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).

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
• Male eSt 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 stimulus was applied 4 hours after drug injection. The difference between the extracellular dopamine levels before and after drug injection 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.

Acclimatization 240 min
Basal dopamine release 80 min Post drug dopamine release 80 min Drug injection

Acclimatization
Basal dopamine release
Post CS dopamine release
Pre CS dopamine release

Drug injection

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 D2 receptor full antagonism versus multiple effects (5-HT2A, 5-HT4, and D1), 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.

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

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 80 min) / (Mean value of pre CS dopamine release of 80 min)

Result 1.
The drug effect on the basal dopamine level in the BLA

Result 2.
The drug effect on the dopamine fear response in the BLA

The extracellular dopamine level in the basolateral amygdala was significantly elevated after conditioned stress (##).

Both clozapine and haloperidol suppressed this dopamine fear response. In addition, clozapine significantly suppressed it, superior to haloperidol (###).

The data shows the rate of dopamine fear response in the BLA after conditioned stress application.

The data shows the rate of dopamine level above the mean level.

The extracellular dopamine levels in the BLA were measured by microdialysis and high-performance liquid chromatography on day 5.

Both drugs significantly increased basal dopamine release in the basolateral amygdala. The maximum proportion increase in the clozapine groups was significantly greater than in the haloperidol groups (##).