THE RELATION BETWEEN PLACEBO EFFECT AND SEROTONIN TRANSPORTER GENETIC POLYMORPHISM: A DOUBLE-BLIND CLINICAL TRIAL IN HEALTHY ADULTS

Minae Isawa, Mayumi Mochizuki
Faculty of Pharmacy, Koku University, 1-5-30, ShibaKoen, Minato-Ku, Tokyo, Japan

Objective
Clinical benefit of drugs for patients is not only through pharmacological mechanisms, but also through non-pharmacological action (placebo effect). The placebo effect may involve expectation based on previous experience (conditionality) (Finney et al. 2010). In terms of the placebo effect, individuals can be grouped into two categories: responders and non-responders. There are several reports that the placebo effect was involved in brain activity and gene polymorphisms of chemical mediator (Hall et al. 2015). To study the hypothesis, we conducted a clinical trial using caffeine in order to examine whether responder or non-responder to placebo is associated with blood flow changes in the prefrontal area of the brain and particular polymorphisms of the serotonin transporter-linked polymorphic region (5-HTTLPR).

Methods
Study design
The study was designed to compare the effects of 200mg dosage of placebo (lactose) and caffeine. Participants were block-randomized (block size of two) to randomized single studies. The block A participants took active drug (caffeine group) on the first day, and placebo on the third day (caffeine-conditioned placebo group), while the block B participants took placebo (placebo group) on the first and third days (placebo-conditioned placebo group). The second day was a washout period.

The preparation of test drugs
We prepared one capsule contained 100 mg lactose and caffeine.

Evaluation Items
Subjective indicators:
Self-reported feelings of drowsiness on established scales (Stanford Sleepiness Scale). Feeling of drowsiness = VAS (Visual analogue scale). Objective indicator:
Activity in the prefrontal area of the brain was measured in terms of blood flow using near-infrared spectroscopy (NIRS). Polymorphisms of 5-HTTLPR were evaluated by PCR methods. This study was approved by the Ethics Committee of our University.

NIRS measurement
NIRS non-invasively measures relative changes in the concentrations and blood flow in increased in the corresponding area.

Results & Discussion
Genotyping
SS type: 52.4 % (n=22)
SL type: 40.5 % (n=17)
LL type: 17.1 % (n=3)
The frequency of the L/L genotype in Japanese people is 3.2 %, whereas it is 32.2 % in Americans. As for S/S type, the frequency is 61.1 % in Japanese people, but 18.8 % in Americans (Blizinsky et al. 2010). There may be an ethnic difference in placebo reaction.

The frequency of the L/L genotype in the placebo conditionality group was 18.8 % in Americans (Chiao et al. 2010). We found that subjects with the L/L type were susceptible to the placebo effect in terms of subjective indicators.

Conclusion
Our results indicate that subjects with L/L genotype showed a significantly greater placebo response in terms of both self-reported feeling of drowsiness and blood flow in the prefrontal area of the brain associated with working memory (46 area). And the L/L genotype of 5-HTTLPR, which is rare in Japanese (3.2 %) but common in Americans (32.2 %) may be associated with a greater placebo effect.

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