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Pupil dilation response to noxious stimulation: Effect of varying nitrous oxide concentration

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Abstract

Objective: This report examines the pain-related pupil dilation response (PDR), tracking it across mixture concentrations of nitrous oxide (N_2O) in oxygen (O_2) and relating its variation to change in long latency somatosensory evoked potentials (SEPs) and visual analogue scale (VAS) pain report.
Methods: We varied mixture concentrations of N_2O in O_2 (0%, 10%, 30%, and 50%), measuring PDR, SEP and VAS responses to painful electrical fingertip stimulation at high and low intensities in 15 volunteers.
Results: Mixed effect model statistical analyses revealed that: (1) PDR increased significantly with stimulus intensity and constricted significantly with mixture concentration; (2) SEP and VAS decreased significantly with increasing mixture concentration; (3) PDR correlated with SEP amplitude and VAS across mixture concentrations; (4) subjects differed significantly in: (a) baseline PDR and SEP amplitudes, (b) rate of change of these measures across mixture concentrations; and (5) VAS increased significantly with stimulus intensity and decreased significantly with mixture concentration without significant individual differences.
Conclusions: The findings support the hypothesis that the pain-related PDR is a complex brain-mediated response rather than a simple sympathetic reflex.
Significance: PDR may provide a useful indicator for studying the central processing of noxious stimuli and the effects of analgesic interventions.

Keywords: Somatosensory evoked potentials; Pain; Pupil dilation response; Nitrous oxide; Visual analogue scale; Human

1. Introduction

The pupil dilates markedly and in a graded fashion in response to increasing noxious stimulation, and therefore it may prove useful for gauging analgesia or anesthetic depth (Cullen et al., 1972; Asbury et al., 1984; Ellermeier and Westphal, 1995; Chapman et al., 1999; Oka et al., 2000; Yang et al., 2003). However, interpretation of the pupillary response is difficult because many physiological and pharmacological factors can affect pupil diameter (Rawstron and Hutchinson, 1963; Larson et al., 1993; Larson and Talke, 2001). Noxious stimuli are, by definition, threatening and therefore may elicit a defense response. A central, unresolved issue is whether the pupil response to nociceptor activation in awake subjects is a spinal sympathetic reflex (Yang et al., 2003), or a more complex, brain-mediated defensive response, as Chapman et al. and Oka et al. contend (Chapman et al., 1999; Oka et al., 2000).

To address this issue, we examined the pupillary response in subjects inhaling graded concentrations of

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nitrous oxide (N_2O) in oxygen (O_2), which differs from the volatile anesthetics in its superior ability to preserve sympathetic tone (Hornbein et al., 1969). The pupil dilation response (PDR) to a brief noxious stimulus is a rapid, event related increase in pupil diameter that emerges from noise with signal averaging over repeated trials (Chapman et al., 1999; Oka et al., 2000). Comparing PDR patterns to patterns of response in simultaneously obtained late near field vertex somatosensory evoked potentials (SEPs) and visual analogue scale (VAS) pain reports reveals whether the PDR is an independent spinal reflex or part of a supraspinally-mediated response reflecting complex, defense-related brain activity.

The primary purpose of this study is to evaluate the hypothesis that the PDR to a noxious event is a supraspinally-mediated component of a larger pattern of defensive response. If this is the case, then its pattern of response to a noxious event across varying concentrations of inhaled N_2O in O_2 should resemble the patterns of response for SEP and VAS. The secondary purpose is to define the PDR response to graded concentrations of inhaled N_2O in O_2. A third purpose of the study was to evaluate the common assumption that study volunteers do not differ systematically from one another. We evaluated the following hypotheses: (1) The PDR to noxious stimulation will diminish in a graded fashion as the concentration of N_2O in O_2 increases; (2) correlated effects will occur in the SEP and the VAS, supporting the hypothesis that PDR is part of a larger defense response rather than an independent sympathetic reflex; and (3) subjects will demonstrate significant individual differences in PDR, SEP and VAS at baseline and in the rate of change in these measures across increasing concentrations of N_2O in O_2.

2. Methods

2.1. Subjects

Because gender differences exist in pupil reactions to painful stimulation (Ellermeier and Westphal, 1995; Oka et al., 2000), we limited the study to one gender. Fifteen paid, female volunteers aged 25–28 years participated in a single test session. All were in good health, well rested at the time of testing and none were taking analgesic or psychoactive medications. We conducted the work in accordance with the Declaration of Helsinki and the Nihon University School of Dentistry Human Subjects Review Committee gave permission for the study. Each subject gave signed, informed consent.

2.2. Dolorimetry

Subjects received repeated noxious electrical stimuli delivered to their fingertips, a standard noxious stimulation technology (Bromm and Meier, 1984; Chapman et al., 1999). The cathode was a 2.0 mm silver ball electrode affixed to a plastic housing, fitted into a crater in the epidermis and taped in place. The anode was 3 cm diameter electrocardiograph monitoring electrode taped to the volar surface of the ipsilateral forearm. The resistance between electrodes was always less than 20 KΩ and most preparations had impedances less than 10 KΩ.

The stimuli consisted of square wave pulses of 5 ms duration, delivered by a SEN-3301 stimulator (Nihon Kohden, Tokyo, Japan), with stimulus isolation and constant current unit in series. We worked with each subject to set two stimulus intensities for testing, asking each to accept a faint pain (VAS = 3 on 10) and strong pain (VAS = 7 on 10) stimulus intensity level during testing. The mean stimulus intensities ± SD that subjects chose for themselves were 1.86 ± 0.31 mA for faint pain and 3.43 ± 0.61 mA for strong pain.

2.3. Procedure

Subjects sat in a dental chair inside a sound-attenuated testing chamber with ambient light set at approximately 150 lux and fixed their gaze at a picture on the test chamber wall about 3.0 m away. One investigator administered the painful fingertip shocks, maintaining video and voice contact with the subject. The second investigator administered the N_2O in O_2 mixture, monitoring each subject with blood pressure and pulse oximetry. This investigator privately controlled the mixture concentrations and their changes so that neither the subject nor the other investigator knew at any time which mixture concentration the subject was inhaling.

The computer coordinated and controlled stimulus presentation, sampling and processing signals of EP and pupil diameter via a custom designed program. Software screened trials for eye artifacts, and repeated flawed trials by deferring repetition until the end of each trial block.

Each subject experienced two blocks of 36 stimulus trials each per level of mixture concentration for a total of 288 trials. Within each block, stimulus intensities varied randomly over two levels, and inter-stimulus intervals (ISIs) varied randomly between 9 and 11 s. To minimize fatigue and habituation, each subject took a 5 min break between the two blocks, and a 60 s break after the first 18 trials of each block.

2.3.1. Electroencephalographic recording

We recorded the electroencephalogram (EEG) at the vertex (Cz) using an 8 mm diameter gold disk electrode, with reference to linked earlobe electrodes, and taped to the forehead for ground, maintaining electrode resistances below 2 KΩ. EOG leads affixed above and below the external canthus of one eye detected eye blinks and ocular rotation artifacts. A 2–100 Hz band pass filtered EEG, with digitizing at a sampling rate of 250 Hz. Averaging samples taken 200 ms before and 800 ms after the stimulus produced long latency SEPs. Fig. 1 shows summation-averaged SEP waveforms for a representative subject across the four concentrations of N_2O in O_2. As in other studies