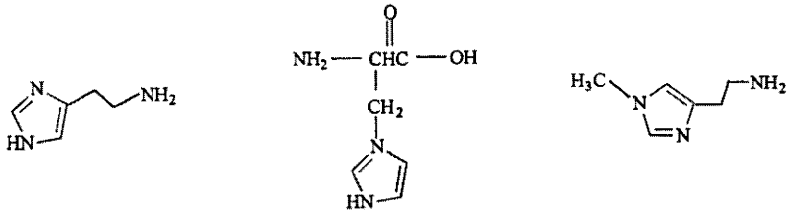

Fig. (1). Some examples of structure of histamine-related molecules.

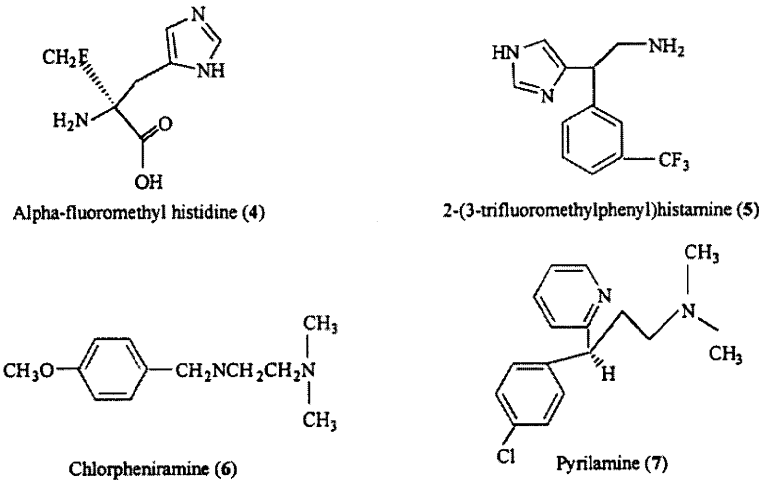

Fig. (2). Some examples of structure of histamine and H_1 receptor-related molecules.

dementia and Meniere's disease, for which it is still used [33]. The unique pharmacologic properties of betahistine point to its potential use as an antiobesity agent [33]. Recent study showed that betahistine induced significant weight loss with minimal adverse events in women [34].

NEURONAL HISTAMINE AND H_3-R ON FOOD INTAKE AND OBESITY

H_3-Rs are pharmacologically identified and predominantly expressed in the brain, where they negatively regulate histamine release, acting as presynaptic autoreceptors [11]. Therefore, H_3-R antagonists/inverse agonists (IAs) have therapeutic potential for treating obesity. Investigations into the role of histamine as a neurotransmitter have shown that histamine inhibits its own neuronal synthesis and release from depolarized slices of the rat cortex *via* presynaptic feedback mechanisms [6-8]. H_3-R IAs are believed to suppress appetite by activating H_1-Rs in post-synaptic areas, because H_3-Rs negatively regulate the release of HA in the brain [6-8]. To address the therapeutic potential of H_3-R ligands as anti-obesity agents, several studies have reported the pharmacological profiles of H_3-R IAs in animal studies [35, 36]. Thioperamide (**8**), an imidazole-containing H_3-R IAs, suppresses food consumption in spontaneous, fast-induced, schedule-induced, and NPY-induced feeding in rodents [35]. In addition, clobenpropit (**9**) and ciproxifan (**10**), imidazole-based compounds, both decreased short-term or long-term energy intake [37, 38]. Contrary, administration of imetit (**11**), H_3-R agonist, to hamsters in the lean state increased food intake [39] (Fig. **3**). Although these reports have suggested the therapeutic potential of H_3-R IAs, their anti-obesity effects remain controversial.

