Continuous and intermittent exposure to the hypoxia of altitude: implications for glutamine metabolism and exercise performance

D M Bailey, L M Castell, E A Newsholme, B Davies

Although most elite athletes invest a considerable amount of time and resources training at altitude, the practical benefits gained remain to be clearly established despite almost half a century of investigation. Elucidating the potential factors that affect physical performance after return to sea level has been the subject of much interest and controversy.

The time spent exposed to the hypoxia of altitude would appear to be an important mediator of sea level performance. A combination of physical exercise and intermittent hypoxia (defined as an exposure time of 30 minutes to 12 hours a day) has been shown to accelerate the normal adaptations invoked by a comparable programme of normoxic training with cardioprotective and performance enhancing benefits. In contrast, increased free radical mediated oxidative stress, decreased cell mediated immunity, and increased incidence of infectious episodes have been reported in continuous hypoxia (defined as an exposure time of 24 hours a day). We have previously reported two cases of infectious mononucleosis following chronic exposure to 1500–2000 m.

Glutamine has been identified as a conditionally essential amino acid required for lymphocyte proliferation and macrophage phagocytosis, and it has been suggested that any physiological decrease in plasma glutamine may impair the host’s defence against opportunistic infections. In the light of these findings, we examined changes in plasma glutamine, the incidence of overt physical illness, and maximal exercise performance as a function of continuous and intermittent hypoxic training at comparable inspiratory partial pressures of oxygen (PIO₂) or simulated altitudes.

METHODS

SUBJECTS

After ethical approval, volunteers were solicited from two separate cohorts of international standard endurance runners (continuous group, n = 22) and endurance trained university students (intermittent group, n = 32).

EXPERIMENTAL DESIGN

In study 1 (continuous group), 22 elite distance runners had the option of spending four weeks at an altitude training camp based at 1640 m in Johannesburg, South Africa (PIO₂ = 122 (1) mm Hg). Of these, 10 volunteers travelled to altitude (continuous EXP) and 12 trained at sea level in the United Kingdom (PIO₂ = 151 (3) mm Hg; intermittent CON). Although it was not possible to randomly assign volunteers to the altitude or sea level training camps, retrospective analysis identified that the two subgroups drawn from a homogeneous group of distance runners had comparable performance capabilities.

In study 2 (intermittent group), 18 volunteers were randomly assigned in a double blind manner to train for four weeks in a laboratory inspiring a medical grade normobaric hypoxic gas (PIO₂ = 115 (2) mm Hg; intermittent EXP), and 14 performance matched volunteers trained while exposed to normobaric normoxia (PIO₂ = 150 (2) mm Hg; intermittent CON). These gases were designed to approximate the PIO₂ experienced in study 1.

All volunteers performed a standardised exercise test in normobaric normoxia before and after training for the determination of maximal aerobic capacity (VO₂MAX). The incidence of physical symptoms associated with an upper respiratory tract or gastrointestinal tract illness was assessed, and resting venous blood samples were analysed for a differential white blood cell count and plasma glutamine.

HYPOMONOCCELLULAR NUTRITION PROGRAMMES

Both the normoxic and hypoxically trained subgroups performed the same volume of physical training at the same percentage of heart rate maximum, which was enforced using electrocardiograph calibrated bipolar telemetry (Vantage, Polar Electro, Oy, Finland).

STATISTICAL ANALYSIS

Changes in selected dependent variables as a function of timing (before v altitude v after) and group (exposure to hypoxia (EXP) v controls (CON)) were analysed using a two factor mixed analysis of variance. After a significant interaction and simple main effects, a posteriori comparisons within groups were analysed using Bonferroni paired samples t tests. Simple effects between groups were assessed using a one way analysis of variance and a Tukey honestly significant test. The α level was set at p<0.05 for all two tailed tests, and values are reported as means (SD).

RESULTS

A considerable increase in the incidence of respiratory tract or gastrointestinal tract illness was observed during continuous exposure to the hypoxia of terrestrial altitude (fig 1). This was accompanied by a decrease in plasma glutamine (fig 2), which was more pronounced in those volunteers presenting with an illness than in those who remained apparently healthy (~182 (38) µmol/l v −92 (32) µmol/l; p<0.05). Plasma...
glutamine concentration remained depressed and total white blood cell count decreased after return to sea level (table 1), whereas no changes were observed for VO₂MAX. In contrast, fig 3 illustrates the increase in plasma glutamine (+78 (109) µmol/l, p<0.05) invoked by intermittent hypoxia, whereas changes in the differential white blood cell count (table 1) and the incidence of illness were unremarkable.

