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PLASMA IMMUNOREACTIVE β -MELANOCYTE STIMULATING HORMONE (LIPOTROPIN) LEVELS IN INDIVIDUALS WITH PRADER-LABHART-WILLI SYNDROME

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Abstract

Plasma immunoreactive β -melanocyte-stimulating hormone (β -MSH) levels, which actually represent the combined concentrations of β -lipotropin (β -LPH) and γ -LPH in normal individuals, were measured in 12 patients (6 males and 6 females with an average age of 16.8 years, range 4 months to 27 years) with the Prader-Labhart-Willi syndrome (PLWS). Five patients were previously identified with high-resolution analysis as having the 15q chromosomal deletion, whereas 7 patients had normal chromosomes. Hypopigmentation was observed in all 5 patients with the 15q deletion. Of the 7 individuals with normal chromosomes, two were hypopigmented and 5 had normal pigmentation. Fasting (6 to 12 hours) plasma samples were analyzed for immunoreactive β -MSH in the 12 PLWS individuals. Plasma immunoreactive β -MSH (LPH) levels were within the normal range in all 12 individuals. There was no significant difference in the plasma immunoreactive β -MSH concentrations between patients who did and did not have the chromosomal deletion or in those who were or were not hypopigmented. Thus, a decrease in circulating plasma immunoreactive β -MSH (LPH) does not appear to be the cause of the hypopigmentation observed in some patients with PLWS.

Keywords

Prader-Labhart-Willi syndrome; β -melanocyte stimulating hormones; hypopigmentation; chromosome 15 deletion

INTRODUCTION

Prader-Labhart-Willi syndrome (PLWS) was first described by Prader et al [1956], and subsequently over 500 cases have been reported [Holm et al, 1981; Butler et al, 1986]. Individuals with PLWS, which is generally sporadic in occurrence, have infantile hypotonia, early childhood obesity, mental deficiency, short stature, small hands and feet, hypogonadism and a characteristic facial appearance. About 50% of patients with PLWS

have a deletion of the proximal long arm (15q11-q12) of chromosome 15 [Ledbetter et al, 1982; Mattei et al, 1984; Butler et al, 1986].

Decreased cutaneous pigmentation in patients with PLWS has been observed in several individuals, but was not a recognized component of this syndrome until recently. In 1982, Hittner et al described hypopigmentation in 9 PLWS individuals with the 15q deletion. Butler et al [1986] reported a series of 39 PLWS individuals (21 with 15q deletion and 18 without deletion) and noted that those individuals with the chromosome deletion had lighter hair, eye, and skin color and greater sun sensitivity than individuals with normal chromosomes. They proposed that a DNA segment on proximal 15q, which is deleted in approximately one-half of PLWS patients, plays a role in pigment development. More recently, Wiesner et al [1987] studied 29 individuals with PLWS for cutaneous and ocular pigmentation and found that 48% of the PLWS individuals were hypopigmented. The presence of hypopigmentation also correlated with the 15q deletion. They concluded that the mechanism for hypopigmentation in PLWS is unknown, although hairbulb tyrosinase activity and glutathione levels were low in PLWS patients with and without hypopigmentation. They also reported that hypopigmentation was not limited to neural crest-derived melanocytes.

We studied 12 PLWS patients in order to determine if hypopigmentation in these individuals is secondary to decreased levels of immunoreactive (IR) β -melanocyte-stimulating hormone (β -MSH), which in normal subjects reflects the combined concentrations of β -lipotropin (β -LPH) and γ -lipotropin (γ -LPH), both of which contain the full β -MSH amino acid sequence.

MATERIALS AND METHODS

Twelve PLWS patients (6 males and 6 females with an average age of 16.8 years and a range of 4 months to 27 years) were studied. All patients had been characterized previously by high resolution chromosome procedures [Butler et al, 1986]. Five PLWS individuals were identified with the deletion of the proximal long arm of chromosome 15, including our youngest patient, and 7 individuals had normal chromosomes. In all 5 individuals with the 15q deletion, hypopigmentation was observed. Of the 7 individuals with normal chromosomes, 2 were found to have hypopigmentation, based on criteria established by Butler et al [1986], while 5 had normal pigmentation.

