The effect of food deprivation on brain and gastrointestinal tissue levels of tryptophan, serotonin, 5-hydroxyindoleacetic acid, and melatonin

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Abstract: In order to investigate the effect of food deprivation on the levels of indoles in the brain and the gastrointestinal tissues, we have determined tissue levels of tryptophan (TRP), serotonin (5-HT), 5-hydroxyindoleacetic acid (5-HIAA), and melatonin in the brain and the gastrointestinal tract (GIT) of mice on ad libitum diet as well as in mice deprived of food for 24 and 48 hr. The reduction of food intake 1) had no effect on TRP levels in the brain, but increased TRP concentrations in the stomach and the gut, especially in the colon; 2) decreased 5-HT levels in the brain, but increased values in the stomach and the intestines; 3) decreased 5-HIAA levels in the brain, but increased them in the stomach and the intestines; 4) did not change 5-HT conversion to 5-HIAA in the brain, stomach, and the jejunum, but increased the conversion in the ileum and colon and; 5) increased melatonin levels in all tissues investigated, particularly in the stomach and the brain. The changes of indole levels induced by food deprivation were compared to their known function in the brain and the individual segments of the GIT. A possible serotonin-melatonin antagonism in the brain and GIT function is considered.

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Introduction

Serotonin (5-hydroxytryptamine) (5-HT), which is a metabolite of tryptophan, is a well established neurotransmitter produced and active in nervous tissues [Ungerstedt, 1971; Garattini et al., 1989], the circulatory system [Folk and Long, 1988] and the digestive tract [Ormsbee and Fondacaro, 1982; Furness and Costa, 1987].

Melatonin (5-methoxy-N-acetyltryptamine) is a biological derivative of serotonin, which was first isolated from the bovine pineal gland [Lerner et al., 1958]. Despite the fact that the M-synthesizing enzyme HIOMT (hydroxyindole-O-methyltransferase) has been also measured in the retina [Quay, 1965], Harderian gland [Cardinali and Wurtman, 1972] and the gut [Quay and Ma, 1976], localization of melatonin in these tissues by immunohistology [Bubenik et al., 1974, 1976, 1977; Raikhlin and Kvetnoy, 1976; Holloway et al., 1980; Vivien-Roels et al., 1981] was initially greeted with skepticism.

During the last 10 years, the localization, the origin, and the physiological function of melatonin in the retina [Pang and Allen, 1986; Wiechmann and Steen, 1990] and the Harderian gland [Hoffman et al., 1989; Menendez-Pelaez et al., 1988] have been studied to a great extent. Conversely, the localization and origin of melatonin and its physiological role in the digestive system have been investigated only rarely [Fioretti et al., 1974; Quastel and Rahamimoff, 1965; Bubenik, 1980, 1986; Vakkuri et al., 1985; Harlow and Weekly, 1986; Bubenik and Dhanvantari, 1989].

In several studies investigating the role of indoles in digestive physiology, an antagonistic relationship between 5-HT and melatonin has been discovered [Quastel and Rahamimoff, 1965; Fioretti et al., 1974; Bubenik, 1986; Bubenik and Dhanvantari,

1989]. These findings increased our interest in this topic and led us to postulate a mutually antagonistic serotonin-melatonin equilibrium system contributing to the maintenance of gastrointestinal homeostasis [Bubenik and Dhanvantari, 1989].

In order to foster the investigation of the role of serotonin and melatonin in gastrointestinal physiology and to explore the possible mechanisms of brain-gut interactions, we have herein studied the effect of food intake on brain, stomach, and gut levels of 5-HT and melatonin and of the 5-HT precursor and metabolite, tryptophan (TRP) and 5-hydroxyindoleacetic acid (5-HIAA) respectively.

Material and methods

Experimental animals

Three groups of adult Swiss-Webster mice (six animals per group) kept on a 12:12 light:darkness photoperiod were either fed Purine Rat Chow (Ralston Purine Canada, Lonqueuilè, Quebec) ad libitum (controls—C), or kept without food for 24 hr (post-absorptive—PA) or 48 hr (fasted—F). Animals in each group were sacrificed in the middle of a photophase by decapitation and their brain, stomach, and the gut tissues were quickly removed and frozen in liquid nitrogen. The small intestine was divided into two equal parts labelled as "jejunum" (containing also the duodenum) and "ileum". The large intestine, including the colon, caecum, and rectum, was removed separately and labelled as "colon". The samples were frozen at −70°C for later assay by high performance liquid chromatography (HPLC). Three other groups (C, PA, and F; N = 13, 6, 6) of mice were handled identically, and the tissues frozen in dry ice were shipped to University of Hong Kong for the determination of melatonin.

Since no differences in indole levels of males and females were detected in preliminary experiments, animals of both sexes were used in this study.

Detection techniques

HPLC detection. TRP, 5-HT and 5-HIAA were determined from the same tissue sampling using HPLC according to the method described previously [Laycock and Ball, 1990]. The values were expressed in nmol per gram of tissue.

