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ORIGINAL INVESTIGATION

Mark C. Moss · Andrew B. Scholey

Oxygen administration enhances memory formation in healthy young adults

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Abstract Despite numerous studies indicating that transient cerebral oxygen depletion has a detrimental effect on cognition, surprisingly little research has examined the possibility of cognitive enhancement following elevated oxygen levels in healthy adults. Here, we present evidence demonstrating that oxygen administration improves memory formation. Inhalation of oxygen immediately prior to learning a word list resulted in a significant increase in mean number of words recalled 10 min later, compared to subjects who inhaled oxygen immediately prior to recall or to controls who underwent no intervention. In a second experiment, the learning-test interval was increased to 24 h and, again, only pre-learning (but not pre-test) oxygen administration resulted in significant memory facilitation. In experiment 3, inhalation of oxygen prior to learning was compared to inhalation of compressed air, oxygen (but not compressed air) resulted in a significant increase in word recall 24 h later. In no experiment did oxygen have a significant effect on any mood item measured. We interpret these data as indicating that increased availability of cerebral oxygen facilitates cognition, including memory consolidation. The implications for the psychopharmacology of cognitive enhancement are considered in the context of cholinergic systems and neural metabolism.

Key words Oxygen · Cognition · Memory · Metabolism · Glucose

Introduction

It is well established that manipulation of oxygen levels has an effect on cognition. In particular, induction of hypoxic states can impair cognitive processes, including memory formation, in animals and humans.

The global anterograde amnesia resulting from hypoxic ischemia has been thoroughly documented. Mnemonic deficits in humans (described in Volpe and Hirst 1983; Graf et al. 1985) are believed to stem from hypoxic damage to the medial temporal lobe and its thalamic projections as measured by regional cerebral blood flow in human ischemia-amnesics (Kuwert et al. 1993). Experimental hypoxia in animals leads to focal hippocampal damage (e.g. Zola-Morgan et al. 1992; Wood et al. 1993) and following even transient oxygen deprivation functional deficits are evident (Yamatoto et al. 1993) though reversible (Delatorre et al. 1993).

There is indirect evidence that fleeting fluctuations in cerebral oxygen delivery via blood supply, within normal physiological limits, can impact on cognitive performance. Sandman and colleagues have investigated the effects on stimulus processing and electroencephalographic parameters of tachistoscopic digit presentation during the various cycles of cardiac output. Stimuli were presented synchronously with either the P wave (immediately prior to systolic contraction of the heart) or during the T wave (at the end of contraction). The former were perceived more accurately (Sandman et al. 1977) and produced a larger average evoked response (Walker and Sandman 1979). It follows that slight increases in the availability of metabolic substrates may augment cognitive function.

The delivery of oxygen via cerebral vasculature may also affect cognitive function during ageing. There is a reduction of cortical blood supply of up 30% with age (Naritomi et al. 1979; Melamed et al. 1980; Davis et al. 1981), with regional and total blood flow being further reduced in patients with memory problems (Lassen and Ingvar 1980; Rowan et al. 1981; Ferszt and Cervos-Navarro 1983).

To date, few authors have examined the cognitive effects of specifically enhancing oxygen levels. Altitude-induced hypoxia and its reversal through

M.C. Moss · A.B. Scholey (✉)
Division of Psychology, University of Northumbria, Newcastle upon Tyne NE1 8ST, UK

supplemental oxygen was investigated by Crowley and colleagues (1992), who demonstrated a transient (less than 1 day) impairment of aspects of memory, grammatical reasoning and the Stroop test in a rarefied atmosphere at an altitude of 4500 m. Oxygen administration significantly enhanced previously impaired performance on code substitution, serial addition/subtraction, and elevated the activity index on a mood scale on altitude day 1 but not thereafter.

The effects of oxygen enhancement on cognitive function has also been studied in healthy elderly outpatients suffering from memory lapses (Edwards and Hart 1974). Subjects were treated with 100% oxygen at 2 atmospheres pressure for 15 daily sessions of 2 h each. Oxygen treatment resulted in substantial improvement on tests concerned with short term memory and visual organisation. Indeed, Strehler (1983) has suggested that transitory fluctuations of lucidity and alertness in the elderly may result from variability in cortical oxygen delivery.

