Sildenafil and the response to functional and hypercapnic activation - a BOLD and VEP study

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Introduction

Sildenafil (Viagra ®), a selective inhibitor of the cGMP-hydrolyzing phosphodiesterase5 enzyme (PDE5), induces migraine without immediate changes in cerebral blood flow or cerebral artery diameter[1]. Sildenafil prolongs the clearance of the second messenger cGMP (cyclic guanosine monophosphate), and was therefore proposed to increase the neuronal or a local vascular response to external stimuli[2]. We evaluated the effect of sildenafil administration on the visual response to checkerboard stimulation in healthy subjects using BOLD fMRI, and visual evoked potential (VEP) measurements. Additionally, the possible effect of sildenafil on the hypercapnic BOLD response was investigated, because the vascular response to CO_2 may also involve cGMP[3].

Methods

12 healthy females (mean age 23±1 year, mean weight 70.3±1.9 kg) were included and examined on two separate days, at least one week apart and separated from the menstrual period by 5 days. 100 mg oral sildenafil was administered on each examination days (one day for VEP examination and one for BOLD imaging). Measurements were performed at baseline, 1 and 2 hours after sildenafil administration.

During visual stimulation evoked potential p100 and latency was recorded. BOLD responses were recorded in a 3T MR scanner (Achieva Philips). Visual stimulation was done with a checkerboard reversing at 8 Hz and CO_2 6% was administered to the patients during CO_2 stimulation experiments.

During the study blood pressure, heart rate and side effects including headache scores (verbal rating scale from 0-10, 10 = worst) were obtained.

Results

Headache was induced on both study days, median peak headache score was 1.5 (range 0-4) on the day of fMRI and 1 (range 0-3) on the day of VEP (NS) (Figure 1). Sildenafil has no effect on amplitude or latency (P100) by VEP compared to baseline. The BOLD response to visual stimulation or CO_2 inhalation did not change after sildenafil administration (Figure 2a-b)

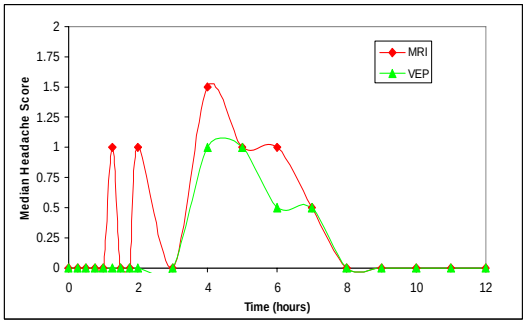
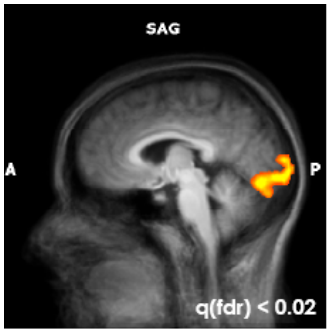


Figure 1, Headache score increased 4-6 hrs after sildenafil, and curves were similar between MRI and VEP sessions (median of 12 subjects)



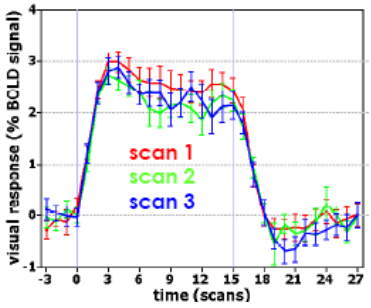


Figure 2a, Area of significant BOLD-activation during visual stimulation. Fig. 2b timecourse averaged over visual stimulation periods.

Discussion

Sildenafil 100 mg induced headache in healthy subjects but had no effect on visual fMRI BOLD imaging nor on VEP responses. The visual response paradigm was chosen since migraine may be induced by visual stimulation and CO_2 response in order to evaluate a global effect of sildenafil. The present results suggest that sildenafil does not potentiate a neuronal or local cerebrovascular visual response in healthy subjects nor a global cerebrovascular response to CO_2 inhalation. They support the idea of the NO/cGMP system having a permissive role in the hypercapnic response.

Conclusion

Sildenafil 100 mg induced headache in healthy subjects but had no effect on visual fMRI BOLD imaging nor on VEP responses. Thus, the data does not support the hypothesis of an increased neuronal reactivity induced by sildenafil. Other effects of sildenafil in the headache pathogenesis may be involved.

References:

1. Kruuse et al, Brain 2003, 126, 241-7
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