RIA determination. Brain, stomach, and gut samples were first weighed and then extracted as described earlier [Pang et al., 1982]. Melatonin levels were measured by a specific RIA as previously detailed [Brown et al., 1985]. The intraassay and interassay coefficient of variations of our RIA were 6.2% (N = 5) and 16.5% (N = 7), respectively [Pang and Yip, 1988]. The detection limit of our assay is about 0.02 pmol per gram of tissue.

Data evaluation

Statistical analysis. To calculate statistical differences a one-way analysis of variances (ANOVA) was performed after Scheffe. The level of significance was expressed either as $P < 0.05$ or $P < 0.001$. Differences between C, PA, and F groups for each organ, e.g., brain, stomach, jejunum, ileum, and colon as well as differences in levels of indoles between organs in each treatment group, e.g., C, PA, and F were then determined.

5-HIAA/5-HT index. This index expresses ratio of 5-HIAA to 5-HT. A high index indicates a rapid utilization of 5-HT, which is converted to its main metabolite, 5-HIAA [Perez-Cruet et al., 1972].

Results

Tryptophan (Fig. 1)

Brain: No differences were found between groups. *Stomach:* C levels were lower than those in PA ($P < 0.05$). *Jejunum:* C levels were lower than those in PA and F ($P < 0.001$) and PA values were lower than those in F ($P < 0.001$). *Ileum:* Both C and PA levels were lower than F values ($P < 0.001$). *Colon:* C values were lower than those in PA and F groups ($P < 0.001$), and PA was lower than F ($P < 0.001$).

Controls. Brain levels were higher than those in the stomach and jejunum ($P < 0.001$) but lower than values in the ileum ($P < 0.001$). Stomach and jejunum levels were lower than those in brain, colon, and ileum ($P < 0.001$). *Post-absorptive:* No difference between samples was found. *Fasted:* Stomach levels were lower than any other organ but brain ($P < 0.001$). Brain values were higher than those in the stomach and jejunum ($P < 0.001$) but lower than levels in the ileum and colon ($P < 0.001$).

Serotonin (Fig. 2)

Brain: C levels were higher than those in PA or F ($P < 0.001$). *Stomach:* C levels were lower than values in PA or F ($P < 0.001$), but PA levels were higher than those in F ($P < 0.05$). *Jejunum:* Control levels were lower than those in PA ($P < 0.05$) and F ($P < 0.001$). PA levels were lower than those

