Psychopharmacological and Endocrinological Effects of Melanocyte Stimulating Hormones in Normal Man

HEATHER ASHTON 1, J. E. MILLMAN 1, ROSEMARY TELFORD 1, J. W. THOMPSON 1, TERRY F. DAVIES 2, REGINALD HALL 2, S. SHUSTER 3, A. J. THODY 3, DAVID H. COY 4, and ABBA J. KASTIN 4

1 Clinical Psychopharmacology Unit, Department of Pharmacological Sciences, University of Newcastle-upon-Tyne, United Kingdom
2 Department of Medicine, Royal Victoria Infirmery, Newcastle-upon-Tyne, United Kingdom
3 Department of Dermatology, Royal Victoria Infirmery, Newcastle-upon-Tyne, United Kingdom
4 Veterans Administration Hospital and Tulane University School of Medicine, New Orleans, Louisiana, U.S.A.

Abstract. A double blind crossover trial of the effects of synthetic alpha melanocyte stimulating hormone (alpha MSH) and synthetic beta melanocyte stimulating hormone (beta 1-22 MSH) on the contingent negative variation (CNV), performance (mental arithmetic; verbal and visual memory), and mood (self-rating scale) was carried out on four normal male subjects. All subjects received three 10-min infusions in random order at weekly intervals (10 ml diluent alone, 10 mg alpha MSH or 10 mg beta 1-22 MSH, both in 10 ml acid saline) and were observed for 1 h after the infusion and again 24 h later. Plasma concentrations of alpha and beta MSH, thyrotrophin, growth hormone, gastrin, cortisol, calcium, cholesterol, and triglycerides were measured before and after the infusions in addition to the CNV and mental performance tests.

Plasma half-lives were found to be 20.8 min for alpha MSH and 15.1 min for beta MSH. The infusions had little effect on most measures, but after alpha MSH there was a significant improvement in verbal memory, and in two subjects there was a significant rise in plasma growth hormone without a rise in plasma cortisol. After beta 1-22 MSH there was a significant decline in verbal memory in all four subjects. These results lend support to the accumulating evidence that peptides similar to the melanocyte stimulating hormones have a neuroendocrine effect in man.

Evidence is now accumulating that melanocyte stimulating hormones from the anterior pituitary have psychological and neurophysiological effects in man (Lancet, 1975; Kastin et al., 1971; Itil, 1974). The fact that derivatives of beta-lipotrophin (β-LPH), probably the source of the melanocyte stimulating hormones (Scott and Lowry, 1974), bind to opiate receptors of brain provides further validity to these reports (Lazarus et al., 1976) and suggests a morphinomimetic function for β-LPH. When a limited quantity of synthetic human alpha and beta 1-22 MSH became available for study, it seemed of interest to investigate their effects on brain function and autonomic activity as well as certain endocrine and biochemical variables.

This paper describes a small double blind crossover trial of some effects of synthetic alpha melanocyte stimulating hormone (alpha MSH) and for the first time synthetic beta melanocyte stimulating hormone (beta 1-22 MSH) in four normal male subjects. Brain activity and performance were measured by means of the contingent negative variation (CNV), mood rating scales, mental arithmetic, and verbal and visual memory tests. Measures of autonomic activity included heart rate and blood pressure. The physiological responses to infusions of alpha and beta MSH were assessed by measuring the serum calcium, cholesterol and triglycerides, gastrin, and thyrotrophin (TSH) together with the plasma cortisol and growth hormone before and after the peptide infusions. Plasma alpha MSH and beta MSH were assayed concurrently. A small study of the effects of melanocyte stimulating hormone inhibiting factor (l-prolyl-l-leucylglycinamide-bovine MIF-1) on CNV magnitude in six normal male subjects is also reported.

The CNV (Walter et al., 1964) was chosen as one measure of brain function since it has been shown to be a sensitive objective method of detecting both stimulant and depressant effects of centrally acting drugs in man (Ashton et al., 1974, 1975; Tecce, 1975).
Evidence from previous studies suggests that CNV magnitude, as well as mood ratings and performance in some tests of memory, may be altered by melanocyte stimulating hormones (Kastin et al., 1971; Miller, 1974) and confirmatory evidence for these findings was sought.

SUBJECTS, MATERIALS, AND METHODS

A. Alpha and Beta MSH

Subjects

The subjects were four healthy male volunteers who were members of the hospital staff (mean age: 33 years). None were taking any other drugs. Approval was obtained from the appropriate ethical committees.

