Lorazepam effects on brain activity pattern related to cholecystokinin tetrapeptide (CCK-4)-induced panic attack

T. Schunck[1], G. Erb[1], A. Mathis[1], C. Cisterni[2], and R. Luthringer[2]
[1]MR Department, Forenap-Frp, Rouffach, Bas-Rhin, France, [2]Forenap, Rouffach, Bas-Rhin, France

The aim of this study was to use blood oxygenation level-dependent functional magnetic resonance imaging (fMRI) to test the hypothesis that lorazepam modifies the brain activity pattern related to cholecystokinin tetrapeptide (CCK-4)-induced panic attack (PA) in healthy volunteers. The effects on behavioural data and heart rate increase induced by CCK-4 were also investigated.
The study was a 2-period cross-over, double-blind, placebo-controlled study. Each period was constituted by one MRI session and the periods were separated at least by one week. The subjects were fifteen healthy males with a mean age of 30 years, they were randomly assigned to one of the following treatments: placebo × lorazepam (n=7), lorazepam × placebo (n=8). One mg of lorazepam (Wyeth-Lederlé France) was administered 2 hours before CCK-4 administration. During fMRI scan, the subjects were injected with 50 µg of CCK-4. The scan lasted 10 minutes: 3 minutes of baseline, before CCK-4 injection, and 7 minutes after the injection. Baseline levels of anxiety were collected before the MRI session, using the DSMIII-R-derived Panic Symptoms Scale (PSS) and the state subscale of the Spielberg State and Trait Anxiety Inventory (Y1 STAI). At the end of the MRI session, the subjects were asked to fill in the same scales by referring to how they felt during the CCK-4 injection. Heart rate (HR) was also recorded throughout the MRI session. In keeping with previous CCK-4 challenge studies involving healthy volunteer, subjects were classified as panickers if they had a total symptom score of at least 4 and a score of 2 or higher on the "anxiety or fear or apprehension" item.
Functional images realignment was performed using an automated rigid registration algorithm (Medimax, GITIM, Université Louis Pasteur, Strasbourg). Then other image pre-processing and statistical analyses were carried out using SPM2 (Wellcome Department of Cognitive Neurology, London, UK). Pre-processing consisted in normalization of subject's image into the SPM2 brain template and smoothing with an 8 mm FWHM Gaussian filter. In the scan, CCK-4 injection effect was modeled as boxcar function (duration 16 s), convoluted with a hemodynamic response function. Signal change image was computed for each subject in the drug and placebo conditions and they were statistically compared voxel by voxel.
CCK-4 elicited an anxiogenic response demonstrated by a rise in anxiety measures and acceleration in HR. Indeed significant increases in mean STAI score and PSS- sum intensity and total symptom scores as compared to pre-scan scores were obtained. CCK-4 administration also induced cerebral activation in anxiety-related brain regions. Signal change was found in inferior frontal gyrus, insular cortex, temporal poles, brainstem, thalamus, cingulate gyrus and cerebellum. Axial slices showing the patterns of brain activity are presented in Figure 1. There were no significant differences between any STAI scores obtained under placebo and lorazepam, whether for the whole subject group or the panickers. For PSS, there were also no significant differences between any scores obtained under placebo and lorazepam for the whole subject group. However a significant decrease of number of CCK-4 induced symptoms was found under lorazepam for panickers and this decrease was more robust for anxiety than for somatic symptoms. No significant differences were found between heart rate increase induced by CCK-4 under Placebo and under Lorazepam. In spite of a higher mean signal change under placebo in temporal poles (BA 38) (Figure 1), the only significant difference found between the drug and placebo conditions was located in nucleus accumbens area. Signal variation was significantly higher under lorazepam in this region (Figure 2) whether for the whole subject group or the panickers.
This finding supports the role of a selective effect of lorazepam in the nucleus accumbens.

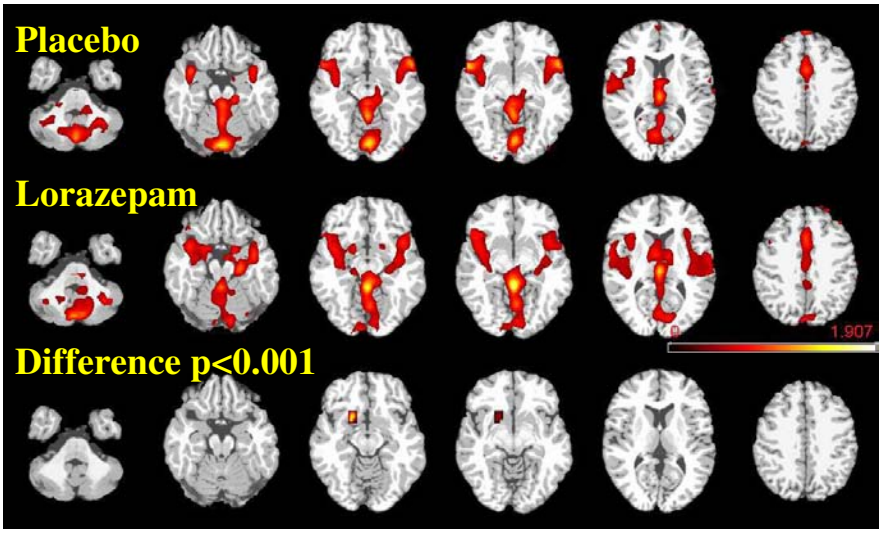

Figure 1. Signal change image averaged across subjects in the lorazepam and placebo conditions. Paired -t-test between signal change image of each subject in the drug and placebo conditions (p<0.001 uncorrected).