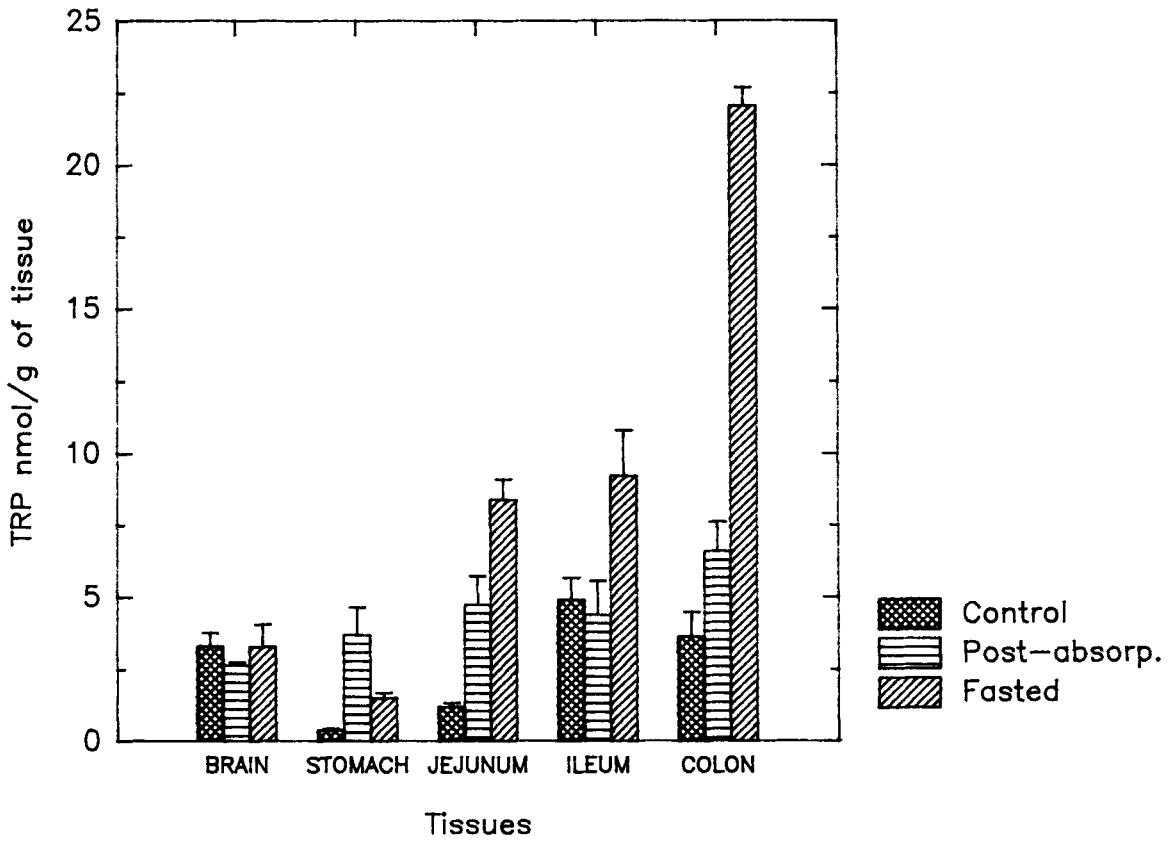

Fig. 1. Tissue levels of tryptophan (TRP) in the whole brain and the individual segments of the GIT of mice fed ad libitum (control) and food deprived for 24 hr (post-absorptive), and 48 hr (fasted). Vertical bars represent standard errors. N is 6 for each group. Sample labelled jejunum also contains duodenum and sample labelled colon contains the whole large intestine including caecum. Note the very low levels of TRP in the stomach of controls and very high TRP concentrations in the colon of fasted mice.

in F ($P < 0.001$). *Ileum:* Lower levels were detected in PA as compared to C ($P < 0.001$). *Colon:* Lower levels were detected in PA and F as compared to C ($P < 0.001$).

Control. Brain levels were lower than concentrations in the ileum ($P < 0.05$) and colon ($P < 0.05$). Colon levels were higher than those in brain, stomach, jejunum ($P < 0.001$) and ileum ($P < 0.05$). *Post-absorptive:* Levels in brain were lower than those in the stomach and colon ($P < 0.001$). Stomach levels were higher than those in the brain, jejunum, and ileum ($P < 0.001$), but not different from those in the colon. Jejunum levels were lower than those in the colon ($P < 0.001$). *Fasted:* Brain concentrations were lower than those in the stomach, ileum, or colon ($P < 0.001$). Stomach levels were lower than those in the colon ($P < 0.001$).

5-Hydroxyindoleacetic acid (Fig. 3)

Brain: Levels in C were higher than those in PA or F ($P < 0.001$). Levels in PA were higher than values in F ($P < 0.05$). *Stomach:* Levels were lower in C than in PA ($P < 0.05$) or F ($P < 0.001$). P levels were lower than in those in F ($P < 0.05$). *Jejunum:* C levels were lower than values in PA or F ($P < 0.001$). PA levels were lower than in F ($P < 0.001$). *Ileum:* C levels were lower than values in PA or F ($P < 0.001$). PA levels were lower than those in F ($P < 0.05$). *Colon:* C levels were lower than PA or F values ($P < 0.001$). PA levels were lower than those in F ($P < 0.05$).

Control: Significantly higher levels were determined in the brain than in any other tissue ($P < 0.001$). Colon values were higher than levels in all other tissues but brain ($P < 0.001$). *Post-absorptive:* Brain values were higher than levels in any other tissue ($P < 0.001$). Colon levels were higher than those in the stomach, jejunum, and ileum ($P < 0.001$). Jejunum values were higher than those in the stomach ($P < 0.001$). *Fasted:* Brain levels were higher than those in the stomach and the ileum ($P < 0.001$). Colon levels were higher than values in the stomach and the ileum ($P < 0.001$).