Glucose, as well as oxygen, is a fundamental requirement for cellular metabolism. Just as cognitive deficits are evident following ischemia, so memory performance is reduced by mild hypoglycaemia (Lapp 1981; Benton 1989, 1990). The effect on specific cognitive tasks of manipulation of blood glucose levels within physiological limits has been extensively investigated in Benton's laboratory. During post-administration periods of elevated glucose, significant increases were found in speed of cognitive processing (Owens and Benton 1994), the Stroop test and a rapid information processing task, and the number of items recalled from a word list (Benton and Owens 1993a; Benton et al. 1994), independent of pre-treatment, basal blood glucose levels.

The mechanisms of glucose's cognitive enhancing properties are not well understood although various authors have proposed that increased availability of central glucose may increase cholinergic function (e.g. Messier et al. 1990; Durkin et al 1992; Kopf and Baratti, 1994). However, it is equally plausible that elevation of cerebral blood glucose augments cognitive performance simply by allowing task-sensitive brain areas to metabolise at higher rates than basal glucose levels otherwise permit. The latter hypothesis may account for the selective, glucose-dependent enhancement of word recall from the unattended ear in a dichotic listening task (Parker and Benton 1995).

Since glucose utilisation is oxygen-dependent and oxygen has a more immediate impact on cellular (including neuronal) metabolism, we postulated that enhancement of blood oxygen levels via inhalation of pure oxygen would similarly facilitate cognitive processes. To this end, we tested the effects of oxygen administration on a simple word recall task. Three issues were addressed in this study. Firstly, does enhancement of blood oxygen facilitate memory? Secondly, over what time period does any enhancement persist and, thirdly, is any effect on memory due to consolidation or recall?

Materials and methods

Subjects

A total of 105 male and female undergraduate volunteers (aged between 18 and 21 years) from the Universities of Northumbria and Newcastle, Newcastle upon Tyne took part in the study.

Word list

A list of 15 words, each having six letters and two syllables was used. The words were identical to those used by Benton and Owens (1993a) and chosen to be high in imagery, concreteness and frequency (after Paivio 1968). The words were presented verbally at the rate of one per second.

Oxygen/air

Participants self-administered oxygen from a face mask attached tocanisters of "O-Pur" 100% Oxygen (Newpharm SA, CH-6915, Pambio - Noranco, Switzerland) according to the manufacturer's instructions. In experiment 3 (see below), subjects self-administered air by inhalation through a face mask identical to that used for the oxygen condition attached by rubber tubing to an "Elite" 800 compressed air pump [Rolf C. Hagen (UK) Ltd., Castleford, W. Yorkshire, England].

Mood data

The Profile of Mood States (POMS) mood questionnaire (Lorr and McNair 1980) acts as an ideal standardised distractor over short learn-test intervals. Additionally, Benton and Owens (1993b) found that higher levels of blood glucose corresponded to lower feelings of tension. Non-specific arousal effects of oxygen may therefore be detected from analysis of mood data. Mood data were collected using the POMS B1 questionnaire. The measure consists of a 4-point scale for each of 72 items which make up six subscales; "energetic-tired", "agreeable-hostile", "composed-anxious", "confident-unsure", "elated-depressed" and "clear headed-confused".

Experiment 1

The first experiment was aimed at determining whether inhalation of oxygen had any effect on memory formation or recall. Upon entering the laboratory, each subject was randomly assigned to one of three conditions ($n = 15$ in each case); oxygen at learning (O_2-learning), oxygen at test (O_2-test) or control. Individual subjects were presented with the word list at a rate of one item per second (learning phase), in the ensuing 7 min 45 s individuals filled out the mood questionnaire (all subjects completed the questionnaire before this time elapsed and were instructed to check

over their responses). There then followed a "pre-test" interval of 60 s after which subjects were instructed to recall as many of the words as possible. Recall time was unlimited although subjects were asked to indicate when they could recall no more words. In the two experimental conditions, subjects were instructed to breathe normally while self-administering oxygen via a face mask attached to the canister. In the O_2-learning condition, subjects inhaled oxygen for 60 s immediately prior to presentation of the word list; in the O_2-test condition the oxygen was similarly delivered but during the "pre-test" interval immediately prior to recall. Controls underwent no oxygen manipulation. The number of words correctly recalled by each subject was recorded.

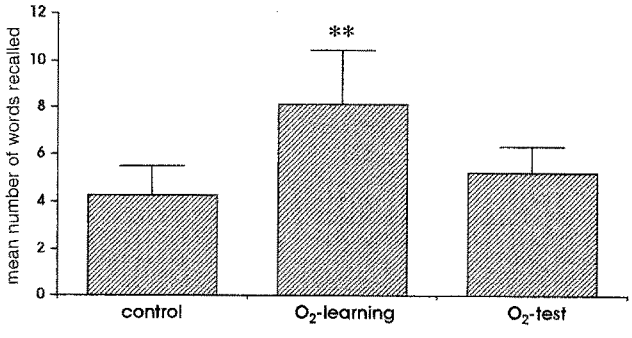
Statistics

Data were analysed using a one-way analysis of variance followed by Scheffe all pairwise post hoc comparison of means.

