GPR52 agonists represent a novel approach to treat psychotic disorders and improve cognitive function

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INTRODUCTION

To date there are no treatment options for the cognitive impairments associated with schizophrenia (CIAS). Additionally, Alzheimer's Disease (AD) patients suffering from neuropsychiatric symptoms (NPS) are not adequately treated with current anti-psychotics. Therefore, innovative approaches to address these symptoms are under investigation. Based partly on its expression pattern and functional coupling, GPR52 agonists may treat symptoms in both of these indications. GPR52 is an orphan GPCR expressed primarily in the brain. In cortex, GPR52 is expressed on glutamatergic neurons and co-localized with the D1 receptor (D1R). Deficiencies in D1R activation are associated with CIAS. In striatum, GPR52 is co-expressed with the D2 receptor (D2R). Therefore, GPR52 agonists may show D1R agonist-like pro-cognitive effects and D2R antagonist anti-psychotic activity, thus improving the cognitive symptoms of schizophrenia and the psychotic symptoms of AD patients.

To explore the potential of GPR52 agonists, CNS Diseases Research entered a collaboration with Beacon Discovery, providing potent and selective compounds to be assessed in pre-clinical tasks of cognition and anti-psychotic activity. GPR52 agonists show concentration dependent, GPR52 specific, synaptic potentiation in rat cortical slices and are effective in the rat social recognition task, suggesting pro-cognitive efficacy. Furthermore, GPR52 agonists are effective in the amphetamine induced hyperlocomotion test, a task associated with anti-psychotic efficacy.

MEHTODS & RESULTS

1. Effect on synaptic transmission in cortical slices

fEPSPs were measured with coronal slices of infralimbic and prelimbic prefrontal cortex with a thickness of 400µM from 5-7 week old male Sprague Dawley rats. The fEPSPs were recorded from layer V and evoked by electrical stimulus pulses (100 µs duration, every 30 sec) of the superficial layer II-III.
The amplitude of the fEPSPs were measured for 30 min as baseline, followed by subsequent 30 to 60 min period of drug administration followed by 60 min washout with ACSF. Changes in the fEPSP amplitude were calculated in relation to the baseline fEPSP responses (100%) during the 30 min. post agonist washout. All compounds were dissolved in DMSO and diluted in ACSF to a DMSO concentration of 0.05%

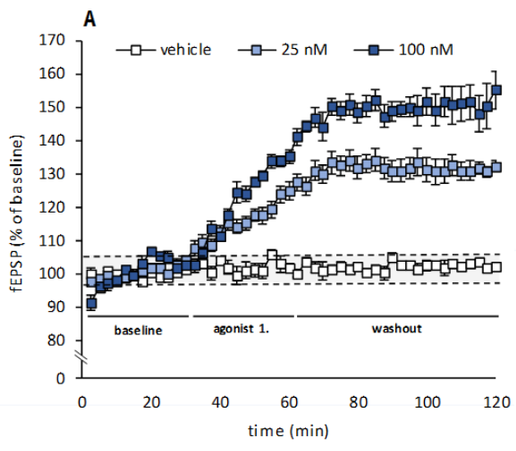

Figure 1A: GPR52 agonist 1 dose-dependently stimulated fEPSP amplitudes measured in prefrontal cortex from rats.
After 30 min baseline measurement, either vehicle, 25 nM or 100 nM agonist 1 was superfused over the slices for 30 min, after which a washout with aCSF was performed for 1h. Agonist 1 progressively increased fEPSP amplitude during superfusion, and this increase was maintained post-washout, suggesting a long-lasting stimulation of synaptic potentiation. n=6-8 slices per measurement.

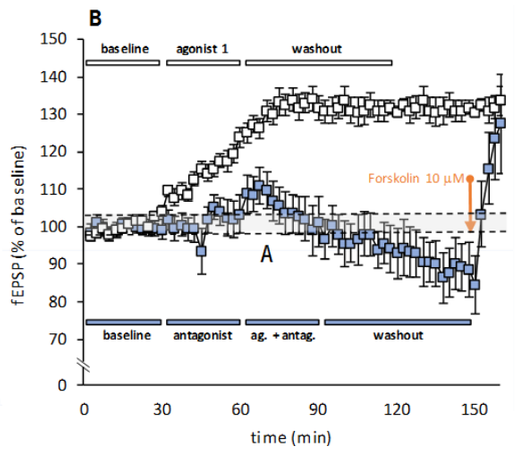

Figure 1B: Agonist-induced synaptic potentiation was prevented by pre-treatment with a GPR52 inverse agonist
After a 30-min baseline measurement, inverse agonist (25nM) was applied for 30 min (□), which had little to no influence on fEPSP amplitudes. Subsequently, 25 nM GPR52 agonist 1 was superfused in addition to the GPR52 inverse agonist for a further 30 min, again showing no stimulation of fEPSP amplitudes. To confirm the vitality of the slices after inverse agonist treatment, the slices were incubated with 10µM forskolin, which induced a strong increase in fEPSP amplitude. In comparison, stimulation with agonist 1 alone (25nM) again led to a robust potentiation of fEPSP amplitudes (□).