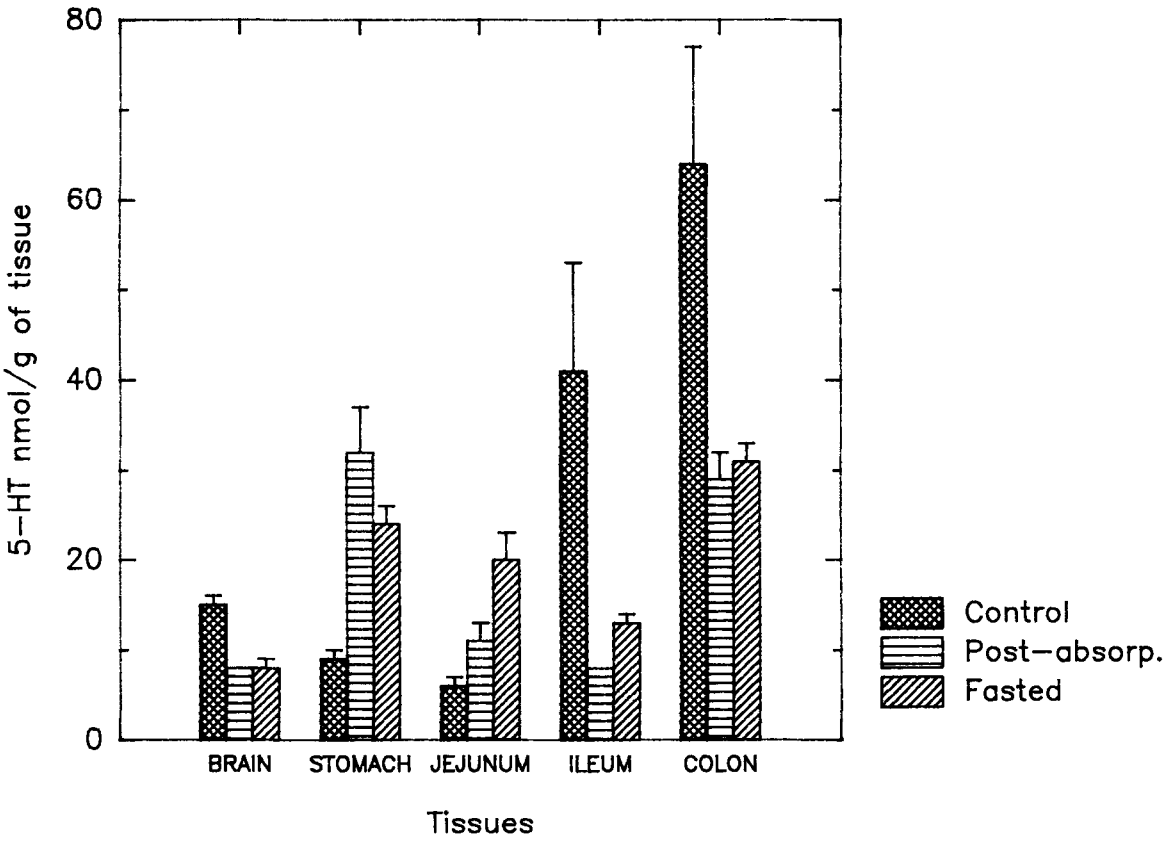

Fig. 2. Tissue levels of serotonin (5-HT) in the brain and the GIT of control, post-absorptive, and fasted mice. See Figure 1 for experiment details. Note the high 5-HT levels in the ileum and the colon of control mice.

5-HIAA/5-HT index (Fig. 4)

Brain, Stomach and Jejunum: No difference was found between samples. *Ileum:* Control levels were lower than those in PA and F ($P < 0.001$). *Colon:* Control values were lower than those in PA and F ($P < 0.001$).

Control: Brain levels were higher than in any other tissue ($P < 0.001$). Jejunum values were higher than those in the stomach and the ileum ($P < 0.001$). *Post-absorptive:* Brain levels were higher than those in any other tissue ($P < 0.001$). Ileum levels were higher than values in the stomach ($P < 0.001$). *Fasted:* Brain levels were higher than those in any other tissue but the jejunum ($P < 0.001$). Jejunum values were higher than those of ileum ($P < 0.001$) and the stomach ($P < 0.001$).

Melatonin (Fig. 5)

Brain: Significantly higher melatonin levels were detected in F as compared to C and PA ($P < 0.001$). *Stomach:* Levels in F were higher than levels in C or PA ($P < 0.001$); PA levels were lower than those in C ($P < 0.001$). *Jejunum:* F levels were higher than PA or C values ($P < 0.001$). *Ileum:* No significant differences between groups were found. *Colon:* F levels were higher than those in PA ($P < 0.05$) or C ($P < 0.001$).

Control: Stomach values were higher than any other tissue ($P < 0.001$). Brain levels were lower than those in the stomach and the ileum ($P < 0.001$). *Post-absorptive:* Brain values were lower than concentrations in any other tissue but the stomach ($P < 0.001$). Jejunum and ileum levels were higher than those in the stomach ($P < 0.001$). Stomach levels were lower than those in the colon ($P < 0.05$). *Fasted:* Stomach levels were higher than those in any other tissue ($P < 0.001$).

In summary, the reduction of food intake in mice had 1) no effect on TRP concentrations in the brain but increased TRP levels in the stomach and the gut, especially in the colon; 2) decreased 5-HT levels in the brain, ileum, and colon, but increased concentrations in the jejunum and ileum; 3) decreased 5-HIAA levels in the brain but increased values in the stomach and in the intestines; 4) no influence on

