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A Review of Cognitive and Behavioral Effects of Increased Carbon Dioxide Exposure in Humans

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INTRODUCTION

Existing research has reliably demonstrated the respiratory and cardiovascular effects of carbon dioxide (CO_2) inhalation at moderately increased levels, with documented physiological changes to heart rate, blood pressure, tissue pH, and blood solubility (for a review of the human health risks of acute elevated CO_2 exposure, see Rice, 2004). Studies of indoor air quality have linked increased levels of ambient CO_2 with physiological symptoms such as headache, fatigue, and sore throat (Apte et al., 2000; Seppanen et al., 1999; Wargocki et al., 2000). High levels of CO_2 (35%) have reliably resulted in activation of the hypothalamic-pituitary-adrenocortical (HPA) axis and subjective anxiety responses in healthy individuals (Argyropoulos et al., 2002), as well as panic attack-like symptoms (Colasanti et al., 2008; Griez et al., 2007) and experiences of physiological stress (Consolazio & Fisher, 1947; Kaye et al., 2004).

While significant neurological findings correspond to high levels of CO_2 exposure, less clinically significant cognitive effects may occur at a much lower level. These cognitive changes and the exposure thresholds at which they occur are less well established than their physiological counterparts; this paper, therefore, reviews the existing literature on the cognitive, neurological, and psychomotor effects of increased CO_2 exposure, with the objective of identifying research areas in which further investigation remains necessary.

In particular, this investigation is motivated by the chronic exposure to elevated ambient CO_2 concentrations experienced by astronauts aboard the International Space Station (ISS), and the CO_2 exposure-related symptoms that have been reported by astronauts on orbit (James, 2007; Law & Watkins, 2009). Such exposure may negatively affect crew health and operations, including mission safety and the successful completion of scientific goals.

PHYSIOLOGICAL EFFECTS OF CO_2 EXPOSURE

Carbon dioxide (CO_2) alters physiology in well-described ways terrestrially. In the bloodstream, CO_2 reacts with water to form carbonic acid (H_2CO_3), which then dissociates into bicarbonate (HCO_3^-) and H^+. The decrease in pH activates the medullary and peripheral arterial chemoreceptors, stimulating ventilation in the respiratory muscles and resulting in increased tidal volume and expiratory drive (SMAC, 1996).

CO_2 is also a potent vasodilator. As CO_2 levels rise to 3% (23 mm Hg), exercise tolerance decreases, while heart rate, blood pressure, and resting energy expenditures increase (Cooper, 1970). Early symptoms of exposure include air hunger and increased respiration.

Dizziness, headaches, and shortness of breath are also common. Exposure to higher CO_2 concentrations may result in confusion, heart palpitations, sweating, chest pain, anxiety, and panic attacks (Maresh, 1997; Beck, 1999; Woods, 1988). At levels as high as 10% (76 mm Hg) inhaled CO_2, severe dyspnea, vomiting, disorientation, and hypertension will develop, with prolonged exposure resulting in seizures and the eventual loss of consciousness (Cooper, 1970).

A rapid rise to 30% CO_2 (228 mm Hg) will result in acidosis, premature ventricular contractions, low or inverted P waves, increased T-wave voltages, and a marked increase in the QT interval (SMAC, 1996). Death has been reported at 20% to 22% CO_2 (152-168 mm Hg) (Dalgaard, 1972).

A single inhalation of 35% CO_2 reliably triggers the human stress system neuroendocrine response (HPA axis activation), as measured by plasma cortisol, cardiovascular change, and subjective anxiety responses in healthy participants (Argyropoulos et al., 2002).

Persistent, long-term health effects of acute high-level CO_2 exposure may include chronic headaches, vertigo, memory and concentration impairments, and poor sleep. Prolonged low-level CO_2 exposure, in turn, may lead to long-term negative effects on bone metabolism and related blood calcium concentrations (Rice, 2004).

