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BRIEF REPORT

The Effect of Acetazolamide on Saccadic Latency at 3459 Meters

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Objective.—The effect of altitude on brain function is not yet well understood, nor is the influence of height and speed of ascent. Additionally, the relationship between acute mountain sickness (AMS) symptoms and brain function at altitude is unclear. We hypothesized that a deterioration from baseline measures of brain function occurs after rapid, mechanical ascent to 3459 m and would be less pronounced in persons taking acetazolamide.

Methods.—In this double blind, randomized, placebo-controlled study, 20 healthy volunteers (14 men, 6 women; mean age [±SD] 43 ± 16 years) were alternately allocated to acetazolamide 250 mg or to placebo, taken every 12 hours commencing 3 days before ascent. Prosaccadic and antisaccadic eye movements, heart rate, arterial saturation, and Lake Louise AMS scores were assessed at sea level and 15 to 22 hours after ascent to 3459 m.

Results.—Arterial oxygen saturation was significantly lower in the placebo group compared to the acetazolamide group at altitude (Wilcoxon signed-rank test, median [interquartile range]: acetazolamide vs placebo: 92% [5] vs 85% [5]; $P = .007$), with no differences in prosaccadic latency, heart rate, or Lake Louise score. No differences in saccadic latencies from baseline to altitude were observed in the placebo group, whereas prosaccadic latencies were significantly longer at altitude with acetazolamide (altitude vs baseline: 153 ms [41] vs 176 ms [52], $P = .008$).

Conclusions.—Brain function, measured by saccadic eye movements, appears to be unimpaired after rapid ascent to 3459 m. Although acetazolamide improves oxygen saturations, it may worsen prosaccades, possibly indicating adverse effects of acetazolamide on brain function at moderate altitude.

Key words: acetazolamide, saccadic latency, altitude

Introduction

Descriptions of climbing at extreme altitude are rife with stories of poor decision making. Such judgment errors may be caused by tissue hypoxia impairing brain function. Levels of hypoxia impairing brain function may cause reduced performance in a wide range of responses, from simple reflexes to more complex brain functions.[1] Yet, the measurement of altitude effects upon brain function in a reproducible and clinically useful way has remained elusive. A variety of memory and decision-making tasks have been tested previously, but are confounded by learning effects[2] and poor test-retest reliability. Therefore, accurately and reliably testing these deficits is still a major hurdle within altitude research.

A novel way to measure brain function is with the use of saccadometry, which is measurement of saccadic eye movements, or the rapid eye response, toward (prosaccades) or away from (antisaccades) a visual target. Saccadic latencies (the time delay between the appearance of a target to the beginning of a saccade in response to that target) provide a quantitative and sensitive measure of brain function and are considered more robust and reproducible than neuropsychological testing, with considerably weaker learning effects.[3] Prosaccade changes are observed in a range of conditions affecting brain function, including

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alcohol,[4] antipyschotics,[5] benzodiazepines,[6] and Parkinson's disease.[7] Antisaccade changes involve more complex cognitive processes and may be more sensitive to brain (dys)function.[3]

A small number of studies has looked into measuring saccadic eye movements with high altitude. Early work using saccades (a conference abstract) indicated that saccadic latency does not appear to be affected by 10 minutes of mild hypoxia;[8] however, it is difficult to determine the relevance of such a short hypoxic exposure. More recently, it was demonstrated that both prosaccades and antisaccades are not affected in well-acclimatized persons up to 7500 m.[9] In addition to saccadic latencies, Merz et al[9] considered the rate of antisaccade errors (error rate) as an alternative measure of brain function, but also found no changes in acclimatized persons up to 7500 m. However, the effects of acute ascent to altitude on saccadic parameters have yet to be explored.

Acetazolamide is an established prophylactic for acute mountain sickness (AMS) that is often taken at altitudes above 3000 m. Acetazolamide increases arterial oxygenation by stimulating respiration.[10] Although acetazolamide has been reported to increase brain blood flow at sea level, that was not coupled to any change in cognitive performance.[11] The effect of acetazolamide on brain function at altitude has produced mixed results, however, using traditional measures of neuropsychological testing, despite reduced AMS scores.[12,13] We hypothesized that acute ascent to an altitude of 3459 m would result in decreased performance in tests of saccadic latency, and that this effect would be lessened in persons taking acetazolamide, in conjunction with higher arterial oxygen saturations and improved Lake Louise AMS score. If proved useful, measurements of saccades could provide a robust and straightforward measure of subtle impairments in cognitive performance at high altitude and could lead to new ways to identify which mountaineers may be at risk of significant deterioration.

Methods

In this double blind, randomized, placebo-controlled study, 20 healthy volunteers (14 men, 6 women; mean age [±SD] 43 ± 16 years) were studied. Minimization was used to reduce group differences in AMS susceptibility, age, and sex. Subjects were randomly allocated to receive either 250 mg acetazolamide or identically matching placebo, resulting in 2 groups of 10 subjects balanced for AMS susceptibility, age, and sex. Acetazolamide and placebo was self-administered every 12 hours for 3 days before ascent and continued until after completion of testing.

All participants resided at elevations between 50 m and 150 m; they had no recent (within 2 months) exposure to high altitudes. The Research and Ethics Committee of the University of Chichester granted approval for these studies, and participants gave their written and informed consent. Participants were studied on 2 occasions, at sea level approximately 4 weeks before departure and on the second the day after an acute ascent by cable car to 3459 m (Refugio Guide del Cervino, Aosta, Italy). All saccadic latencies and physiological data were preprocessed by a blinded investigator before group analysis.

Visually guided horizontal saccades were recorded using a saccadometer (portable miniaturized infrared 1 kHz saccadometer, low-pass filtered at 250 Hz with 12-bit resolution).[7] The participants wore the oculometer on their head, secured by an elastic strap and resting on the bridge of the nose (Figure 1); 3 built-in low-power lasers projected red 13 cd m^{-2} spots subtending some 0.1 degrees in a horizontal line in the midline at ±10 degrees.[10] Each trial started with a central fixation light, and then after a random delay, a second target light appeared randomly either to left or to right, to which the participants were instructed to make a saccade. Prosaccadic and antisaccadic eye movements were measured at baseline (2 weeks preceding ascent) and after 15 to 22 hours at altitude (3459 m). As the testing protocol required approximately 20 minutes per subject, to minimize group differences in altitude exposure, the order of testing was determined by an independent investigator so that experimental subjects alternated between placebo and active drug and paired according to randomization minimization, as above. Prosaccadic latency was taken as the time for the eyes to move from a central fixation point to an unexpected new target either to the right or left (10 degrees), and during antisaccades, the latency was calculated as the time to move their eyes away to the opposite direction from the new fixation. Five saccadic blocks were recorded at each timepoint, following an internationally standardized antisaccade protocol.[3]

Heart rate, arterial oxygen saturation (Go2 fingertip pulse oximeter; Nonin Medical, Plymouth, MN) and Lake Louise AMS scores were assessed at baseline and altitude (3459 m). Lake Louise scores consisted of a cumulative score of a 0 to 4 point scale for each of the following: headache, gastrointestinal symptoms, fatigue or weakness, dizziness/lightheadedness, and difficulty sleeping (Figure 2).

STATISTICS

Although normality tests (Shapiro-Wilk) were above significance ($P > .05$), nonparametric statistics