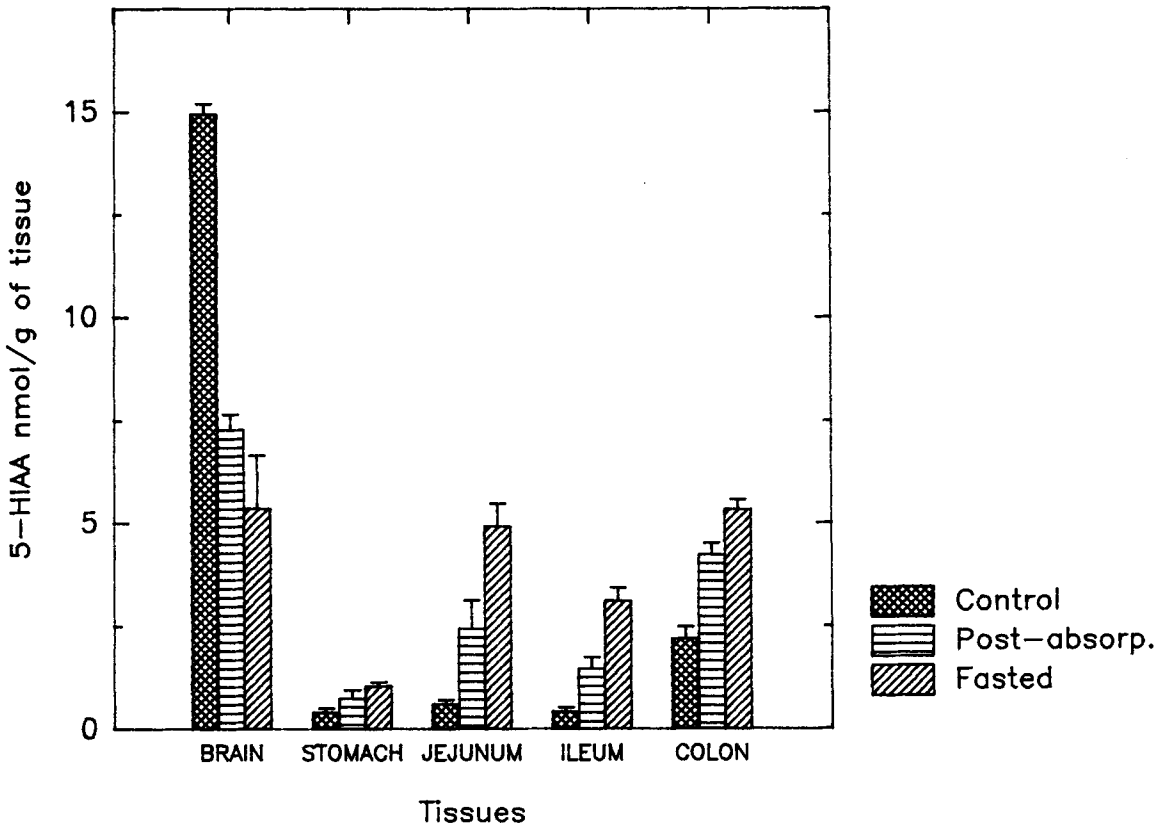

Fig. 3. Tissue levels of 5-hydroxindoleacetic acid (5-HIAA) in the brain and the GIT of control, post-absorptive, and fasted mice. Note the high levels of 5-HIAA in the brain tissue.

the 5-HT conversion to 5-HIAA in the brain, stomach, and the jejunum, but increased the conversion in the ileum and the colon and, 5) increased melatonin levels in most tissues, particularly in the stomach and the brain.

Discussion

Regulation of food intake and digestion is a complex, not yet well understood process, which requires an interaction between the CNS and the gastrointestinal tract (GIT). It involves variety of gastrointestinal hormones (e.g., gastrin, somatostatin, endorphins, cholecystokinin, substance P, VIP), biogenic amines, (such as noradrenalin and dopamine), and indoles (such as 5-HT and melatonin), which are located and acting in both the CNS and the GIT [Ahslkog and Hoebel, 1973, Powell and Skrabanek, 1973]. Recently, it was suggested that indoles may act as auxiliary substances that modulate levels of GIT hormones, particularly gastrin [Levinski et al., 1990].

The contribution to the central as well as peripheral regulation of GIT activity by 5-HT is well documented. 5-HT has been discovered in the enterochromaffin cells (EC) of the GIT mucosa by Erspamer and Asero [1952]. 5-HT affects smooth muscles of the intestine either directly or indirectly via enteric or extrinsic nerves [Furness and Costa, 1987]. Experimental evidence indicates that 5-HT may serve as a local regulator of gastrointestinal motility [Holloway et al., 1980; Bubenik, 1986; Bubenik and Dhanvantari, 1989]. Beside the effect on the GIT muscles, 5-HT is also directly or indirectly involved in the regulation of food intake [Pollock and Rowland 1981; Garrattini et al., 1989; Morley 1989; Leibowitz 1990].

The role of melatonin in the food intake and digestion is still very much obscure. Melatonin has been localized in the GIT primarily by immunohistology [Raikhlin and Kvetnoy, 1976; Bubenik et al., 1977; Bubenik, 1980; Holloway et al., 1980]. Only Vakkuri and co-workers [1985] identified melatonin in the duodenum of a pigeon by RIA, but Gern and co-workers [1986] failed to detect melatonin by RIA in the gut of a trout.