MOTIVATIONS

Terrestrial levels of ambient CO_2 are about 0.03% by volume (0.23 mm Hg). These levels are chronically elevated on the ISS: typically, CO_2 concentrations aboard the ISS are about 0.5±0.2% (2.3-5.3 mm Hg), with large variations experienced; mean 7-day CO_2 levels have been recorded at 3.39 mm Hg, with a mean 7-day peak CO_2 level at 4.50 mm Hg (Law, 2014).

Assessing the cognitive and psychomotor effects of increased CO_2 has particular relevance for safety in spaceflight: in their review of challenges associated with psychosocial and neurobehavioral health in long-duration spaceflight, De La Torre et al. (2012) address the importance of cognitive functioning and the monitoring of decision-making in operational spaceflight.

In their 2009 paper, Law and Watkins discuss the physiological symptoms resulting from increased environmental exposure to CO_2 in spaceflight and the operational implications for crew biomedical health. Symptoms included headaches and lethargy, and findings were based largely on informal crew reporting. Individual predisposition to CO_2 retention and differences in adaptation to microgravity were identified as possible contributing factors to variability in symptom incidence; the authors also stressed the need for further research to review occupational limits for CO_2 exposure.

A review of the physiological effects of prolonged exposure (>30 days) to increased CO_2 concentrations did not produce findings useful for determining exposure standards or predicting inter-individual susceptibility (James & Macatangay, 2009; James, 2009). However, findings suggest that CO_2-related symptoms may occur in spaceflight at lower concentrations than predicted by terrestrial studies, warranting further directed study of human performance effects of increased CO_2 exposure in microgravity (Cronyn et al., 2010).

METHODS

This review surveyed 75 research articles, identified through a keyword-driven literature search. Of the articles surveyed, 28 were identified as relevant to cognition (including memory, attention, reasoning, performance, and decision-making) and/or psychomotor functioning and 12 to sleep (including vigilance, alertness, and circadian effects of elevated CO_2 exposure); all others were limited to physiological effects, the vast majority of which included headache as a symptom. Research fields of the assessed articles spanned neuroscience, naval research, diving physiology, aviation, mountaineering, and medical sciences. Three articles pertained directly to CO_2 exposure effects observed in astronauts aboard the ISS.

The studies surveyed were categorized in 2 ways: exposure duration ("acute" or "chronic") and relative level of increased exposure ("low," "medium," or "high"). "Acute" exposure was defined as a one-time or short-duration exposure (lasting less than 1 hour) to elevated levels of CO_2, whereas "chronic" exposure was defined as repetitive or prolonged inhalation at increased CO_2. The level of exposure was determined relative to the concentration range experienced on the ISS, to highlight which studies were methodologically most consistent with ISS levels of CO_2; in this respect, studies that assessed CO_2 concentrations up to 3% were designated "low" level (most operationally relevant), whereas studies with ranges from 3% to 10% were designated "medium," and those above 10% were designated "high" (least operationally relevant); these designations will be referred to in the discussion of findings.

EFFECTS ON COGNITION AND PSYCHOMOTOR FUNCTIONING

Existing studies offer conflicting indications of CO_2 exposure effects on perception, motor functioning, and inhibitory control, as well as higher-order cognitive processes such as memory, concentration, decision-making, and task performance. Several studies point to decreased alertness and concentration following increased CO_2 exposure (Frey et al., 1998, low-chronic exposure category; Rice, 2004, medium-acute exposure category), and a decline in the visual perception of motion (Yang et al., 1997, low-acute exposure category).

In a diving chamber study, 4 participants experienced prolonged exposure (26 days) to modestly elevated ambient CO_2 (0.7% and 1.2% concentrations). Cognitive and visiomotor performance were assessed before, during, and after exposure; only visiomotor performance impairments were observed, although these effects may have been related to the time course of chamber adaptation (Manzey et al., 1995; Manzey & Lorenz, 1998).

