatment with aripiprazole led to a PPI-increase for the low subgroups in the SOA 60 ms ($p<0.05$) and SOA 120 ms ($p<0.05$) conditions. In contrast, modafinil and lorazepam attenuated PPI ($p<0.5$), whereas risperidone, amisulpride, and valproate did not influence sensorimotor gating (Fig. 2).

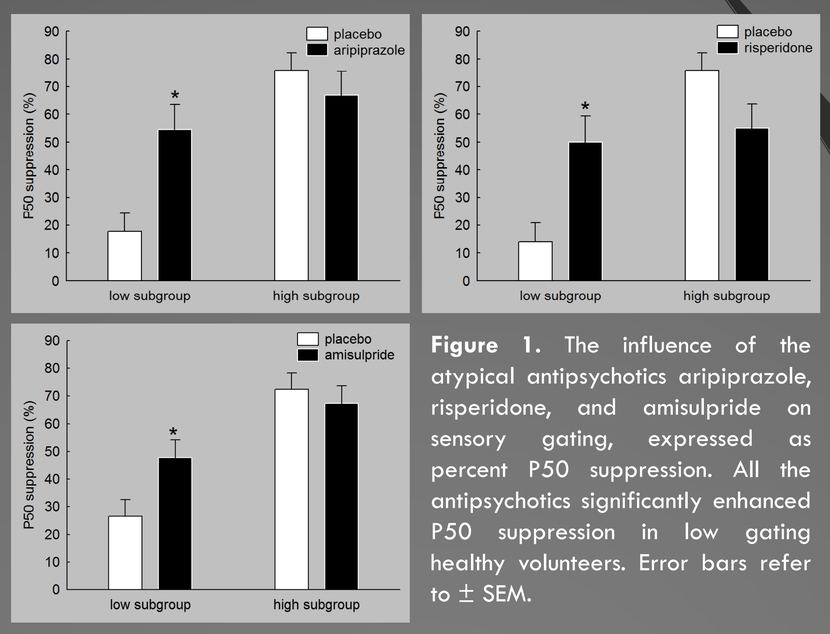

Figure 1. The influence of the atypical antipsychotics aripiprazole, risperidone, and amisulpride on sensory gating, expressed as percent P50 suppression. All the antipsychotics significantly enhanced P50 suppression in low gating healthy volunteers. Error bars refer to ± SEM.

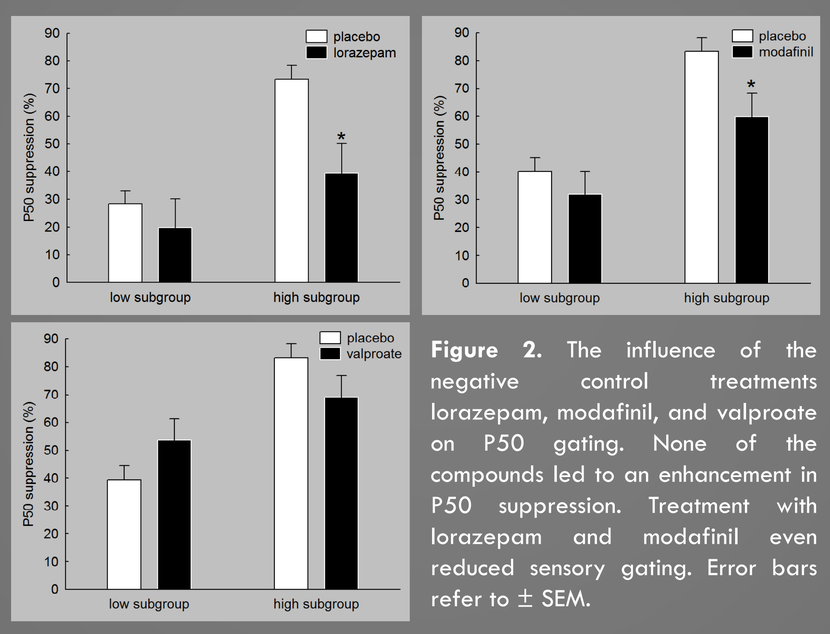

Figure 2. The influence of the negative control treatments lorazepam, modafinil, and valproate on P50 gating. None of the compounds led to an enhancement in P50 suppression. Treatment with lorazepam and modafinil even reduced sensory gating. Error bars refer to ± SEM.