The antagonistic relationship between 5-HT and melatonin on the activity of smooth muscles was first described by Rahamimoff and co-workers [Rahamimoff and Brudermann, 1965; Quastell and

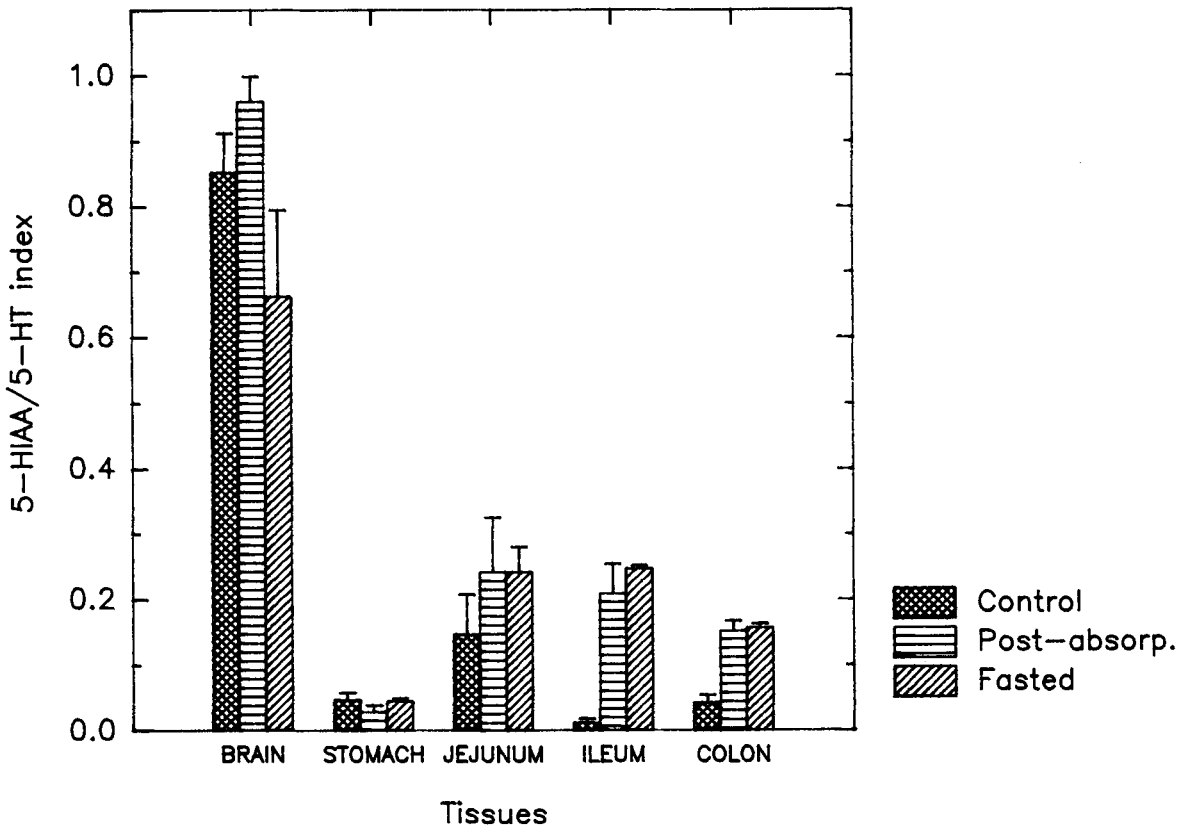

Fig. 4. 5-HIAA/5-HT index in the brain and the GIT of control, post-absorptive, and fasted mice. Compare especially the different indices in the brain and GIT.

Rahamimoff, 1965] and later confirmed by others [Fioretti et al., 1974; Bubenik, 1986]. A recent study by Bubenik and Dhanvantari [1989] indicated that some of the antagonistic action of melatonin on the 5-HT-induced motility changes may be mediated by extra-intestinal structures, presumably the brain. This led us to investigate the effect of food restriction on indole and melatonin levels not only in the GIT tissues, but also in the brain.

Tryptophan levels in the brain changes in response to blood levels of glucose [Fernstrom and Wurtman, 1971]. That brain levels of TRP did not change in our experimental mice (Fig. 1) suggests that blood levels of glucose did not change during the fasting period to the extent that would initiate any alteration of TRP levels in blood. On the other hand, the increase of TRP levels in all other GIT tissue, especially in the colon, may indicate a strong activation of EC cells during starvation, presumably to increase the production of indoles, such as the 5-HIAA (Fig. 3) and melatonin (Fig. 5).

In our study, 5-HT levels in fasted mice were significantly lower in the brain, ileum, and colon, but higher in the stomach and jejunum (Fig. 2). A decrease of brain 5-HT found in our fasted mice may be due to an increase of 5-HT turnover in the brain as reported by Schweiger and co-workers [1989]. Conversely, 5-HT administration decreases food intake in hungry rats [Pollock and Rowland, 1981]. It has been speculated by Morley [1989] that 5-HT causes anorexia by stimulating secretion of CRH within the paraventricular nucleus (PVN) of the hypothalamus. According to this hypothesis gamma-aminobutyric acid (GABA) acts in an opposite way, i.e., it decreases CRH and thus increases food intake. Our data on brain levels of 5-HT and melatonin in fasting mice fits well into that regulatory paradigm. Recent data indicates that melatonin action in the brain is mediated via GABA [Rosenstein and Cardinali, 1986; Niles et al., 1987]. Based on these results, we speculate that fasting stimulates the secretion or uptake of melatonin in the brain (presumably in the hypothalamus) and simultaneously reduces production of 5-HT (Fig. 2). Both actions lead to a reduction of CRH secretion within PVN and thus to the stimulation of the appetite in the fasting animal.