Satish et al. (2012) have reported an association between increasing CO_2 concentrations and impairments in decision-making performance when healthy subjects were exposed to CO_2 at 0.06% (0.46 mm Hg), 0.1% (0.76 mm Hg), and 0.25% (1.9 mm Hg). Similarly, Sayers et al. (1987) noted that operational reasoning was significantly slower after acute exposure (20 min duration) to increased levels of CO_2 (at 4.5, 5.5, 6.5, or 7.5%); no impairments of short-term memory were seen, although increased irritability and discomfort were noted.

Environmental exposure to low levels of elevated CO_2 (at 550 ppm, 945 ppm, and 1400 ppm; low-chronic exposure level category) during the course of a full workday was found to impair performance on higher-order decision-making tasks, with higher levels of CO_2 related to greater decline in cognitive functioning (Allen et al., 2015); the exposure-response relationship between CO_2 level and cognitive performance in this study was found to be approximately linear across the experimental concentrations administered.

Fothergill et al. (1991) assessed cognitive and psychomotor performance at varying CO_2 concentrations at 1 and 6 atmospheres absolute (within the medium-acute exposure level category). Tasks used included a modified Stroop test, an arithmetic test, a number comparison task, and a figure-copying test. High CO_2 tension was found to significantly impair cognitive and psychomotor performance at both atmospheric levels.

Harter (1967), in an exploration of the potential effects of acute CO_2 exposure (5 min) on reaction time, found that reaction time decreased in the initial minutes of exposure; over time, however, reaction time increased with exposure time. Furthermore, reaction time impairment was found to be significantly greater for exposure to 7.9% CO_2 than for exposure to 0% to 5.5%. This study, however, found a high degree of individual variability in subject sensitivity to CO_2 effects, pointing to the importance of considering individual differences in response to CO_2 exposure.

Findings from a study conducted by the Environmental Protection Agency (EPA) in 2000 suggest that poor indoor air quality and higher levels of air pollutants may impair cognitive performance on mental tasks requiring concentration, calculation, or memory. In their examination of indoor air quality and student academic achievement, Bakó-Biró et al. (2012) demonstrated a decrease in cognitive task performance after exposure to elevated levels of ambient CO_2 (at the low-chronic exposure level category).

On the other hand, several investigations have contradicted these observations entirely, finding no consistent relationships between CO_2 exposure and either cognitive or motor functioning, in terms of speed, accuracy, or throughput (Bloch-Salisbury et al., 2000; Caretti, 1999; Frey et al., 1998; Garner et al., 2011; Henning et al., 1990; Selkirk et al., 2010; Sheehy et al., 1982; Vercruyssen, 1984; Vercruyssen et al., 2007).

In one study, while exposure to increased CO_2 predictably resulted in higher incidence of sore throats, nasal congestion, headaches, heightened pulse and breathing rate, and difficulty breathing, among other symptoms of physiological stress, no significant effects were seen on visual, auditory, or motor coordination performance (Consolazio & Fisher, 1947). In another investigation, intermittent exposure to 3% CO_2 across 6 days resulted in no significant changes in vigilance, eye-hand coordination, or problem-solving abilities (Weybrew, 1970).

In a 2-week bed rest study simulating CO_2 exposure (at about 5% concentration) in weightlessness, no detrimental effects were observed from bed rest or CO_2 exposure, either alone or in combination, on complex tracking performance, hand-eye coordination, or problem-solving ability (Storm & Giannetta, 1974).

Bennett and colleagues (1985) assessed cognitive performance during arithmetic and reaction-time tasks in 14 male subjects during submarine confinement; no CO_2-related findings emerged. End-tidal CO_2 from a sample of Navy divers was correlated with cognitive performance (in terms of reaction time, visual scanning, visiospatial processing, and learning); no dose-related effects of CO_2 were observed (Selkirk et al., 2010).

