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Central effects of sildenafil (Viagra) on auditory selective attention and verbal recognition memory in humans: a study with event-related brain potentials

Abstract The purpose of this study was to assess possible central side-effects of sildenafil (Viagra) on attention and memory functions. Sildenafil and placebo were administered in young male subjects in a double-blind balanced cross-over design. Behavioral patterns and event-related brain potentials (ERP) were recorded in a spatial auditory attention and a visual word recognition task. While behavioral patterns did not reveal any overt effects of sildenafil, auditory ERPs were indicative of an enhanced ability to focus attention (amplitude enhancement of N2-effect) and to select relevant target stimuli in the sildenafil condition (P3 component). In the memory task, CNS-effects of sildenafil were evident in a reduction of a negativity in the 150–250 ms range. No overt effects on behavior were observed. Nevertheless, the data reveal CNS-effects of sildenafil necessitating further studies.

Key words Event-related potentials · Recognition memory · Auditory attention · Central nervous system · Sildenafil

Treatment of sexual dysfunction with sildenafil (Viagra) has gained widespread acceptance over the last few years. Orally administered sildenafil competitively inhibits phosphodiesterase type 5 (PDE-5), which physiologically inactivates cyclic GMP in the erectile bodies. Thus, sildenafil increases the NO-stimulated cyclic GMP concentration in men with erectile dysfunction and thereby improves erection. Side effects are related to the mode of action of sildenafil and include headache and flushing, gastrointestinal side effects [4, 14, 18, 26], and visual disturbances caused by retinal effects, which occur in about 5% of patients [29, 30]. Up to now, there have been no reports as to the possible cognitive effects of sildenafil, although the presence of PDE-5 in brain tissue has been verified [13, 16]. Such cognitive effects could be of possible importance for the patients and require additional recommendations as to the use of the drug.

As recent years have seen significant progress in the application of electrophysiological techniques to the evaluation of pharmacopsychological effects [15, 19, 20], we decided to assess behavioral indices (reaction times and detection performance) as well as event-related brain potentials (ERPs) in volunteers taking sildenafil or placebo. ERPs are small voltage fluctuations in the scalp electroencephalogram that occur in response to stimuli and can be extracted from the EEG, using averaging methods. They have been shown to be valuable for the investigation of cognitive processes, since it is possible to link certain stages of information processing to the various components of the ERP. For the specific details of the recording technique and the logic of interpretation, the reader is referred to the pertinent reviews [7, 24]. Here, it should suffice to say that the main advantage of the ERPs over quantitative analysis of the spontaneous EEG is the possibility of interpreting electrophysiological changes in terms of changes of the underlying cognitive process. The advantage over standard psychological tests
(reaction times, pencil and paper tests) is that the continuum of processes between the presentation of a stimulus and the execution of a response can be monitored with ERPs rather than just the end-result of the cognitive operations.

Two experiments were included in the present study. In the first, subjects had to selectively attend one of two rapid streams of auditory information in order to detect rare target events in the attended channel. This situation, often compared with a cocktail-party situation in which we effortlessly direct our attention to one of several simultaneous conversations, gives rise to robust attention-related ERP effects for both standard and target stimuli [5, 6]. Attended standards are associated with an enhanced negativity starting at about 100 ms post-stimulus and extending for several hundred milliseconds that has been interpreted as a sign of an attentional filter process, while attended target stimuli are characterized by three successive components, indexing automatic (mismatch negativity, MMN) [23] and controlled (N2b, P3) [10] processes of target selection.

The second experiment of this study addressed the area of learning and memory. A continuous visual word recognition paradigm [2, 3, 11, 17, 21, 22, 25] was chosen, for this is known to produce large effects related to stimulus repetition and recognition. In the ERP to the words, typically a difference arises between correctly classified old and new words, termed the old/new effect, that takes the form of a more positive going waveform for the old (repeated) items beginning at 250 ms or later after the occurrence of the stimulus. The old/new effect can therefore be taken as an electrophysiological measure of memory, with smaller effects indicating impaired memory performance.

Materials and methods

Ten male subjects (age range 24–41, mean age 32.6 and SD 7.8) gave informed consent to participate in the study. All were neurologically healthy and had normal or corrected to normal vision. They were taking no centrally acting medication at the time of study.

Procedure

The study followed a double-blind cross-over design. Placebo (lactose) and verum (100 mg of sildenafil) were packed into identical capsules and further packaged into coded envelopes. At the beginning of each session, subjects ingested the medication, then the electrodes were placed. Approximately 60 min after drug intake the electrophysiological experiments were started. The whole session lasted about 160 min.

Psychophysiological experiments

Auditory attention experiment

Sine wave tone pips of 60 ms duration, including a 5-ms rise and fall time, were presented with an inter-stimulus interval of 150–350 ms (rectangular distribution) in random order over two speakers situated 100 cm in front of and 60 cm to the left or right of the subject. The tone series over the left speaker comprised 90% 800-Hz stimuli that served as a standard stimulus and 10% 840-Hz target stimuli, while the right sequence consisted of 1500 and 1560 Hz stimuli respectively. Each run comprised a total of 800 stimuli and lasted 4 min. Before each run, subjects were instructed to fixate on a point before them and to attend one of the tone series in order to answer the rare target events from that stimulus channel by a speeded button press. For half of the runs the assignment of tone series to speakers was switched. The order of attention conditions was balanced across subjects.

Word recognition experiment

From a body of 1200 German nouns 2 × 300 words were selected. Each of these lists was used to construct a stimulus scenario for one of the experimental days. Of the 300 words, 150 each were used for an experimental block. Of these 150 words, 75 were repeated after 3–6 (early repetitions) or 10–20 (late repetitions) intervening items. The stimuli were arranged to yield pseudo-randomized lists. Stimuli appeared in yellow letters in the middle of a video screen against a blue background. They subtended about 1 degree in height and between 1.5° and 4° of visual angle in width. The stimulus appeared for 200 ms on the screen and the inter-stimulus-interval was 2000 ms. For each word the subject had to decide whether it was new or whether it had been presented before, by pressing one of two buttons positioned beneath each index finger. For each experimental day the subjects received a different scenario. The order of the scenarios was balanced across subjects.

Recording

EEG was recorded from the scalp using tin electrodes mounted in an electrode cap (Electro-cap International) located at 29 scalp positions, including all standard sites of the international 10/20 system [1]. The horizontal EOG (HEOG) was recorded between the left and right external canthi to monitor lateral eye position and the vertical EOG was recorded from beneath the right eye, referenced to the right mastoid, to monitor blink activity. The EEG channels were amplified using a 10-s time constant and digitized on line at a rate of 250 Hz. The EEG was averaged off-line using an automatic artifact detection system that rejected trials contaminated with eye blinks, eye movements, excessive muscular activity, or amplifier blocking.

Quantification

Waveforms were quantified by mean amplitude or peak latency measures relative to a 100-ms baseline at the sites of maximal effects. These data were entered into repeated measures analyses of variance. The specific time windows for quantification are given in the results section.

Results

Auditory attention experiment

Reaction times for target tones were 446 ms (SD 52) in the placebo and 437 ms (SD 39) in the verum condition \( t(10) = 0.5; n.s. \). In addition, the target detection performance, assessed with the d’ measure from signal detection theory [27], did not differ between the two medication conditions (placebo 1.98, verum 2.03; n.s.). To increase signal to noise ratio the ERPs were averaged across pitch levels (800 and 1500 Hz) and side of presentation (left, right speaker) separately for attended