The increase of 5-HT levels we found in the stomach and jejunum, which in our study also contained the duodenum, (Fig. 2) is in agreement

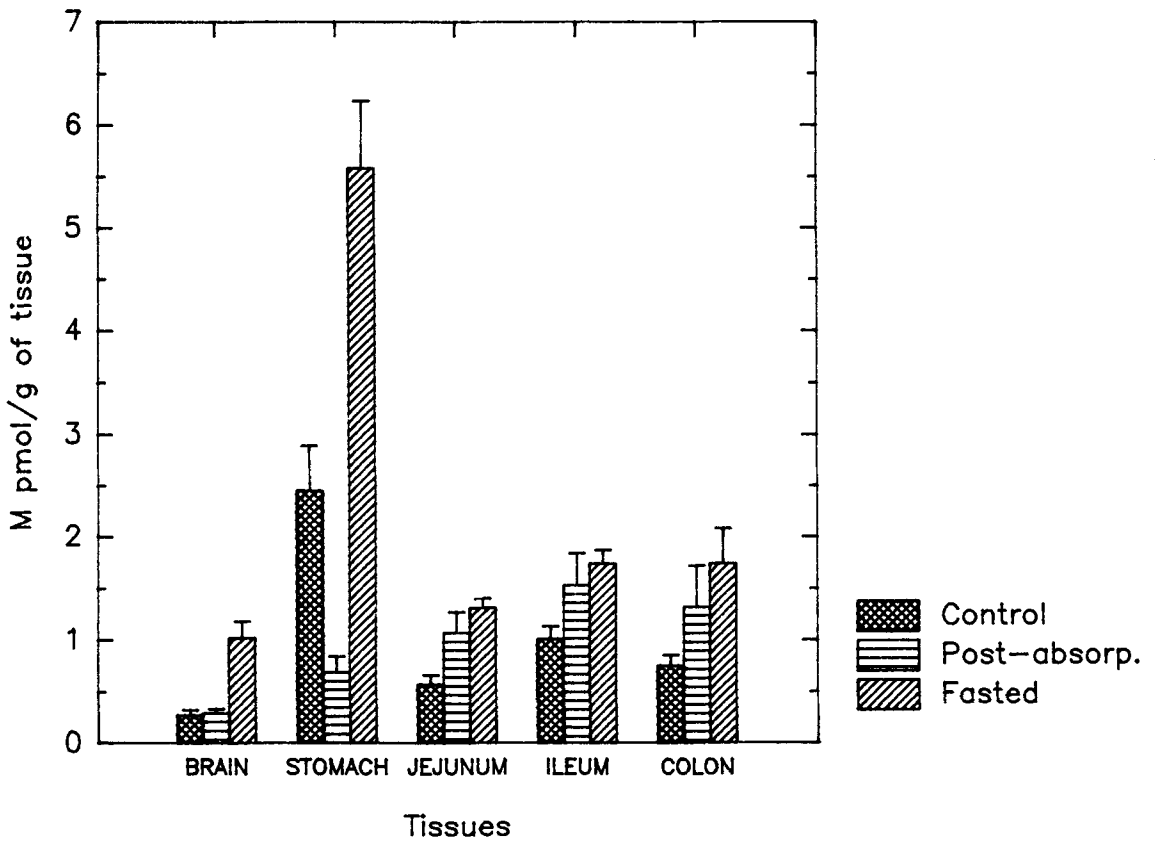

Fig. 5. Melatonin levels in the brain and the GIT of control, post-absorptive, and fasted mice. N = 13 for control, 6 for both post-absorptive, and fasted. Note the remarkable increase of melatonin in the stomach of fasted mice.

with published data. Fasting increased and feeding decreased 5-HT concentration in the stomach and the duodenum [Biggio et al., 1977; Brown, 1979] and an exogenous dose of 5-HT inhibited gastric motor activity [Misiewicz et al., 1966], reduced secretion of hydrochloric acid, and stimulated production of mucus in the stomach [Ormsbee and Fondacaro, 1985]. It can be speculated, therefore, that in fasted animals, all these actions occur in order to reduce stomach activity and to prevent damage to the gastric tissues.

A decrease of 5-HT in the ileum found in our study (Fig. 2) may be related to the degree of propulsive activity, the contractile force, and the intestinal motility that are facilitated by 5-HT [Pilot et al., 1983; Schemann and Ehrlein, 1986; Bubenik, 1986). A similar reduction of 5-HT levels in the colon may be also related to the stimulatory action of 5-HT on the production of colonic mucus [Ormsbee and Fondacaro, 1985]. Activation of mucus synthesis and secretion would be counterproductive in the empty colon.