Results

There was an effect of experimental condition on the mean number of words recalled (see Fig. 1) with a one-way analysis of variance revealing a statistically significant effect of the manipulation [F (2, 42) = 8.49; $P < 0.001$]. Scheffe all pairwise post hoc comparisons of the means indicated that the mean O_2-learning score was significantly higher than that of controls (mean number of word recalled = 8.133 and 4.267, respectively) and of the O_2-test group (mean = 5.267) ($P < 0.01$ in each case). The results of experiment 1 also indicated that there may be a trend for enhanced recall above controls in the O_2-test group, however this difference was not significant.

Fig. 1 Influence of oxygen administration on word recall with a 10 min learning-test interval, error bars show standard deviations (** $P < 0.01$ compared to controls and the oxygen-test group)



Experiment 2

We interpreted the results of experiment 1 as indicating that oxygen was affecting memory consolidation rather than recall (see Discussion for detailed consideration of the results). This was investigated further in experiment 2 by increasing the learn-test interval to ensure that oxygen levels had returned to basal levels at the time of recall. Subjects were randomly allocated to one of three groups ($n = 12$ in each case); O_2-learning (oxygen inhalation for 60 s immediately prior to word presentation), O_2-test (oxygen immediately prior to test) and control (no manipulation). The procedure for the second experiment was essentially similar to experiment 1 except that, following the presentation of the word list, there was a delay of 24 h after which subjects returned to the laboratory for mood data gathering and the recall phase.

Statistics

Statistical analyses were similar to those used in experiment 1, except that post hoc comparisons were performed using the Dunnet test.

Results

The results of experiment 2 showed a similar pattern to those of experiment 1 (see Fig. 2). When the interval between learning and recall was increased to 24 h, the significant effect of oxygen administration was maintained [F (2, 33) = 4.13; $P < 0.05$]. Post hoc comparison of means revealed that recall in the O_2-learning group (mean number of word recalled = 7.167) was significantly better than the O_2-test group (mean = 5.417, $P < 0.05$) and the control group (mean = 5.083, $P < 0.01$)

Experiment 3

The third experiment was directed at determining whether the effects observed in the previous experiments were due to subjects' expectancies rather than the experimental manipulation. To this end, subjects were randomly allocated to one of two groups ($n = 12$ in both cases), O_2-learning (identical to that group in experiment 2) or air-learning where the subjects inhaled compressed air for 60 s immediately prior to the learning phase. Administration in the air-learning condition was through an identical face mask to the one used for oxygen but attached to a compressed air source (participants were blind as to their experimental condition). Subjects inhaled either oxygen or compressed air for 1 min prior to presentation of the word list and

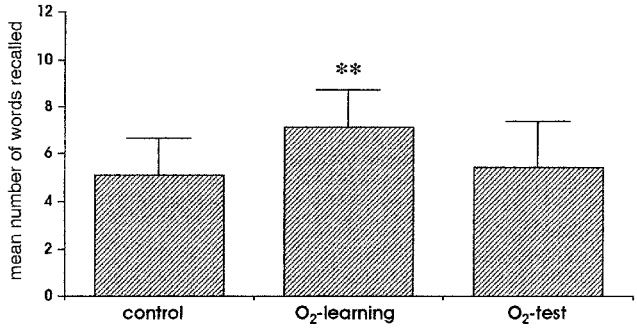


Fig. 2 Influence of oxygen administration on word recall with a 24 h learning-test interval, error bars show standard deviations (** $P < 0.01$ compared to controls and $P < 0.05$ compared to oxygen-test group)

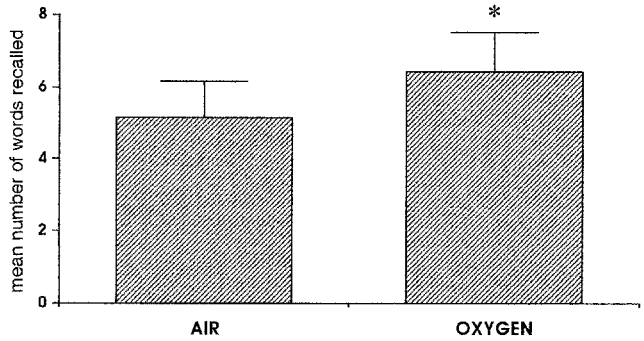


Fig. 3 Comparison of oxygen inhalation and inhalation of compressed air on word recall with a 24 h learning-test interval, error bars show standard deviations (* $P < 0.05$)

returned to complete the mood questionnaire and recall phase 24 h later as in experiment 2.

