GROWTH HORMONE RESPONSE TO GASTRECTOMY

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It is widely known that increase of plasma human growth hormone (HGH) levels during the period of surgical trauma is due to a mechanism which is different to that producing hypoglycemic stimulation. However, no evidence has yet been found to explain the role of HGH increment in the patient who has undergone surgery nor the disparity of HGH response between such patients. It is thought that the adipokinetic factor and the diabetogenic action of this hormone are greatly influenced in subjects under surgical stress. In this study, the plasma HGH levels were determined by the radioimmunoassay technique during the pre-, intra- and post-operative periods in either peptic ulcer or gastric cancer patients who had undergone gastrectomy. Simultaneous analysis of plasma non-esterified fatty acid (NEFA) and blood sugar was carried out in an attempt to relate these levels to that of HGH.

SUBJECTS AND METHODS

Twenty subjects with peptic ulcer and fourteen subjects with gastric cancer were selected for this study from the surgical ward of the Keio University Hospital. These subjects, 28 male and 6 female, showed no clinical evidence of endocrine, renal, hepatic or neurogenic disorder. Preoperative patients showing poor risk were absolutely excluded from this study, as were those who underwent emergency surgery due to bleeding or perforation. General anesthesia was given to all the subjects, with the introduction of intravenous sodium pentothal and anesthesia was maintained with nitrous oxide and fluothane inhalations. Infusions administered during surgery were limited to either 5% glucose solution

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or lactated Ringer's solution. Blood specimens were taken at 8 a.m. on the operative day, immediately after induction of anesthesia, on commencement of surgery and thereafter at 15, 30 and 60 minutes and 2, 4, and 6 hours, and at 8 a.m. on the postoperative days 1, 3, 5 and 7. All specimens were withdrawn by heparinized syringes, centrifuged immediately and the plasma samples kept at $-20^\circ$C in a freezer prior to assay. HGH was quantified by a modification of the method of Schalch and Parker, blood sugar by an autoanalyser incorporating a modification of Hoffman's method, and plasma NEFA by Dole's method.

RESULTS

PLASMA HGH.—The preoperative levels of all the subjects except two were under 5 ng/ml with a mean value of 2.82 ng/ml ± 0.42 S.E. These levels were raised in all the subjects immediately after the commencement of surgery, reached a mean peak value of 30.0 ng/ml ± 4.89 S.E. at 60 minutes, gradually fell despite the continuation of surgery, and regained their preoperative levels at four to six hours after commencement of surgery. In our results, it is likely that the peak levels of the subjects with cancer were higher than those of the benign subjects. The smallest fluctuations from the preoperative levels were seen during the 1st to 7th postoperative days (Fig. 1).

FACTORS INFLUENCING HGH RELEASE.

Age: Comparison was made between the seven subjects below 40 years of age and the five subjects above 60 years of age. In the former subjects, the HGH levels reached a peak at one hour after the commencement of surgery and were maintained for up to two hours after. However, in the latter subjects, the levels showed a decreasing tendency after passing the peak at one hour after the commencement of surgery and recovered to levels under 10 ng/ml after two hours (Fig. 2a). The HGH response to surgical stress in the older age group is thought to be terminated earlier than that of the younger group.

Sex: The female subjects were few, limited to five in this study, and, no significant difference in the mean values was found when compared with the men (Fig. 2b).

Obesity: No abnormally obese subjects were observed. In order to distinguish the difference of response to surgical stress between obese and lean subjects, those which exceeded the range of ±10% from the standard weight defined by Broca's modification ((Height-100)/100) were classified as obese or lean. The former group included 3 subjects and the latter 15. In the obese group, the HGH response was relatively more rapid attaining a higher peak than in the lean group within 15 minutes after commencement of surgery (Fig. 3a).
Fig. 1. (mean ± S.E.) The level of plasma human growth hormone (HGH) is elevated immediately after the commencement of surgery regardless of fluctuation of blood sugar, arrived at a peak after 30 to 60 minutes, and thereafter gradually fell despite the continuation of surgery.

P.: preoperative, Anes.: induction of anesthesia, OP: 0, 15 and 30 minutes after commencement of surgery, POD: postoperative days.

Fig. 2. (a-upper, b-lower) (mean ± S.E.) (Comparison of plasma human growth hormone (HGH) levels divided by the sex and age. a) Elevated levels of HGH are kept to two hours after the commencement of surgery in the subjects above 60 years of age. b) The difference between male and female subjects is insignificant.

P.: preoperative, Anes.: induction of anesthesia, OP: 0, 15 and 30 minutes after commencement of surgery, POD: postoperative days.
Fig. 3. (a-upper, b-lower) (mean ± S.E.) a) Comparison between obese and lean. The immediate elevation to the peak is observed in obese subjects. b) Comparisons of magnitude of surgical stress. No marked difference between two groups; (A) extensive radical gastrectomy for carcinoma, lasting 3 hours and with intraoperative bleeding exceeding 300 ml, (B) simple gastrectomy, lasting 50 to 80 minutes.

P.: preoperative, Anes.: induction of anesthesia, OP.: 0, 15 and 30 minutes after commencement of surgery, POD: postoperative days.

Fig. 4. (mean ± S.E.) Comparison of the nature of infusions during surgery. The human growth hormone (HGH) responses showed similar patterns in the two groups received either glucose or lactated Ringer's despite the existence of these differences in fluctuation of blood sugar.