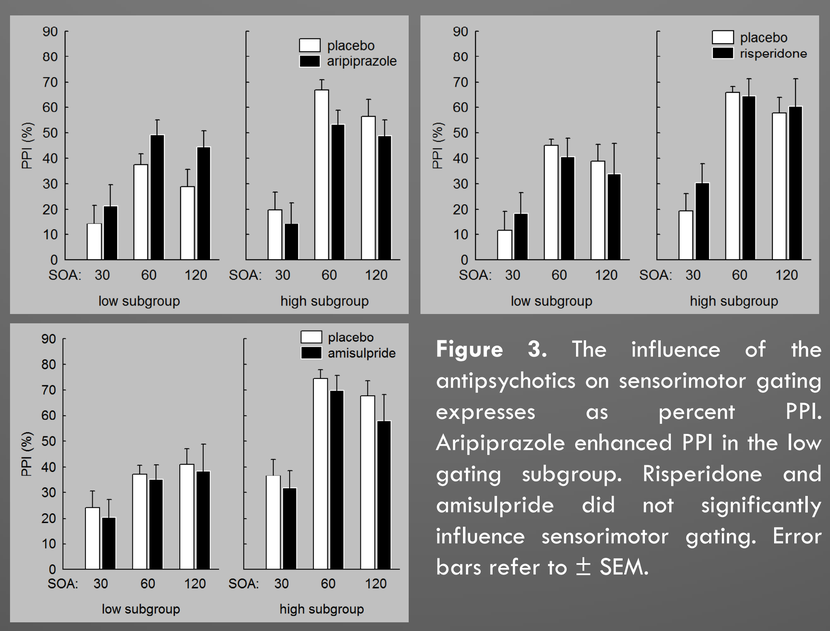

Figure 3. The influence of the antipsychotics on sensorimotor gating expresses as percent PPI. Aripiprazole enhanced PPI in the low gating subgroup. Risperidone and amisulpride did not significantly influence sensorimotor gating. Error bars refer to ± SEM.

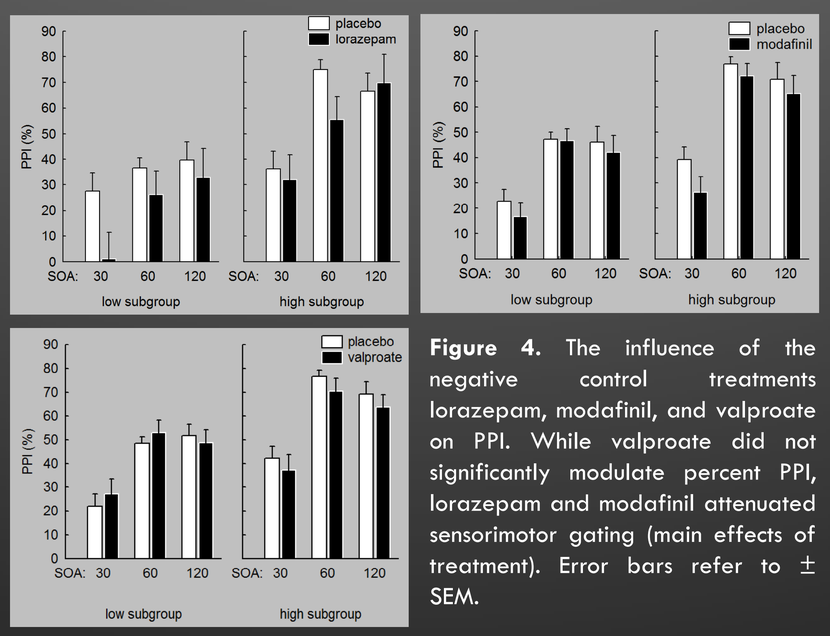

Figure 4. The influence of the negative control treatments lorazepam, modafinil, and valproate on PPI. While valproate did not significantly modulate percent PPI, lorazepam and modafinil attenuated sensorimotor gating (main effects of treatment). Error bars refer to ± SEM.