EFFECTS ON SLEEP AND WAKEFULNESS

Animal model studies have indicated an increase in sleep onset latency and a decrease in sleep duration in rats exposed to 6% to 8% CO_2 for 2-3 hours, but no change in the percentage of sleep time spent in rapid eye movement (REM) sleep (Ioffe et al., 1984). Exposure to elevated CO_2 resulted in no sleep phase delay in hamsters (Jarsky & Stephenson, 2000). The effects of modulated CO_2 levels on sleep disruptions at high altitudes were also investigated using cats; only a decrease of CO_2 levels below the normal concentration resulted in a detectable sleep effect, a lowered rate of REM (Lovering et al., 2003). Another cat study revealed that CO_2 exposure at 6% resulted in a worsening of sleep parameters: the duration of wakefulness increased by 24.2%, while REM and non-REM (NREM) sleep decreased in both duration and frequency (Fraigne et al., 2008); however exposure to 2% inspired CO_2 increased sleep duration and decreased wake time.

In humans, mild trends have been found in CO_2 impact on sleep and arousal, with CO_2 causing arousal from sleep (Ayas et al., 2000; Berry et al., 1993; Berthon-Jones & Sullivan, 1984) and increased alertness, orienting, and autonomic response (Garner et al., 2012); all these studies exposed participants to CO_2 levels in the "medium" designation range.

Increased levels of ambient CO_2 were not found to have a negative impact on general sleep quality. Sleep architecture, however, was somewhat altered: the amount of slow-wave sleep increased with the duration of CO_2 exposure (Frey, 1998; Gundel et al., 1998a; both studies were conducted in the low exposure category).

A study examining prolonged exposure (across 24 days) to increased CO_2 levels (in the low exposure category) via ambient environment found no significant sleep disruptions and no impairment of circadian functioning (Samel et al., 1998). In a series of studies conducted in a deep-diving chamber to investigate the effects of increased CO_2 on metabolism, cardiorespiratory function, sleep, and circadian rhythms, physiological findings were consistent with typical somatic responses of headaches, increased vasodilation, and increased heart rate (Frey et al., 1998). Sleep quality was not significantly affected by ambient CO_2 levels, although participants did report decreased alertness; however, accurate interpretation of these findings is limited by the small sample size (n=4). Exposure levels of CO_2 approximated those experienced on the ISS.

DISCUSSION

This assessment of existing research into the psychomotor, cognitive, and sleep effects of elevated CO_2 exposure revealed conflicting, often contradictory findings. The majority of studies demonstrated no significant cognitive effects, although some results suggest mild impairments of psychomotor coordination, memory, and concentration. Additionally, some findings demonstrated no sleep impairments, while others showed disruptions of circadian functioning, hypervigilance, or changes in sleep architecture.

When taken together, the studies surveyed in this paper offered comprehensive assessments of cognitive functioning, including tasks of arithmetic, memory, pattern recognition, match-to-sample, logical reasoning, visual search, reaction time, and alertness. Of the 28 articles related to cognitive and/or motor functioning that were examined, 5 indicated impaired higher-order cognitive performance (including reasoning, memory, pattern recognition, and decision-making), while 6 demonstrated impairments of visiomotor coordination; 14 revealed no significant cognitive or psychomotor impact. Of the 11 articles that demonstrated statistically significant impacts of CO_2 exposure on cognition or motor functioning, 7 were in the "low" exposure designation category and therefore had greatest relevance to the operational conditions aboard the ISS. Of these 7 studies, 3 examined acute exposure and the other 4 chronic exposure; both of these categories of exposure duration are important for consideration in spaceflight, as astronauts may at various points experience elevated CO_2 levels either for a short duration or over a long period, and often repeatedly.