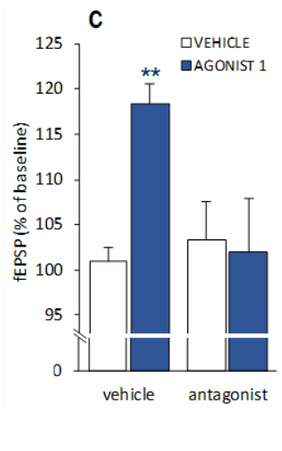

Figure 1C: Quantitation of fEPSP amplitudes
For the quantitation, baseline was set as the last 15 min. of the baseline measurement, whereas the last 15 min. of either agonist, inverse agonist or both were quantitated and displayed.

CONCLUSIONS

- GPR52 agonists potentiated synaptic transmission in rat cortical slices in a concentration-dependent manner
- This potentiation persisted after compound was no longer present
- A GPR52 inverse agonist did not alter synaptic transmission when administered alone, but prevented the increase in electrical activity effected by the agonist
- GPR52 agonists improve episodic memory as measured in a social recognition task
- GPR52 agonists decreased amphetamine stimulated locomotor activity at doses that do not affect baseline activity, a profile indicative of antipsychotic activity

➢ **When taken together, these data suggest that GPR52 agonists may have therapeutic utility as novel treatments for both psychotic symptoms and for cognitive symptoms associated with cortical dysfunction, such as those seen in schizophrenia.**

MEHTODS & RESULTS

2. Effect on episodic memory in the rat social recognition task

The social recognition task was performed according to van der Staay et al. (2008). At the start of trial 1 (T1) a juvenile (male, ~180 g, group-housed) was placed into the testing arena of the adult (male, ~400 g, group-housed) and they were allowed to interact for 3 min. At the end of T1, both adult and juvenile were returned to their home cages. 24 hours later, rats were reintroduced to their testing arena for another 30 min habituation, and juveniles singly housed. At the end of this time, a familiar juvenile (same as T1) was introduced to the testing arena of the adult and allowed to interact for 3 min (T2). Subsequently, all digitalized trials were analyzed by a trained observer blinded to the experiment conditions and treatment group. Sniffing and grooming of body parts, anogenital sniffing, and close following were scored. In all experiments, vehicle (0.5% Natrosol / 0.015% Tween-80) or compound were administered p.o. to the adult rats 1 hr prior to T1.