Results of studies reporting the changes of 5-HIAA/5-HT index in brain tissues as related to food consumption are mixed. In fasted rats, the index increased in the ventromedial nuclei, but decreased in the hypothalamic PVN [Gardier et al., 1989]. In semistarved rats on a high carbohydrate diet, the brain 5-HIAA/5-HT index increased. In contrast, in semistarved rats on a high protein diet, the index decreased 3 hours after the last meal, but increased 24 hr thereafter [Schweiger et al., 1989]. Conversely, Perez-Cruet and co-workers [1972] found a decrease of 5-HIAA in rat brain after food intake. The very high 5-HIAA/5-HT index found in brains of our mice in all three groups indicated a rapid metabolism of 5-HT but fasting does not appear to significantly influence that turnover rate. In contrast, the 5-HIAA/5-HT index increased in the ileum and the colon (Fig. 4). The difference between results in the literature (derived from experiments on rats) and our results (obtained in mice) may be explained by the differences in the duration of fasting. The rats were maintained for several days on a low calorie diet, while our mice were entirely deprived of food for either 24 or 48 hr.

Fasting increased melatonin levels in the brain as well as in most parts of the GIT of our mice (Fig. 5). A literature survey reveals that a reduction in food intake has a significant effect on the pineal activity

and serum melatonin levels. Fasting increases and feeding decreases melatonin binding in the rat pineal [Holloway et al., 1985]. In rats, fasting decreased the N-acetyl-transferase activity in the pineal [Welker and Vollrath, 1984]. In accordance with the above studies, 50% reduction in food intake lasting for 3 weeks, decreased the mid scotophase peak levels of pineal melatonin by 12%. Surprisingly, serum melatonin concentrations were increased by some 34% [Chik et al., 1985]. Underfeeding has also been shown to increase serum melatonin levels in human volunteers [Breitins et al., 1985]. In addition, higher melatonin levels were also reported in blood of human patients suffering from anorexia nervosa [Ferrari et al., 1989; Tortosa et al., 1989]; these patients also exhibited a highly significant reduction in food intake.

If the melatonin synthesis in the pineal is decreased by fasting, what is then causing the increase in the serum levels? It can be speculated that the source of elevated blood levels of melatonin in food deprived animals and humans is the GIT. This elevation of blood melatonin levels in food restricted animals and humans may be the cause of starvation-induced infertility [Brown et al., 1987]. A report of an increased sensitivity of underfed rats to the antigonadotropic effect of exogenously administered melatonin [Blask et al., 1980] supports this hypothesis. Perhaps, the production of melatonin in the GIT in food-deprived animals exceeds the binding capacity of the gut, which causes the release of melatonin into the general circulation. Immunohistological studies indicate that exogenously administered melatonin binds to tissues of the GIT [Bubenik, 1980]. In addition, a preliminary study detected more than a three times higher B_{max} for melatonin in the colon than in the whole brain [Bubenik and Niles, unpublished data]. Higher blood melatonin levels elevated by fasting may then induce a decline of melatonin production in the pineal gland. The relatively low concentration of melatonin in the GIT (the per gram of tissue levels in the stomach of fasted rats are about 28× lower than daytime levels in the pineal [Pang et al., 1985]) are compensated by the huge mass of the GIT tissue. Alternative explanations of higher levels of melatonin in blood of fasting animals would be a decrease of melatonin metabolism or the alteration of levels of hypothalamic catecholamines known to change in relationship to food intake [Ahlskog and Hoebel, 1973].

Fasting significantly increased melatonin levels in most parts of the GIT (Fig. 5). These increases may be related to the previously reported antiserotonin activity of melatonin, such as that reported in vitro in the stomach by Fioretti and co-workers [1974], in the duodenum by Quastell and Rahamimoff [1965] and in the ileum by Bubenik [1986]. Melatonin was also found to reduce gastric ulceration in rats induced by restraint stress [Khan et al., 1990]. Finally, in vivo, melatonin partially alleviated a 5-HT induced facilitation of food transit time in mice [Bubenik and Dhanvantari, 1989].

In our previous publication [Bubenik and Dhanvantari, 1989], we postulated a mutually antagonistic 5-HT-melatonin equilibrium system regulating GIT activity. In our present study, we found opposite changes in tissue levels of 5-HT and melatonin in the brain, ileum, and colon of fasted mice. However, as both hormones simultaneously increased in the stomach and jejunum, the possible confirmation of our hypothesis will have to await the outcome of additional studies. As the regulation of GIT activity is a complex process, the interpretation of our data is limited. Our recent studies investigating the effect of 5-HT and melatonin on the food consumption in mice [G.A. Bubenik, unpublished] appears to confirm that 5-HT and melatonin can influence each other's concentrations [Anton-Tay, 1974; Bubenik and Dhanvantari, 1989]. Therefore, further studies are required to determine the rate of M synthesis in the GIT particularly in relationship to sequential stages of the digestive process. The recent detection and characterization of binding sites for M receptors in the GIT [G.A. Bubenik, L.P. Niles, and P. Pentney, unpublished] is another step in the elucidation of the physiological role of melatonin in the digestive processes.

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