Administration of thioperamide enhanced HA release in the brain, but the treatment did not decrease food intake [40]. In addition, the H_3-R agonist imetit reduces adiposity in DIO mice by inhibiting food intake and increasing energy expenditure. The anti-obese effects of the H_3-R agonist were also confirmed using an H_3-R agonist, *R*-methylhistamine (**12**) [40] (Fig. **3**). Moreover, both intraperitoneal and oral administration of thioperamide enhanced HA release in the brain, while only IP administration caused significant reductions in food intake [41]. Further studies are needed to clarify the involvement of H_3-Rs in food intake and obesity. Several pharmaceutical companies have developed non-imidazole H_3-R IAs [42-44]. As observed in A-331440 (**13**), A-349821(**14**), A-417022 (**15**) and A-423579 (**16**), specific isoforms interacting in different intensities with similar ligands, may have a distinct influence on efficacy in different models [44-46] (Fig. **4**). Among these, A-331440 potently suppresses feeding and body weight gain in diet-induced obese mice [45, 46]. Other imidazole-based H_3 antagonists, including GT-2394 (**17**), reduce cumulative food intake in Sprague Dawley and obese Zucker rats [44]. In addition, NNC-0038-1049 (**18**) and NNC-0038-1202(**19**), structurally distinct H_3-R antagonists, reduced food intake and body weight [47-49] (Fig. **5**). Contrary, ABT-239 (**20**) and JNJ-5207852 (**21**) showed no anti-obesity effects [50, 51]

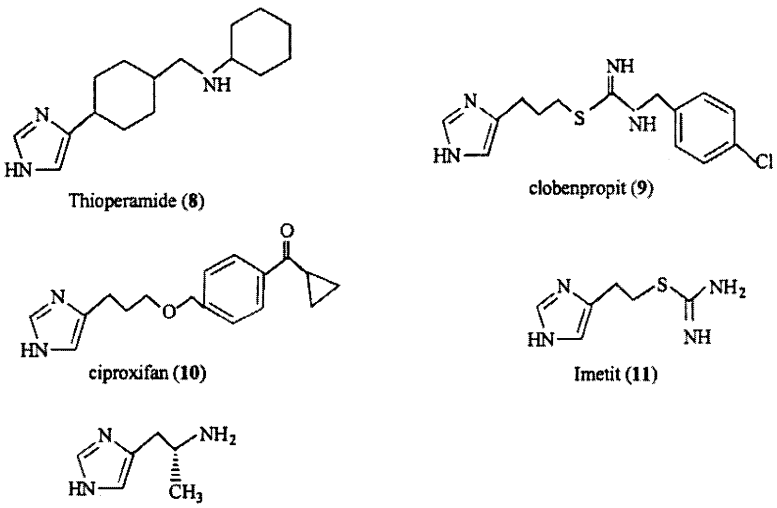

Fig. (3). Some examples of structure of histamine H_3 receptor-related molecules.

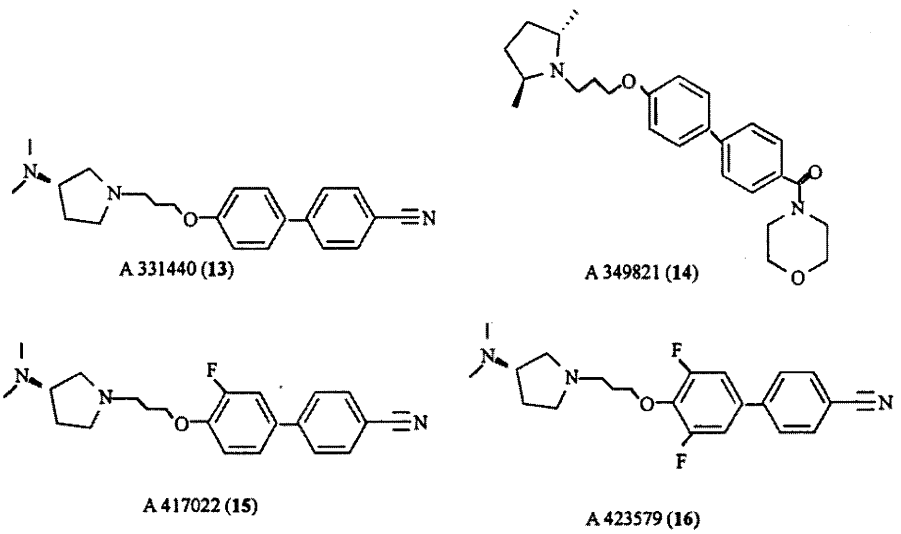

Fig. (4). Some examples of structure of histamine H_3 receptor antagonist (1).

(Fig. 5). Although, these observations may explain why some classes of H_3-R IA exert anti-obesity activity, potentially unknown off-target activity of specific compounds might contribute to their anorectic effects and thus further investigation is required. Following this substantial differences of the outcome, further investigations have to prove the so far unclear concept of H_3-R antagonists in the treatment of obesity and weight gain.

