Antipsychotic agents attenuate dopamine fear response in the basolateral amygdala by modulating basal dopamine release ; an *in vivo* microdialysis study

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Introduction

Although emotional dysfunction in patients with schizophrenia is thought to be associated with poorer outcomes in terms of overall quality of well-being, only a few basic studies have examined the biochemical effect of antipsychotics on emotional function. Conditioned fear stress is a suitable model for studying reactions to psychological stress. Previously, using in vivo microdialysis, we found that dopamine levels in the amygdala were increased by conditioned stress (CS), and that the effect was significantly stronger in rats sensitized to methamphetamine (Suzuki et al, Eur J Pharmacol, 2002) (Fig.1). This suggested that marked increased dopamine release in the amygdala could be considered a marker of hypersensitivity and vulnerability to stress.

In addition, we found that haloperidol attenuated the marked increased dopamine release (Fig. 2). Meanwhile, haloperidol increased basal dopamine levels in the amygdala (Fig. 3).
(Oshibuchi et al , Eur J Pharmacol, 2009).

Fig. 1

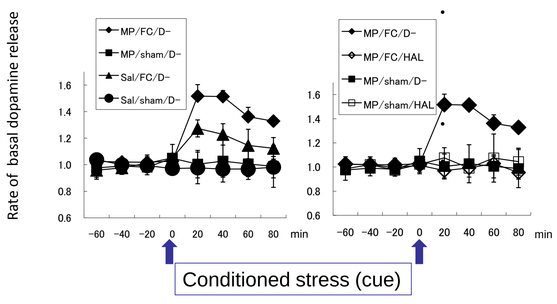


Fig. 2

Fig. 1, 2: Time course of effect of conditioned fear stress and antipsychotics on fear response of amygdala dopamine release

The ordinate represents the proportionate increase of the extracellular dopamine level above the mean level. The abscissa represents time in minutes. Conditioned stress was applied at 0 min.

Fig. 1; The methamphetamine sensitization group showed a significant increase in amygdala dopamine release after application of CS than control group.

Fig. 2; Haloperidol significantly suppressed the increase of dopamine in the methamphetamine-sensitized group.

MP: Methamphetamine-sensitization
Sal: Control; unsensitized
FC: Fear condtioning
Sham: sham conditioning
HAL: haloperidol 1 mg/kg s.c.
D-: Control ; Saline s.c.

Fig. 3

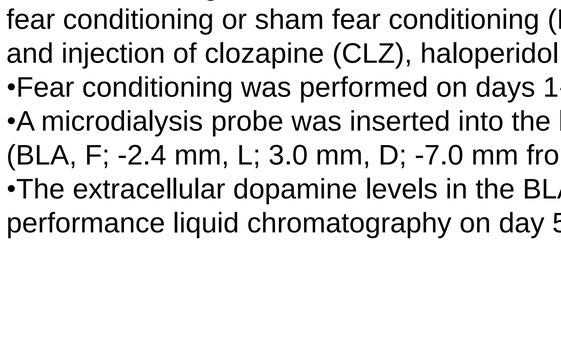


Fig. 3: Time course of effect of haloperidol on basal amygdala dopamine release

The figure represents the time course of the extracellular dopamine level affected by drug treatment in each of the groups ± S.D. The abscissa represents time in minutes. Drugs were applied at 0 min.
Haloperidol significantly increased the basal dopamine levels in the amygdala after application.

HAL: haloperidol 1 mg/kg s.c.
SAL: Saline s.c.

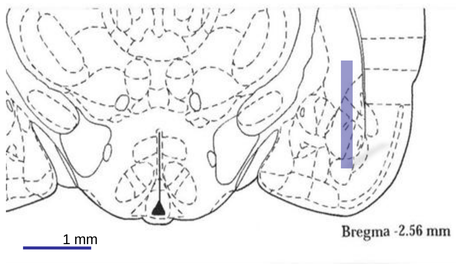
Aim

The objective of the present study was to determine whether attenuating dopamine fear response is formed by the action of antipsychotic agents on basal dopamine release.