Of the 12 sleep-related articles, 3 indicated that arousal from sleep occurs during high CO_2 exposure, 2 pointed to lowered duration of REM, and 2 demonstrated no impact of elevated CO_2 levels on sleep or circadian functioning. Only 3 of the studies showing an effect on sleep, however, were in the operationally relevant "low" exposure range; all 3 of these studies examined effects of chronic (that is, prolonged and/or repeated) exposure to elevated CO_2.

The inconsistency in the literature regarding the cognitive and neuropsychological impacts of increased carbon dioxide exposure may be attributable in part to the wide variability in CO_2 exposure concentrations assessed, ranging from <1% in some studies to up to 35% in others. Additionally, the studies presented here employed a range of gas administration techniques. For example, Caretti (1999) induced heightened CO_2 exposure through a rebreather apparatus worn over the face, through which concentrations were manipulated directly, while Bakó-Biró (2012) monitored effects related to naturally fluctuating ambient levels of CO_2 over time within a confined indoor space. Furthermore, not all of these methods ensured consistent or controlled administration of CO_2 at particular concentrations for all participants.

At the same time, other factors inherent to this research limit the interpretability of cognitive effect findings; for instance, it is difficult to decouple the cognitive indications from purely physiological effects, since impairments in performance and decision-making may arise as secondary effects related to physiological experiences of headache and somatic stress.

CONCLUSION

While many studies have thus far addressed the impact of CO_2 concentration on cognition, the inconsistent and contradictory nature of current findings limits the ability to draw firm conclusions about the impact of elevated CO_2 exposure on sleep, cognition, and psychomotor performance. Further research, therefore, remains necessary to provide a clearer understanding of the risks of adverse cognitive and performance effects of acute and chronic high CO_2, particularly at levels relevant to human spaceflight.

Additionally, this survey highlights the fact that the majority of existing studies focus solely on the physiological mechanisms (e.g., headaches, heightened heart rate) by which increased CO_2 exposure may impact cognition, but fail to consider the possibility that observed performance changes may in fact be attributable to changes in brain or muscle pO_2, which covaries with pCO_2 in a way that may not be consistent across trials and individuals. A thorough examination, therefore, of the fluctuation of pO_2 as inspired CO_2 is manipulated remains critical if the impacts of elevated CO_2 exposure are to be decoupled from other physiological changes.

At the same time, this review demonstrated that limited research has, in fact, been done under environmental conditions analogous to those in operational spaceflight (that is, 0.3% to 0.7% ambient CO_2 exposure). Future investigations exploring more modest increases in CO_2 concentration during ambient exposure and incorporating manipulations such as head-down tilt (to induce fluid shifts associated with microgravity) or prolonged confinement could, therefore, greatly contribute to the establishment of appropriate operational limits and the development of countermeasure procedures for use in human spaceflight, and so are very much recommended given the findings of this survey.

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13. ABSTRACT *(Maximum 200 words)*
Existing research has reliably demonstrated the respiratory and cardiovascular effects of carbon dioxide (CO2) inhalation at moderately increased levels, with documented physiological changes to heart rate, blood pressure, tissue pH, and blood solubility. Studies of indoor air quality have linked increased levels of ambient CO2 with physiological symptoms such as headache, fatigue, and sore throat. High levels of CO2 have reliably resulted in activation of the hypothalamic-pituitary-adrenocortical axis and subjective anxiety responses in healthy individuals, as well as panic attack-like symptoms and experiences of physiological stress. While significant neurological findings correspond to high levels of CO2 exposure, less clinically significant cognitive effects may occur at a much lower level. These cognitive changes and the exposure thresholds at which they occur are less well established than their physiological counterparts; this paper, therefore, reviews the existing literature on the cognitive, neurological, and psychomotor effects of increased CO2 exposure, with the objective of identifying research areas in which further investigation remains necessary. In particular, this investigation is motivated by the chronic exposure to elevated ambient CO2 concentrations experienced by astronauts aboard the International Space Station, and the CO2 exposure-related symptoms that have been reported by astronauts on orbit.

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