Statistics

Group scores were analysed by independent sample *t*-test.

Results

The results of experiment 3 are presented in Fig. 3. The mean number of words recalled in the oxygen-learning condition was higher than in the air-learning group (means = 6.420 and 5.417, respectively; $t = 2.35$; $P < 0.05$).

Mood scores

One-way analyses of variance were performed on the data generated from each experiment from the six subscales of the POMS mood questionnaire. No significant differences were found for any of the subscales in any of the three experiments.

Discussion

The results of this study support the hypothesis that oxygen administration enhances memory function. The *n*s and size of effect in all three experiments indicate that memory enhancement following oxygen administration is highly robust (with increases of up to 191% control values for number of words recalled). The effect appears to be specific to consolidation since oxygen administration immediately prior to test did not improve recall (experiments 1 and 2, O_2-test condition). There was a trend towards increased recall in the oxygen-test condition in experiment 1; however, this may have reflected oxygen's impact on ongoing consolidation mechanisms since the effect was negligible when oxygen was administered prior to recall following a 24 h learning-test interval (experiment 2).

It is arguable that the results in experiments 1 and 2 could be attributed to subjects' expectancies from the act of inhalation alone, rather than a real effect of elevated blood oxygen levels. This possibility was ruled out in experiment 3, where participants were unaware of whether they were inhaling oxygen or compressed air and the significant effect of oxygen administration was again evident. All subjects were briefed in the same way and were told that they might breathe oxygen during the experiment; indeed, those air-learning subjects who commented on the experiment stated that they believed they had inhaled oxygen (although no systematic data collection or analyses were performed on this aspect of the experiment).

No effect on mood data was detected in this study which suggests that oxygen administration was not simply increasing mnemonic performance as a consequence of heightened arousal. Clearly, more precise assessment of arousal levels is required to eliminate this possibility.

Oxygen consumption is the final step, and a rate limiting factor, in respiration. The consequent aerobic production of adenosine triphoshate (ATP), the cellular "energy currency", by mitochondrial metabolism is oxygen-dependent. ATP is a requirement in most biochemical pathways, including glucose metabolism and acetylcholine synthesis. Furthermore, ATP can directly influence postsynaptic receptors, including those for acetylcholine (Tucek 1978). One possible mechanism by which oxygen administration has its effect is by direct or indirect (via glucose) modulation of cholinergic systems used in memory consolidation. However, is also worth noting that transient experimental ischemia reversibly changes levels of hippocampal glutamate, GABA and aspartate in rats (Torp et al. 1993); there is no reason at present to conclude that mnemonic cholinergic systems are the primary target for oxygen enhancement.

One attractive hypothesis as to the effects described here is that neural activity is "fuel-limited" and that

increased circulating oxygen is sequestered by brain areas undergoing task-specific energy demands. This would increase the availability of ATP for energy-demanding processes (signalled by increased adenosine diphosphate (ADP)/ATP ratios). Like glucose, availability of brain oxygen may limit cognitive performance. It follows that increasing the level of either substance may allow for neuronal metabolism above that seen at basal levels, an effect manifested by enhanced cognitive performance. Certainly, changes in cerebral oxygenation, as measured by cerebral perfusion pressure in response to altered oxygen availability, "reflect changes in oxygen *offer* as well as changes in cerebral blood flow" (Maas et al. 1993, our italics). Although blood oxygen levels were not measured in this study, administration of oxygen in the manner described results in an increase in blood oxygen in the order of 30% (data from unpublished study provided by the manufacturer).

Clearly, the effects of oxygen on cognitive processes need to be more clearly delineated. The temporal kinetics and dose-dependency of oxygen's impact should be established as should the possible effect of oxygen administration on other cognitive processes. Further research should also be aimed at the determination of any correlation between blood oxygen levels and cognitive performance.

The precise neurochemical substrates affected by oxygen enrichment are not known but may be determined by the administration of oxygen in combination with specific neurotransmitter agonists and antagonists. Furthermore, the possibility of combinations of oxygen and glucose, or other psychopharmacological agents, acting in synergy on cognitive enhancement is an exciting prospect. Our laboratory is currently actively investigating these possibilities.

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