Characterization of PGM039678, a positive allosteric modulator of the muscarinic M4 receptor, in animals models of schizophrenia.

E. CAYRE[1], D. PARACHOU[1], B. MEOT[1], B. RION[1], C. DRIEU LA ROCHELLE[1], M. SHEARDOWN[2], P. RUPRAH[2], L. WALSH[2], J. REEVES[2], R. FOSBEARY[2], M. BARNES[2], T. PATEL[2]

1 Biotrial Pharmacology, Rennes, France ; 2 Takeda Cambridge Ltd, Cambridge, United Kingdom

Neuroscience 2016

November 12-16 | San Diego

INTRODUCTION

The muscarinic M4 receptor is an attractive therapeutic target for schizophrenia as demonstrated by the preclinical and clinical data achieved with Xanomeline, a mixed M1/M4 orthosteric site agonist (Shekhar A, 2008; Am. J. Psychiatry 165:1033). However, agents targeting the muscarinic receptors have demonstrated significant cholinergic related adverse events such as salivation, bradycardia and nausea. More recent drug discovery efforts have focused on the development of positive allosteric modulators (PAMs) to overcome the challenges of obtaining muscarinic receptor subtype selectivity. We have identified selective muscarinic M4 PAMs with >100 fold selectivity over other muscarinic receptor subtypes.

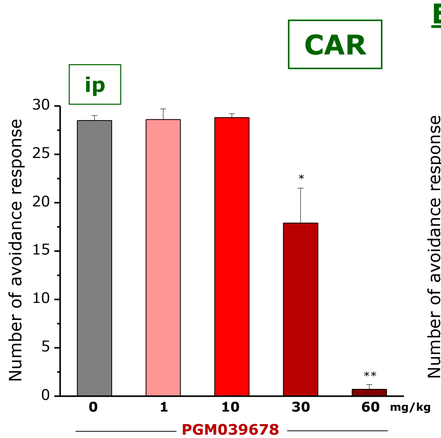
The goal of this study was to evaluate the efficacy of PGM039678 in two animal models relevant to the symptomology of schizophrenia: the conditioned avoidance response (CAR) task and the PCP-induced social withdrawal model. In addition, the efficacy of PGM039678 was investigated in the CAR test when combined with either risperidone or olanzapine.

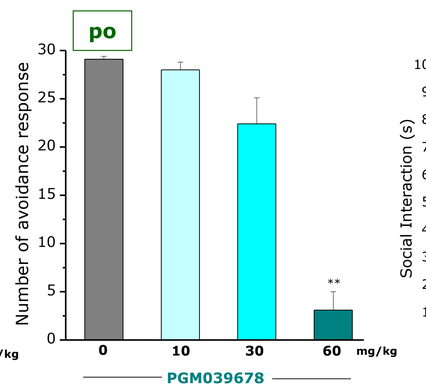
MATERIALS & METHODS

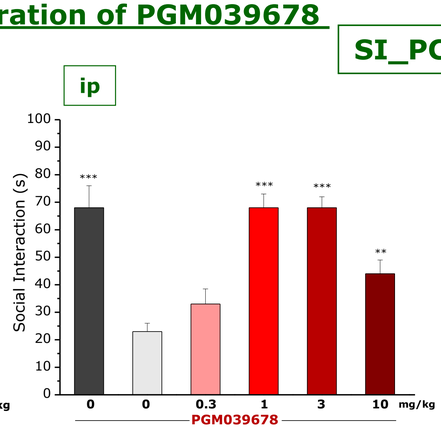
	Conditioned avoidance response task	PCP-induced social withdrawal model
Animal	Male Wistar rats, 200-250 g, social group 2 to 4 individuals per cage	Male Long-Evans rats, 170-240 g, social groups 2 to 4 individuals per cage
	Housing conditions: temperature: 22 ± 2 °C, hygrometry 55 ± 10%, 12/12h light/dark cycle, water and food ad libitum	
Pre treatment		PCP 5 mg/kg or saline i.p., b.i.d. for 7 days Washout period of at least 7 days at the end of the chronic PCP treatment
Drug	PGM039678 was administered i.p. 15 min before the CAR session or p.o. 30 min before the CAR session	PGM039678 was administered i.p. or p.o. 60 min before the Social Interaction (SI) test
	Olanzapine and Risperidone were administered s.c. 30 min before the CAR session	
Test	Shuttle-boxes with white-noise as Conditionned Stimulus (CS), soundproof boxes Training and testing: 1 session of 30 trials per day Training: performance criterion of 80% of correct response for at least 2 consecutive days Testing: cross-over study design **Readout** Avoidance = response to CS	10 min SI test with a non-treated Long-Evans partner **Readout** Scoring of total time spent by the experimental rat in active, non aggressive social behaviour
Statistical analysis	Friedman two-way ANOVA by ranks followed by the Wilcoxon matched-pairs signed-ranks test, or Wilcoxon matched-pairs signed-ranks test One-way ANOVA followed by a Dunnett's test, or two-tailed Student's t test for independent samples.	