Random daytime fasting (6 to 12 hours) plasma samples from the 12 PLWS individuals were obtained and frozen at -70°C for assay at a later time [Nicholson et al, 1984]. Samples were analyzed by radioimmunoassay [Nicholson et al, 1984] using antiserum R2489/12, which cross-reacts 467. and 857. as well with human β -LPH and γ -LPH, respectively, as with synthetic human β -MSH [human LPH-(35–56)] on a molar basis [Wilson et al, 1981]. Synthetic human β -MSH, a gift of Ciba-Geigy, Ltd., Basel, Switzerland, was used as a radioiodinated tracer and reference standard. Student's *t* tests were used throughout for statistical analysis.

RESULTS

The plasma IR- β -MSH levels and clinical data on the PLWS individuals are shown in Table I. The average IR- β -MSH level was 21.6 ± 13.8 pg/ml (mean $\pm$ SD) and 25 ± 10.2 pg/ml for the deletion and normal chromosome PLWS groups, respectively. The average plasma IR- β -MSH concentration for the total PLWS patient group was 23.6 ± 11.4 pg/ml. There was no significant difference in the plasma IR- β -MSH levels between the two PLWS sub-groups ($t=0.04$; $p>.05$), or between individuals with (20.3 ± 11.5 pg/ml) or without (28.2 ± 10.5 pg/ml) hypopigmentation ($t=1.21$; $p>.05$). All of the patients' plasma IR- β -MSH levels were detectable and were within the normal range.

DISCUSSION

The identity of the major pigmentary hormone in man is not clear, and the relative potencies of the various peptides which have been demonstrated to have melanocyte-stimulating activity depends in part upon the bioassay system used. All of the known melanocyte-stimulating hormones are derived from a common biosynthetic precursor molecule called proopiomelanocortin, the gene for which has been assigned to chromosome 2p23–25 [Owerbach et al, 1981; Zabel et al, 1983], and all share a common core amino acid sequence. Adrenocorticotropin (ACTH) and γ -MSH are thought to be weak melanocyte-stimulating hormones. It was long believed that α -MSH, which is derived from the amino-terminus of ACTH, was the most potent melanocyte-stimulating hormone [Ney et al, 1965]. However, α -MSH is present in very low or undetectable concentrations in normal human plasma [Abe et al, 1967; Orth DN, unpublished observations]. The next most potent melanocyte-stimulating hormone was thought to be β -MSH [Pickering and Li, 1963]. However, it was demonstrated first by Bloomfield et al [1974] and subsequently by many others, that β -MSH does not normally exist in human plasma. Immunoreactive β -MSH actually represents γ -LPH and γ -LPH, both proopiomelanocortin products that contain the β - MSH amino acid sequence. The LPHs were thought to be weak melanocyte-stimulating hormones until Carter and Shuster [1979] reported that β -LPH was 2.6 to 4 times more potent than α -MSH itself. This appears to be due to the potentiating effect of the carboxy-terminal tetrapeptide of β -LPH, which is also present in β -endorphin, on the melanocyte-stimulating core sequence in β -LPH and γ -LPH [Carter et al, 1979]. Thus, it would seem that β -LPH or the combination of its two cleavage products, γ -LPH and β -endorphin, are the best candidates for the principal pigmentary hormone(s) in man.

Our results indicate that the hypopigmentation found in PLWS individuals is not associated with low levels of the LPHs. The defect may lie in the melanocyte-stimulating hormone receptor of melanocytes or in post-receptor mechanisms involved in melanocyte-stimulating hormone action. Additional research will be required to elucidate the pathogenesis of the hypopigmentation associated with Prader-Labhart-Willi syndrome.

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Clinical Data and Plasma Immunoreactive β -Melanocyte Stimulating Hormone Concentrations in 12 Individuals With Prader-Labhart-Willi Syndrome**TABLE I.**

Individual	Age(y)	Sex	Chromosome status	Pigmentation status*	Plasma IR- β -MSH (normal <50 pg/ml)
RS	0.3	F	del(15q)	hypopigmentation	40
RM	8	M	del(15q)	hypopigmentation	15
EF	9	F	del(15q)	hypopigmentation	31
DO	18	M	del(15q)	hypopigmentation	5
KO	24	F	del(15q)	hypopigmentation	17
KJ	7	F	46,XX	normal	24
EH	18	M	46,XY	normal	29
SS	19	M	46,XY	normal	21
MP	22	F	46,XX	normal	21
IJZ	24	M	46,XY	hypopigmentation	16
CD	25	F	46,XX	normal	46
RB	27	M	46,XY	hypopigmentation	18

* pigmentation status based on hair and eye color, skin complexion and sun sensitivity as previously described by Butler et al, 1986.