PSYCHOTROPIC DRUG-RELATED WEIGHT GAIN AND BRAIN HISTAMINE

The use of anti-psychotic drug is associated with metabolic side effects including weight gain and diabetes mellitus [52-54]. It has been shown that several anti-psychotic drugs had side effects of appetite stimulation and weight gain [52-54]. These drugs were proved to be potent histamine H_1-R blockers by binding assay, conversely the increased feeding and obesity appeared to result from blockade of H_1-R. Several studies using experimental animals support this hypothesis: the peripheral injection of doxepin and promazine, both of which have anti-histaminic H_1-R antagonized effects, increased food intake. Atypical anti-psychotics such as olanzapine also had side effects of appetite stimulation and weight gain *via* histamine H_1-R signaling [55, 56]. Atypical anti-psychotic olanzapine caused the hyperphagia and body weight gain and it is suggested that the relative receptor affinities of the atypical anti-psychotics for histamine H_1-R appear to be the most robust correlate of the obesity. Orexigenic atypical antipsychotic drugs activate hypothalamic AMP-kinase, an action abolished in mice with deletion of H_1-R [55]. Recent study demonstrated that the effects of antipsychotic drug treatment on weight gain and H_1-R expres-

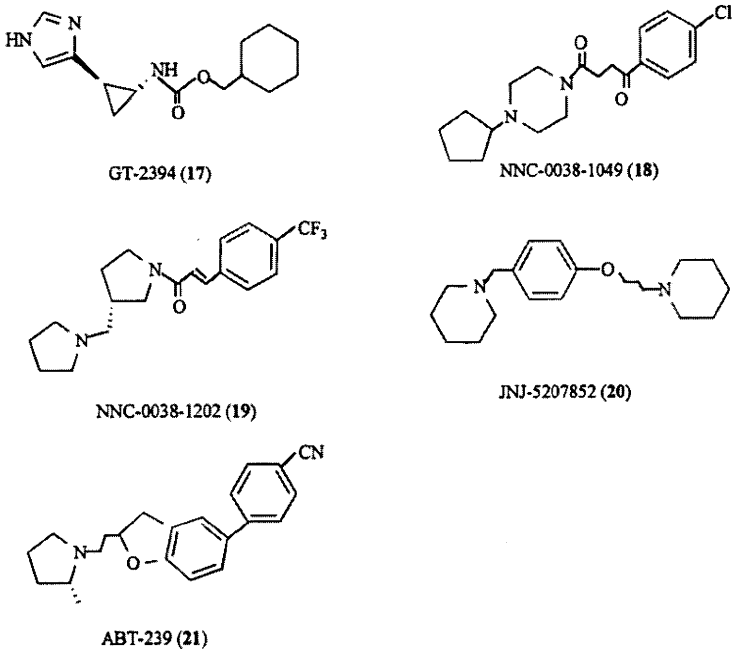

Fig. (5). Some examples of structure of histamine H_3 receptor antagonist (2).

sion in the brain [56].There were negative correlations between the levels of histamine H_1-R mRNA expression, and body weight gain and energy efficiency in the arcuate nucleus (ARC) and ventromedial nucleus (VMH) after antipsychotic treatments (). In addition, H_1-R mRNA expression in the ARC showed a negative correlation with food intake and fat mass. Furthermore, there were negative correlations between H_1-R binding density in the VMH and total fat mass and body weight gain after antipsychotic treatment [56]. The finding suggested that downregulated VMH and ARC H_1-R expression might be a key factor contributing to antipsychotic drug-induced obesity. Thus, the involvement of histamine and H_1-R in antipsychotics-induced hyperphagia and obesity might be tightly related. However, the studies examining the relationship human obesity and histamine H_1-R are relatively not many including genetic analysis. Further studies are needed to examine the relationship human obesity and histamine H_1-R in the future.

CONCLUDING REMARKS

The activation of histamine neurons suppressed food intake and body weight through histamine H_1-R and H_3-R in rodents and human. The involvement of histamine and H_1-R in antipsychotics-induced hyperphagia and obesity is also demonstrated. It is indicated that energy homeostasis is tightly maintained through the formation of a loop bridged between histamine neuron, its receptors in rodents and human. Taken together, therapeutic application of activating of histamine neuron and its receptors might be molecular targets for regulating food intake and obesity in the future.

ACKNOWLEDGMENTS

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REFERENCES

[1] Gurevich-Panigrahi, T.; Panigrahi, S.; Wiechec, E.; Los, M. Obesity: pathophysiology and clinical management. *Curr Med Chem.* **2009**,*16*, 506-521.