Using *in vivo* microdialysis, we examined dose-dependent effects of antipsychotic agents on the basal dopamine level and on the fear response of dopamine in amygdala of fear-conditioned rats, comparing the atypical antipsychotic agent clozapine with the selective dopamine 2 receptor antagonist haloperidol .

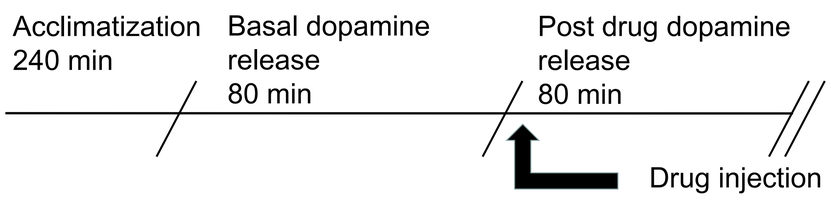
Material and method

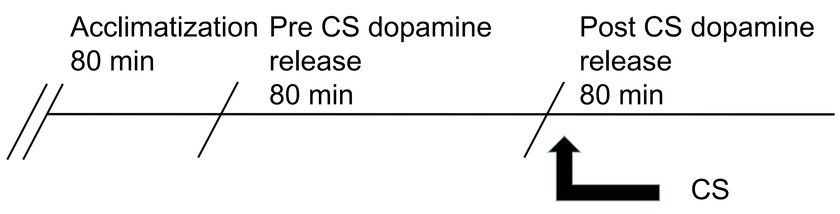
- Mal eSD rats aged 8 weeks were divided into 6 groups:
fear conditioning or sham fear conditioning (FC or Sham),
and injection of clozapine (CLZ), haloperidol (HAL) or saline (SAL; control).
- Fear conditioning was performed on days 1-3.
- A microdialysis probe was inserted into the left basolateral amygdala
(BLA, F; -2.4 mm, L; 3.0 mm, D; -7.0 mm from bregma) on day 4.
- The extracellular dopamine levels in the BLA were measured by microdialysis and high-performance liquid chromatography on day 5.



- Time course of Microdialysis

After acclimation for 4 hours, CLZ (3 mg/kg, 10 mg/kg), HAL (0.3 mg/kg, 1 mg/kg, 5 mg/kg) or saline was injected intraperitoneally. The conditioned fear stimulus was applied 4 hours after drug injection. The difference between the extracellular dopamine levels before and after drug infection was analyzed as the drug effect on the basal dopamine level, and that between the extracellular dopamine levels before and after the conditioned fear stimulus as the drug effect on the dopamine fear response.





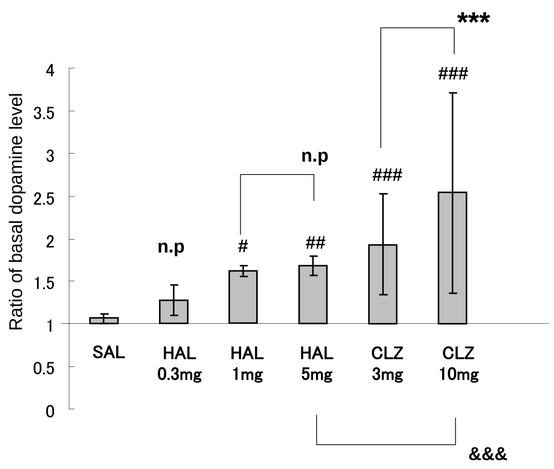
Analysis

The drug effect on the basal dopamine level in the BLA
= (Mean value of post drug dopamine release of 80 min)
/ (mean value of basal dopamine release of 80 min)

The drug effect on the dopamine fear response in the BLA
=(Mean value of post CS dopamine release of 80min)
/ (mean value of pre CS dopamine release of 80 min)

Result 1.