Drugs

Each subject attended three 2-day experiments at intervals of at least 1 week. On the first day of each experiment he received a 10 min i.v. infusion of alpha MSH, beta MSH, or diluent only. The drugs were given in a dose of 10 mg in 10 ml of diluent (0.01 M acetic acid in 0.9% Saline). The drugs and placebo were given in random order, each subject acting as his own control. One of the investigators administered all the infusions and only he knew which drug it contained: neither the subjects nor the observers (the remainder of the investigators) who recorded the CNV and other variables knew the nature of the infusion. The code was not broken until after the results for all subjects had been calculated.

Tests of Brain Activity and Performance

1. CNV Magnitude. The CNV was obtained by the method described by Ashton et al. (1974). Briefly, subjects were presented with series of paired signals. The warning signal was a momentary flash of light and the imperative signal was a tone delivered through a loud-speaker. The subject was required to press a button in response to the imperative signal. The paired warning and imperative signals were separated by an interval of 1.25 s and were presented at random intervals (4–8 s) in a series of 10, each series lasting 1 min 10 s. The EEG was derived between the left mastoid electrode and was amplified by a Devices M19 recorder; an earth electrode was placed on the right mastoid. The output was fed into a PDP8 computer and the averaged response to each series of 10 paired signals was traced out by an X-Y recorder. The magnitude of the CNV thus obtained for a series of 10 paired signals was determined in terms of area and expressed in µV s.

2. Mood Rating. During each experiment subjects completed a self-rating scale for tension, alertness, depression, detachment, and anxiety, rating each scale on a vertical line between 0 and 200, on which 100 represented a normal or average state.

3. Mental Arithmetic. The subjects were asked to add as many columns of 15 single digits as possible in 2 min. The number of columns completed and the number of correct additions were scored.

4. Visual Retention Test. The Benton Visual Retention test was administered in a modified form in that subjects were asked to reproduce geometrical designs after examining them for 1 s instead of 5 s as in the usual test (Kastin et al., 1971; Miller et al., 1974).

3. Verbal Memory Test. The Wechsler Memory Scale was administered. This test the subject’s ability to remember two brief stories reproduced from a tape recording (Kastin et al., 1971; Miller et al., 1974). Subjects were also asked to repeat the stories on the following day.

6. Subjective Effects. Subjects were questioned about any subjective effects experienced during or after the infusions.

Tests of Autonomic Activity

1. Heart Rate. Heart rate was recorded from an ECG and monitored continuously from a Devices rate meter.

2. Blood Pressure. Blood pressure was measured automatically by a Roche Arteriosonde recorder, the pressure cuff being applied to the arm not receiving the drug infusion.

Biochemical Investigations

Specific immunoassays were used for growth hormone (Hartog et al., 1964), thyrotrophin (Hall et al., 1971), gastrin (Blair et al., 1977), alpha MSH (Thody et al., 1975), and beta MSH (Thody and Plummer, 1973). The assay used for beta MSH did not cross react with either alpha MSH or ACTH but did detect β-LPH (Plummer and Thody, personal communication). Plasma cortisol was assayed fluorometrically (Mattingly, 1962), cholesterol was measured on a Technicon Autoanalyser (method N24/a) and triglycerides by a spectrophotometric method (Giegel et al., 1975). Calcium was measured by atomic absorption spectrophotometry.

Procedure

Each experiment consisted of two sessions on consecutive days, Days 1 and 2. On Day 1 the 10-min i.v. infusion of drug or placebo was administered after one series of control measurements and recording was continued for 60 min after the end of the infusion. On Day 2, 24 h later, repeat recordings were made for 30 min. Except for the insertion of the i.v. cannula on Day 1, the general procedure was the same on both days. Subjects fasted overnight and each session commenced at 9.00 a.m.

The subject lay on a couch in the Subject Room. A butterfly cannula was inserted into a vein on the back of the nondominant hand in readiness for the infusion, and a cannula for blood sampling was inserted into an antecubital vein of the same arm. Scalp and chest electrodes were applied for EEG and ECG recordings. The leads from the subject were connected via cables to recording equipment housed in a separate Recording Room from which subjects could be observed through a one-way window and on closed circuit television. The observer who administered the infusions remained in the Subject Room but was in communication with the Recording Room via microphone and earphone. Instructions for the CNV procedure were given from a tape recording (Kastin et al., 1971; Miller et al., 1974).