NEFA: non-esterfied fatty acid, P.: preoperative, Anes.: induction of anesthesia, OP.: 0, 15 and 30 minutes after commencement of surgery, POD: postoperative days.
MAGNITUDE OF SURGICAL STRESS.—In order to investigate the difference in HGH response according to the intensity of surgical stress, 9 subjects with simple gastrectomy lasting 50 to 80 minutes were compared with 6 subjects with surgery lasting 3 hours and with intraoperative bleeding exceeding 300 ml. Except for a divergence of the peak periods between these groups, no marked difference regarding the peak levels and the tendency to recovery was seen (Fig. 3b).

INTRAOPERATIVE INFUSION.—The subjects were divided into two groups according to the nature of infusions received, that is, those receiving 5% glucose and those receiving lactated Ringer's solution. In the group which received lactated Ringer's solution, the blood sugar levels gradually rose up to six hours after commencement of surgery. In the majority of these subjects, plasma NEFA levels increased from the time of anesthetic induction and reached peak levels after four hours. In the group which received 5% glucose, in marked contrast, the blood sugar levels rose rapidly immediately following anesthetic induction, fell following the peak levels at 15 minutes, and rose again after four hours. Despite these differences in fluctuation of blood sugar, the HGH responses showed very similar patterns in the two groups. In the glucose administered group, the NEFA levels decreased from the beginning of glucose administration and gradually recovered from 30 minutes to six hours after (Fig. 4). Although the fluctuation of plasma NEFA was different according to the nature of infusions administered to individual subjects, the peak levels were attendant upon those of HGH. Therefore, it is suggested that the increment of HGH release plays an important role in fat metabolism.

DISCUSSION

Since the recent introduction of an easier technique of radioimmunoassay for the determination of plasma HGH, many reports have been received of an increased release of HGH in response to surgical stress. This HGH response was not found to be restrained by the hyperglycemia which appeared during surgery. It is also reported that HGH response was observed during advanced hyperglycemia in diabetic subjects. It is well recognized that factors such as age, type of stress, and obesity are related to the HGH response. It is also well known that HGH has an adipokinetic and anabolic effect, and diabetogenic action. When HGH is copiously released endogenously during surgical stress, it markedly affects metabolism during the postoperative period, contributing particularly to an increase in fat metabolism and the incidence of diabetogenicity of surgery.
Glick and his associate investigated the HGH response of nine subjects undergoing surgery with general anesthesia, of which six patients undergoing major surgery showed a rise in HGH level, but three subjects with intravenous anesthesia did not. Ketterer and his associate observed a rise in HGH in 11 of 19 subjects undergoing varying types of surgery, the peak level existing at between 2 and 4 hours after commencement of surgery. These peak levels were maintained for from several hours to a few days and it was concluded that HGH response paralleled the magnitude of surgery. Schalch reported a rise of plasma HGH and plasma NEFA in 9 subjects who had undergone laparotomy for major surgery and suggested that between these two there was a reciprocity of response. Charter and his associate observed a fluctuation of the level of pituitary hormone in 13 subjects who had undergone various types of surgery, and found an increased release of HGH with the peak level at one hour after commencement of surgery, a recovery to the preoperative level after 3 hours, and a subsequent rise during fasting on the first postoperative day. From the above it is seen that different workers reported a rise in HGH after surgery at different postoperative times. The main reason for these disparities between investigators is considered to be due to the varying magnitude of surgical stress. We, therefore, investigated HGH response only for subjects who had undergone gastrectomy, and our analysis was confined to factors relating to the surgery. In our investigation, an increase of HGH level exceeding 10 ng/ml was observed in all the subjects, the peak levels recorded at between 30 and 60 minutes after commencement of surgery, and subsequent recovery to the preoperative level observed 4 hours after. In view of this response, it is considered that gastrectomy is a major stimulus for the release of pituitary reserves of HGH. For a major degree of stimulation, HGH release is thought to rise rapidly but to continue at this high level for a relatively short period.

As previously reported, female patients were found to be more sensitive to a small stimulation as regards HGH response than male patients, but it has been observed that HGH response to major surgery, such as gastrectomy, is indiscriminative between the sexes. In our study, there was an earlier response of release of HGH in obese subjects than in lean subjects. Although the mobilisation of fat is related to a response of various hormones, particularly in those of sympathetico-adrenal system and the anterior lobe of the pituitary gland, the growth hormone plays as an important factor regarding fat metabolism. An increase in fat metabolism is related to an increase of plasma NEFA. Previous investigators have reported a two-fold increase of plasma NEFA within one or two hours of administration of 1 to 2 mg of growth hormone in adults. In animal experiments, it was ascertained that blocked free fatty acid mobilisa-
tion due to hypophysectomy is freed to normal level by the replacement of growth hormone. The growth hormone which is intrinsically excessively released was considered to produce these effects. In our investigation, it has been found that the peak period of NEFA rise after surgery is always attendant upon the peak period of HGH rise. This indicates that the released growth hormone on surgical stress plays an important role in fat metabolism during this period.

**SUMMARY**

The fluctuation of the plasma level of human growth hormone (HGH), in relation to blood sugar and plasma non-esterified fatty acid (NEFA) levels, was investigated, both before and after surgery, in thirty-four subjects, who had received gastrectomy due to either peptic ulcer or gastric cancer. The level of HGH was markedly elevated immediately after the commencement of surgery and arrived at a peak after 30 to 60 minutes. Thereafter the level gradually fell despite the continuation of surgery. Up until the seventh postoperative day the levels during fasting showed no marked fluctuation. These HGH fluctuations bore no definite relationship to the nature of intra-operative infusions, age, sex, obesity or magnitude of surgical stress. From the fact that the elevation of NEFA release followed the elevation of HGH, it is recognized that increased release of HGH upon surgical stress greatly contributes to fat metabolism during this period. It is also suggested that the release of HGH might induce a fall in glucose utilization resulting in a diabetogenicity immediately after surgical stress.

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**REFERENCE**