The drug effect on the basal dopamine level in the BLA



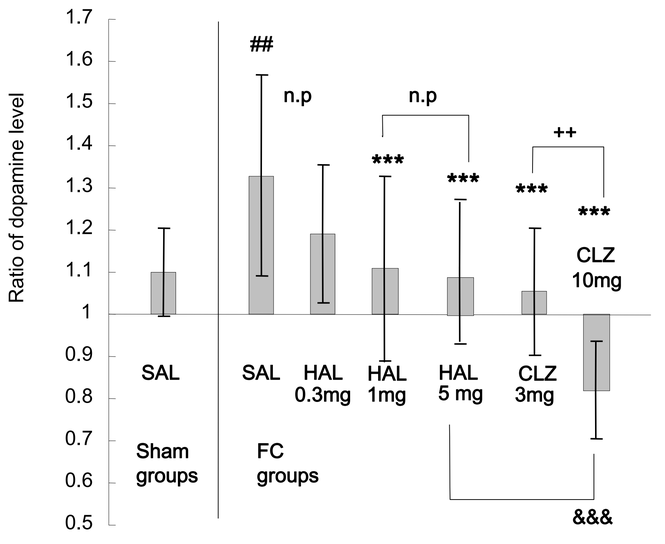
The data shows the rate of change of basal extracellular dopamine level after drug treatment.
Y axis shows the rate of the extracellular dopamine level above the basal dopamine level.
n.p vs. FC/SAL
#: P=0.026 vs. SAL
##: P=0.007 vs. SAL
###: P<0.001 vs. SAL
&&&: P<0.001 HAL 5 mg vs. CLZ 10mg
*******: P<0.001 CLZ 3mg vs. CLZ 10mg
++: P=0.004 vs. SAL
SAL; Saline groups
HAL 0.3mg; Haloperidol 0.3 mg/kg i.p. group
HAL 1mg; Haloperidol 1 mg/kg i.p. group
HAL 5mg; Haloperidol 5 mg/kg i.p. group
CLZ 3mg; Clozapine 3 mg/kg i.p. group
CLZ 10mg; Clozapine 10 mg/kg i.p. group

The data analyzed by 2 way ANOVA.
Interaction between FC and Sham was not significant.

Both drugs significantly increased the basal dopamine level in the basolateral amygdala.
The maximum proportionate increase in the clozapine groups was significantly greater than in the haloperidol groups (&&&).

Result 2.

The drug effect on the dopamine fear response in the BLA



The data shows the rate of dopamine fear response in the BLA after conditioned stress application.
Y axis shows the rate of the extracellular dopamine level above the basal dopamine level.

: P=0.001 vs. Sham/SAL
***: P<0.001 vs. FC/SAL
++: P=0.001
&&&: P<0.001

SAL; Saline groups
HAL 0.3 mg; Haloperidol 0.3 mg/kg i.p. group
HAL 1 mg; Haloperidol 1 mg/kg i.p. group
HAL 5 mg; Haloperidol 5 mg/kg i.p. group
CLZ 3 mg; Clozapine 3 mg/kg i.p. group
CLZ 10 mg; Clozapine 10 mg/kg i.p. group

FC; Fear conditioned groups
Sham; Sham treatment groups

The extracellular dopamine level in the basolateral amygdala was significantly elevated after conditioned fear stress (##).
Both clozapine and haloperidol suppressed this dopamine fear response.
In addition, clozapine significantly suppressed it, superior to haloperidol (&&&).

Discussion

- Effect of drugs on dopamine fear response is proportionate to effect of drugs on basal dopamine level in the BLA.
- The difference in basal dopamine levels between haloperidol and clozapine reflects the drugs' modes of action, i.e. selective dopamine D_2 receptor full antagonism versus multiple effects (5-HT_{2A}, 5-HT_{1A} and D_2), respectively.
- Suppression of elevated dopamine release, which was observed in fear response, by clozapine and haloperidol suggests that these antipsychotic agents affect the mechanism of dopamine release by modulating basal dopamine release, at least amygdala.

Disclosure

Dr. Ishigooka received grant-in-aid scientific research.