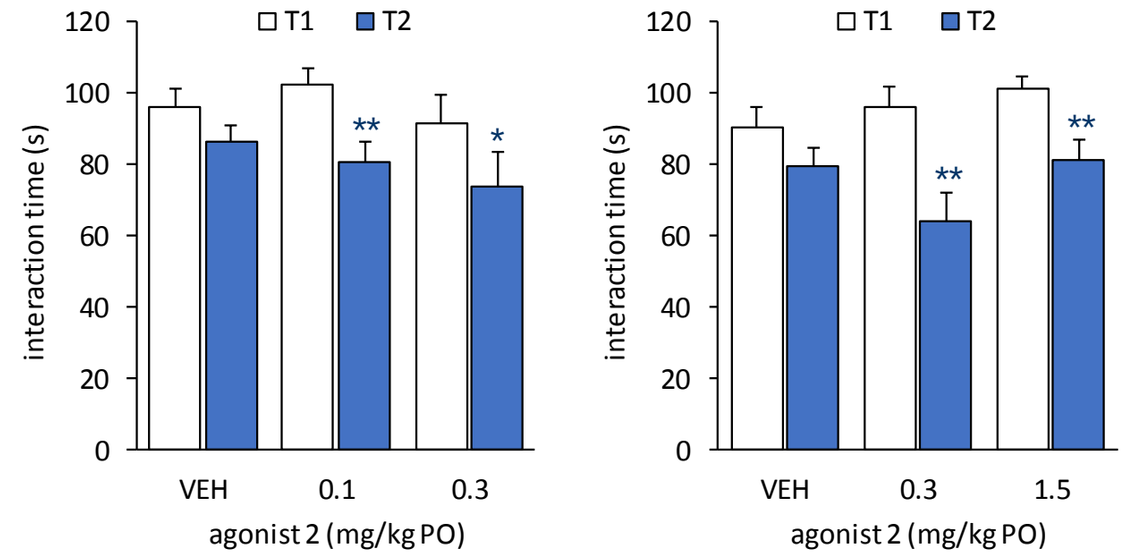

Figure 2: Agonist 2 significantly improved episodic memory in the rat social recognition task depicted as investigation time of the juvenile rat between T1 and T2. T2 is significantly shorter than T1 at both doses, indicating familiarity recognition, while T1 and T2 are not significantly different with vehicle. Data are presented as mean ± SEM (n=9/group). ** p<0.01, T2 vs T1

3. Effect on basal- and amphetamine-stimulated locomotor activity

Male Sprague Dawley rats (Harlan/Envigo, CA, 250g-350g) were used. Rats received food and water ad-libitum. Testing was conducted in clear plastic cages using the Motor Monitor system (Kinder Scientific, Poway, CA). For basal motor activity testing, naïve animals were administered vehicle or compound in home cage, and 30 min later transferred to the testing apparatus, and locomotor activity recorded for 30 min (30-60 min post-administration). For amphetamine-induced hyperactivity, animals were placed into the activity apparatus for a 45-min habituation period, after which they were administered vehicle or agonist 2 and returned to the activity apparatus. 15 min later, animals were administered amphetamine, and locomotor activity was measured for 90 min (15-105 min post-compound).
Data is expressed as total ambulations from 30-60min post-compound.

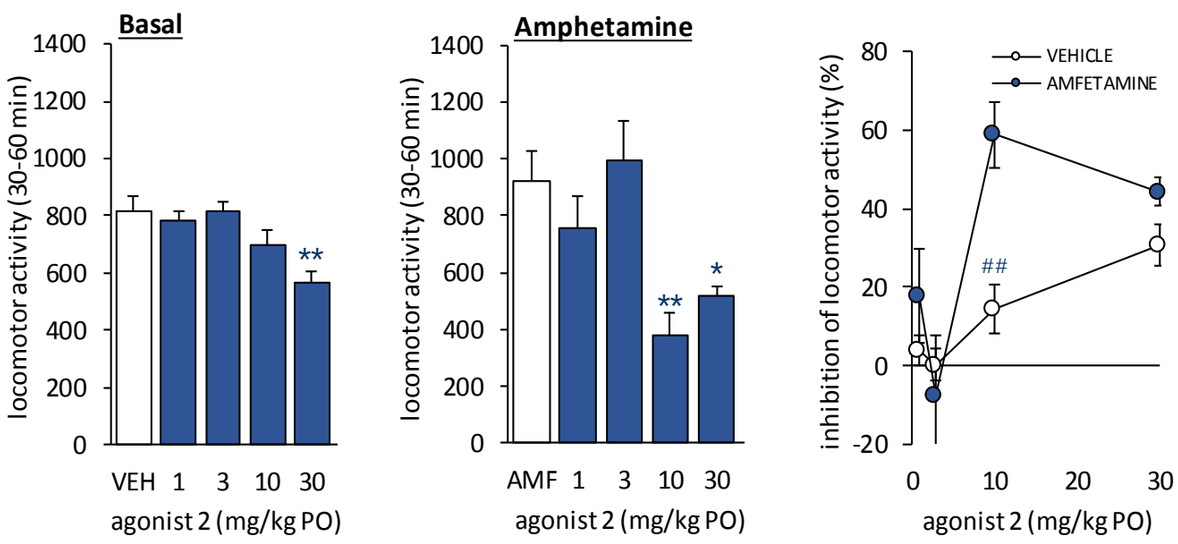

Figure 3: Baseline locomotor activity in non-habituated rats did not differ from that measured in habituated, amphetamine-treated rats (left and center panels respectively), providing a quantitatively similar baseline. When administered alone to non-habituated rats, agonist 2 moderately decreased locomotor activity at 30 mg/kg only. In the presence of amphetamine the agonist dose-response was shifted to the left, and inhibition was more potent.

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REFERENCES

(1) Van der Staay et al., 2008, Neuropharma. 55: 908

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DISCLOSURES

The author and co-authors are employees of either Boehringer Ingelheim Pharma GmbH & Co. KG or Beacon Discovery Inc.