Table 1 Differential white blood cell count before, during, and after continuous/intermittent hypoxic training

<table>
<thead>
<tr>
<th>Group/subgroup</th>
<th>White blood cells (10⁹/l)</th>
<th>Lymphocytes (10⁹/l)</th>
<th>Neutrophils (10⁹/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous PRE</td>
<td>5.02 (1.51)</td>
<td>1.4 (0.5)</td>
<td>3.0 (0.9)</td>
</tr>
<tr>
<td>ALTITUDE EXP</td>
<td>6.50 (1.00)</td>
<td>1.7 (0.4)</td>
<td>3.9 (1.0)</td>
</tr>
<tr>
<td>POST EXP</td>
<td>3.72 (1.35)†</td>
<td>1.5 (0.5)</td>
<td>2.6 (1.0)</td>
</tr>
<tr>
<td>PRE CON</td>
<td>4.84 (0.74)</td>
<td>1.5 (0.4)</td>
<td>2.7 (0.7)</td>
</tr>
<tr>
<td>POST CON</td>
<td>4.07 (0.95)</td>
<td>1.6 (0.9)</td>
<td>2.4 (1.0)</td>
</tr>
<tr>
<td>Intermittent PRE EXP</td>
<td>6.2 (1.6)</td>
<td>2.0 (0.5)</td>
<td>3.6 (1.2)</td>
</tr>
<tr>
<td>POST EXP</td>
<td>5.5 (1.3)†</td>
<td>2.0 (0.7)</td>
<td>2.9 (0.9)†</td>
</tr>
<tr>
<td>PRE CON</td>
<td>5.4 (1.0)</td>
<td>1.8 (0.4)</td>
<td>2.9 (1.0)</td>
</tr>
<tr>
<td>POST CON</td>
<td>4.7 (0.6)†</td>
<td>1.8 (0.4)</td>
<td>2.4 (0.4)</td>
</tr>
</tbody>
</table>

All data expressed as mean (SD). Continuous, continuous exposure; Intermittent, intermittent exposure; EXP, hypoxically trained subgroup; CON, normoxically trained subgroup. PRE, before normoxic/hypoxic training; ALTITUDE, determined on day 19 at 1640 m; POST, after normoxic/hypoxic training. *p<0.05 significantly different from ALTITUDE within subgroup value. †p<0.05 significantly different from within subgroup PRE value.

Discussion

While we acknowledge the limitations imposed by two separate cohorts with different exercise capabilities and the logistical idiosyncrasies of field research, our observations suggest that the duration of the hypoxic stimulus is an important modulator of immune function and physical exercise performance. The appreciable increase in overt physical illness at altitude, either due to the chronicity of hypoxia per se and/or contact with novel infectious pathogens, may suggest possible immunodepression, an observation previously linked to depression of cell mediated immunity.78 The decrease in plasma glutamine, which has been shown to decrease both lymphocyte proliferation and response time in vitro,3 may be a contributory factor implicated in such a response. However, whether the decrease in glutamine was a cause or a consequence of illness remains to be established.

In contrast, physical illness was not prevalent during intermittent hypoxic training despite a similar P̄O₂. The increase in VO₂MAX appeared to be independent of changes in arterial oxygen content (data not shown) and possibly due to other unquantified central and/or peripheral factors. The increase in plasma glutamine was intriguing and to our knowledge has only previously been anecdotally reported in a review.10

In conclusion, a combination of physical exercise and repeated bouts of intermittent hypoxia appears to initiate a disruption in systemic homoeostasis which is followed by an adaptive phase which, in general terms, appears to be beneficial. Adaptation appears to be inadequate during continuous hypoxia, which could have potentially deleterious consequences.

This research was supported by the British Olympic Association, British Athletics Federation, and British Oxygen Company.

Take home message

The duration of exposure to environmental hypoxia during physical exercise is a potential mediator of immune function and athletic performance. Continuous hypoxic training resulted in overt immunodepression whereas intermittent hypoxic training increased physical exercise performance considerably.

Sports medicine? The ultimate folly

“Sports medicine? I suppose that means treating frisbee injuries.” I am told that this comment was made with a slight sneer and a snort of derision by a consultant orthopaedic surgeon. It reminds me of a similar incident about 12 years ago when I was attending a GP refresher course, and a consultant rheumatologist informed his audience that “there is no such thing as a sports injury”. I find such comments sad and not a little frightening. Sad, because they reveal a lack of knowledge, understanding, and a suspiciously closed mind. Frightening because a statement made by an “expert” in this way is taken at face value by the trusting recipients, who, in turn, pass it on, leading to a cascade of misinformation.

Let me set the record straight. I need hardly comment on the reality of sports injuries and the practice of sports medicine; you are already reading this journal. However, I cannot allow the reference to frisbee to pass unanswered! I have been medical advisor to the British Ultimate Federation for 13 years and have seen and treated my fair share of frisbee related injuries in that time.1 Ultimate is the team sport played with a “flying disc”, and, although there are other disciplines (disc golf, double direct court, guts), it is ultimate that is the most athletic. Ultimate is like a number of other minority sports: fast, exciting, requiring fitness, skill, and team-work, and has organisational structures at national and international level (see the British Ultimate Federation website at www.ultimateweb.co.uk/buf/). It remains curious (some might say outrageous) that it is consistently denied Sports Council recognition.

Ultimate is played on a pitch 70 × 30 yards with an end zone at each end. Teams of seven oppose each other, one team attempting to string together a sequence of passes without the disc going to ground, out of bounds, or being intercepted until a final pass can be made to a team mate who is within the end zone, this being a score. The opposition are attempting to intercept (and thus gain possession) or to mark their oppos-

Figure 1 A game of ultimate in progress. Picture courtesy of Jonathan Hope.