Importantly, we have found that also psychopathological indices as assessed by the Hopkins Symptom Checklist (SCL-90-R) (Derogatis et al. 1976) differ between the low and high P50 gating subgroups. The volunteers in the low P50 subgroup scored significantly higher in the SCL-90-R global indices (GSI, PST and GSDI), and in most subscales (Fig. 5).

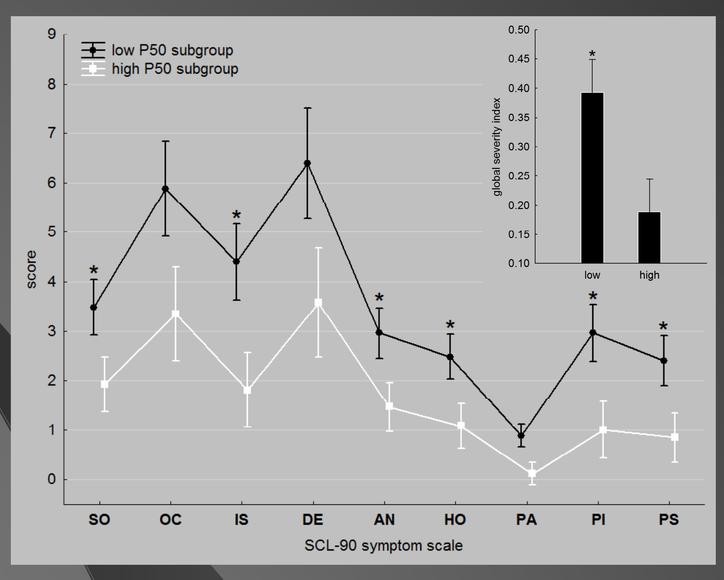

Figure 5. SCL-90 symptom scales in the low and the high P50 subgroups. SO: Somatization; OC: Obsessive-Compulsive; IS: Interpersonal Sensitivity; DE: Depression; AN: Anxiety; HO: Hostility; PA: Phobic Anxiety; PI: Paranoid Ideation; PS: Psychoticism. Error bars refer to ± SEM.

Conclusion

A single dose of psychoactive compounds with antipsychotic properties (aripiprazole, risperidone, and amisulpride) enhanced P50 gating and / or PPI in low gating healthy volunteers. In contrast, lorazepam, modafinil, and valproate serving as negative control treatments did not increase PPI or P50 suppression. The results regarding psychopathological indices as indexed by the SCL-90-R and cognitive performance (results not shown here) are of greatest importance in the context of such a translational model since they bridge deficiencies in basic laboratory measures and clinically relevant indices. In a potential phase Ib trial the low gating subgroup could be considered as a "surrogate patient group", while the high gating group would represent the respective "control group". Results might be beneficial for planning phase II/III development plans by providing additional information for critical decision-making processes, while saving both resources and time. For instance, a dose-response relationship would help to determine an optimal dose on which changes in electrophysiological parameters (gating) are distinct, but no explicit impairment in cognition originating from potential (sedative) side effects are present.

References:

[1]Vollenweider FX et al., Clozapine enhances prepulse inhibition in healthy humans with low but not with high prepulse inhibition levels. Biol Psychiatry. 2006; 60: 597-603.

[2]Csomor PA et al., Haloperidol differentially modulates prepulse inhibition and p50 suppression in healthy humans stratified for low and high gating levels. Neuropsychopharmacology. 2008; 33: 497-512.

[I] stimulus intensities: pulse: 115 dB (40 ms), prepulse: 86 dB (20ms), background noise : 70 dB, all white noise

[II]stimulus intensity: 85 dB (1ms, white noise), interstimulus interval: 500 ms, intertrial interval: 10 s

Financial disclosure:
The authors received financial support from AstraZeneca, USA. There is no conflict of interest.