INTRATECAL KETAMINE IN RATS

Sir,—We have read with interest the article by Ahuja (1983) entitled “Analgesic effect of intrathecal ketamine in rats”, and would like to bring two aspects of the above to your notice.

In the previous communication referred to by Dr Ahuja (Mankowitz et al., 1982) we reported on the pain-relieving properties of extradural ketamine in patients suffering from cancer pain. We have since utilized extradural ketamine for pain relief after operation in a pilot study involving four patients. Even when the dose of extradural ketamine was increased to 50 mg, analgesia was usually inadequate and certainly not as effective as extradural morphine for postoperative pain relief (Rubin et al., 1983). The reason for this discrepancy could lie in the fact that the pathways of chronic pain are very different from those of acute pain.

As to the possible toxic effects of intrathecal ketamine, we concluded in a separate animal study (Brock-Utne et al., 1982) that the drug would seem safe as judged by examination of spinal nerve roots of baboons.

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EXERCISE, CYCLIC AMP AND MALIGNANT HYPERPYREXIA SUSCEPTIBILITY

Sir,—In their study of blood concentrations of cyclic AMP in malignant hyperpyrexia-susceptible (MHS) subjects, Drs Stanec and Stefano (1984) demonstrated higher cyclic AMP concentrations in the MHS group during and following maximal exercise. There are, however, problems with their programme of exercise which detract from the validity of their findings and from their conclusions.

Both groups were given the same work loads (rate and gradient of a treadmill) and these were increased by degrees which were unspecified, but which appear to have been the same in both groups. Individuals vary markedly in their degree of physical fitness or maximal work capacity (maximal aerobic capacity, maximal oxygen uptake or $V_{O_2 \text{max}}$) (Shephard, 1978) and, thus, their ability to cope with a given work load. Hence, if two subjects are given the same work load, a very unfit subject will be "stressed" more than a very fit one, as that work load will take up a greater proportion of the unfit subject’s work capacity than it will of the fit subject’s. The conventional way of exercising two people to a comparable degree is to give them prescribed work loads to perform that take up comparable proportions of their measured $V_{O_2 \text{max}}$ (Bloom et al., 1976). If it is impractical or undesirable to measure $V_{O_2 \text{max}}$ the work loads are prescribed to produce, for subjects of the same age, comparable heart rates. For a given type of exercise there is a linear relationship between oxygen consumption and heart rate and the conventional view is that, in a healthy individual, $V_{O_2 \text{max}}$ is limited by the maximum heart rate he can achieve. Maximal heart rate is normally a function of age (Lange-Anderson et al., 1971). Stanec and Stefano did not exercise their subjects according to their $V_{O_2 \text{max}}$ as a result of which their MHS subjects exercised to their maximum over a significantly shorter period than did the controls.

The metabolic processes underlying exercise are a function of the duration and intensity of the exercise and in the early part of any exercise period are in an unstable state of flux (Felig and Koivisto, 1979). The work presented by Drs Stanec and Stefano could be interpreted as merely demonstrating that their MHS subjects were probably less fit (had a lower $V_{O_2 \text{max}}$) than their controls, and that the greater concentrations of cyclic AMP in the MHS group merely reflect this, along with the fact that the measurements in this group were started earlier in a relatively more unstable part of the exercise period than in the control subjects.

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Sir,—We would like to thank you for an opportunity to reply to Dr Campbell’s letter. Dr Campbell has expressed concern regarding our programme of exercise. However, we believe that most of his reservations have been addressed fully in our article (Stanec and Stefano, 1984). Dr Campbell’s critique of the exercise programme is based on two assumptions: (1) we were comparing professionally trained individuals with untrained subjects; (2) we did not use the maximal predicted heart rate as the measure of the $V_{O_2 \text{max}}$. Obviously, there may be a significant difference in the responses to exercise between professionally trained and untrained individuals. Certainly, “for a given type of exercise there is a linear relationship between oxygen consumption and heart rate” and “maximal heart rate is normally a function of age”.

Our volunteers were selected from college students carefully matched with malignant hyperthermia (MH)-susceptible
individuals of comparable age, weight, muscle bulk and history of exercise tolerance. None of the individuals studied was actively involved in sports. All volunteers were highly motivated to exercise to their maximal capacity. The Bruce Protocol (Bruce et al., 1963; Bruce and McDonough, 1969) is a treadmill exercise test commonly used in the United States. It is a continuous staged stress test in which the work load is progressively increased. The subjects start out at 1.7 mi h⁻¹ on a 10% grade and progress to their maximum capacity at 3-min intervals. The speed is increased by 0.8 mi h⁻¹ and the grade is increased by 2% every 3 min. The test is stopped once the predicted heart rate is reached, or sooner if clinical symptoms of exhaustion develop and the subject cannot continue. Each individual exercises until his/her maximum capacity is reached. Thus, a self-determined end-point of maximal exertion is achieved. The principle of the Bruce Protocol is measurement of an individual's capacity to cope with the stress of exercise.

Dr Campbell correctly notes that the difference between the MH and control groups is in the duration of the test and not in the heart rate. At the peak of the exercise, volunteers from both groups were at 90–100% of their peak heart rate. The maximum predicted heart rate and generalized fatigue developed faster in the MH-susceptible group. Thus, the MH-susceptible individuals reached a self-determined end-point of maximal exertion, or the peak of the test, earlier. Since we studied group I first to observe changes during exercise in normal individuals, we did not want to change the duration of the test after the group II was completed. While subjects from group I also developed symptoms of generalized fatigue, they tolerated the exercise longer. Therefore, times for the end-point of the stress test differ in the two groups.

Our study stressed the system to a maximum tolerance so that any abnormalities would become evident. In addition, we compared the peak of the exercise stress test between the two groups in similar fashion. Had we corrected the time to reach the maximum, we would have compared the normal subjects' data (group I) at moderate level of exercise with the MH-susceptible individuals' data (group II) at maximal level of exercise. On the other hand, if we gave less load to the MH-susceptible group so they could go on longer for comparison of the same times, this comparison would also be incorrect, since individuals from both groups were carefully matched for history of tolerance to exercise. History and physical evaluation did not indicate that group II individuals were less fit. In addition, we were not aware at the beginning of our study that the MH-susceptible individuals would reach their peak faster. This was the finding of the study. We do not have an explanation for the difference in the treadmill test tolerance. We can only speculate that perhaps the MH-susceptible group, although responding during an MH crisis with increased metabolism, in reality cannot handle increased metabolic demands as a result of abnormal cAMP metabolism. Willner, Cerri and Wood (1979, 1981) also found significantly greater concentrations of cAMP in skeletal muscle from MH-susceptible individuals.

In summary, we believe that the two populations were not subjected to different stresses just because the time to reach the maximum was shorter in one group. If we adjusted the work load, we would be assuming before the test that the MH-susceptible group was less fit than the normal group. The Bruce Protocol appears to be the most suitable test for the purpose of our study, to discover the differences, if any. This test has also been used successfully in the differential diagnosis between cardiac patients and normal individuals, and between patients with coronary artery disease and aortic or mitral valve disease (Bruce et al., 1963; Bruce and McDonough, 1969). Interestingly, as the duration of the test of the tolerance to stress decreases below 4 min, the operative and postoperative mortality increases.

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