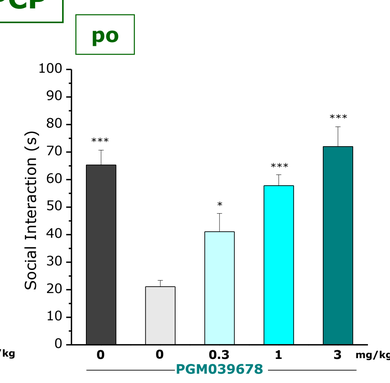
RESULTS

Effect of acute administration of PGM039678





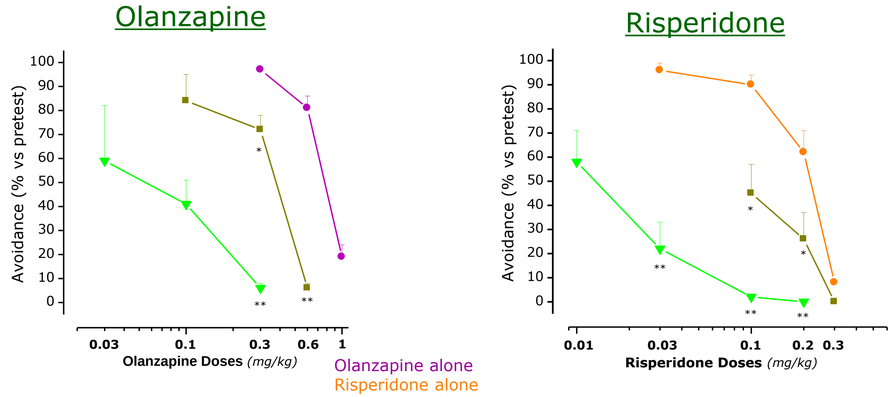


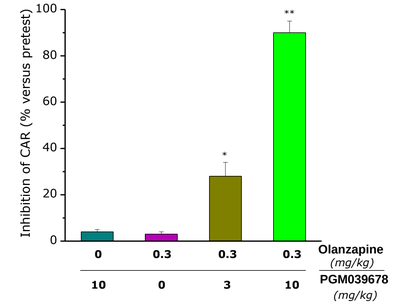


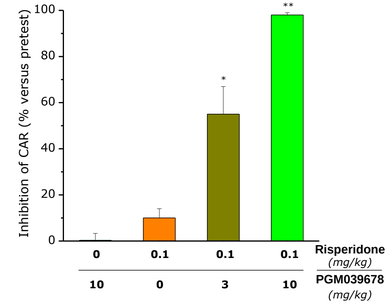
PGM039678 dose-dependently inhibited avoidance responses with ED50 ~ 30 mg/kg, ip and 40 mg/kg, po. (* p<0.05 and ** p<0.01 versus vehicle group)

PGM039678 dose-dependently reversed the SI deficit with ED50 ~ 0.5 mg/kg, ip and 0.3 mg/kg, po. (* p<0.05, ** p<0.01 and *** p<0.001 versus vehicle-PCP group)

Combination of PGM039678 with :







Co-administration of an inactive dose of PGM039678 (3 or 10 mg/kg, po) with risperidone or olanzapine lowered the dose-response curve of each antipsychotic agent (by factor of 2 for both antipsychotic with PGM039678 at 3 mg/kg, by factors of 20 and 13, respectively with PGM039678 at 10 mg/kg).

*** p<0.05, ** p<0.01 and *** p<0.001 versus olanzapine or risperidone alone**

Determination of ED50 in the 2 models

SI-PCP	ED50 PGM039678 ; ip	0.5 mg/kg
	ED50 PGM039678 ; po	0.3 mg/kg
CAR	ED50 PGM039678 ; ip	30 mg/kg
	ED50 PGM039678 ; po	40 mg/kg
	ED50 Olanzapine	0.8 mg/kg
	ED50 Risperidone	0.2 mg/kg
	ED50 Olanzapine with PGM039678 3 mg/kg	0.4 mg/kg
	ED50 Olanzapine with PGM039678 10 mg/kg	0.06 mg/kg
	ED50 Risperidone with PGM039678 3 mg/kg	0.1 mg/kg
	ED50 Risperidone with PGM039678 10 mg/kg	0.01 mg/kg

CONCLUSION

These studies have demonstrated the synergistic effects of a selective M4 positive allosteric modulator and antipsychotic compounds. While the clinical significance remains to be established, the possibility of reducing the dose of atypical antipsychotics in a co-dosing paradigm suggests the utility of M4 PAM molecules in minimizing potential adverse events.

Shekhar A, Potter WZ, Lightfoot J, Lienemann J, Dubé S, Mallinckrodt C, Bymaster FP, McKinzie DL, Felder CC.. Selective muscarinic receptor agonist xanomeline as a novel treatment approach for schizophrenia. *Am J Psychiatry*. 2008 Aug;165(8):1033-9