[2] Nair, RP.; Ren, J. Pharmacotherapy of obesity - benefit, bias and hyperbole. *Curr Med Chem.* **2009**,*16*,1888-1897.

[3] Saiah, E. The role of 11beta-hydroxysteroid dehydrogenase in metabolic disease and therapeutic potential of 11beta-hsd1 inhibitors. *Curr. Med. Chem.* **2008**,*15*, 642-649.

[4] Kuder, K.; Kieć-Kononowicz, K. Fluorescent GPCR ligands as new tools in pharmacology.*Curr Med Chem.* **2008**,*15*, 2132-2143.

[5] Rivera, G.; Bocanegra-García, V.; Galiano, S.; Cirauqui, N.; Ceras. J.; Pérez, S.; Aldana, I.; Monge, A. Melanin-concentrating hormone receptor 1 antagonists: a new perspective for the pharmacologic treatment of obesity.*Curr Med Chem.* **2008**,*15*,1025-1043.

[6] Brown, R.E.; Stevens, D.R.; Haas, H.L. The physiology of brain histamine. *Prog. Neurobiol.* **2001**, *63*, 637-672.

[7] Haas, H.; and Panula, P. The role of histamine and the tuberomamillary nucleus in the nervous system. *Nat. Rev. Neurosci.* **2003**, *4*, 121-130.

[8] Schwartz, J.C.; Arrang, J.M.; Garbarg, M.; Pollard, H.; Ruat, M. Histaminergic transmission in the mammalian brain. *Physiol. Rev.* 1991, *71*, 1-51.

[9] Timmerman, H. Cloning of the H1 histamine receptor. *Trends Pharmacol.Sci.***1992**, *13*, 6-7.

[10] Terao, A.; Steininger, T.L.; Morairty, S.R.; Kilduff, T.S. Age-related changes in histamine receptor mRNA levels in the mouse brain. *Neurosci Lett.* **2004**, *355*, 81-84.

[11] Arrang, J.M.; Garbarg, M.; Schwartz, J.C. Auto-inhibition of brain histamine release mediated by a novel class (H3) of histamine receptor. *Nature* **1983**, *302*, 832-837.

[12] Masaki, T.; Chiba, S.; Tatsukawa, H.; Noguchi, H.; Kakuma, T.; Endo, M.; Seike, M.; Watanabe, T.; Yoshimatsu, H. The role of histamine H1 receptor and H2 receptor in LPS-induced liver injury. *FASEB J.* **2005**,*19*, 1245-1252.

[13] Lecklin, A.; Etu-Seppala, P.; Stark, H.; Tuomisto, L. Effects of intracerebroventricularly infused histamine and selective H1, H2

and H3 agonists on food and water intake and urine flow in Wistar rats. *Brain Res.***1998**, *793*, 279-288.

[14] Sakata, T.; Ookuma, K.; Fukagawa, K.; Fujimoto, K.; Yoshimatsu, H.; Shiraishi, T.; Wada, H. Blockade of the histamine H1-receptor in the rat ventromedial hypothalamus and feeding elicitation. *Brain Res.* **1988**, *441*, 403-407.

[15] Fulop, A.K.; Foldes, A.; Buzas, E.; Hegyi, K.; Miklos, I.H. Romics, L. Kleiber, M. Nagy, A.; Falus, A.; Kovacs, K.J. Hyperleptinemia, visceral adiposity, and decreased glucose tolerance in mice with a targeted disruption of the histidine decarboxylase gene. *Endocrinology* **2003**, *144*, 4306-4314.

[16] Jorgensen, E.A.; Vogelsang, T.W.; Knigge, U.; Watanabe, T.; Warberg, J.; Kjaer, A. Increased susceptibility to diet-induced obesity in histamine-deficient mice. *Neuroendocrinology* **2006**, *83*, 289-294.

[17] Masaki, T.; Yoshimatsu, H. Therapeutic approach of histamine H3 receptors in obesity. *Recent Pat CNS Drug Discov.* **2007**, *2*, 238-240.

[18] Masaki, T.; Yoshimatsu, H. Neuronal histamine and histamine receptors in food intake and obesity. *Mini Rev Med Chem.* **2007**, *7*, 821-825.

[19] Masaki, T.; Yoshimatsu, H. Neuronal histamine and its receptors in obesity and diabetes. *Curr Diabetes Rev.* **2007**,*3*, 212-216.

[20] Sakata, T. ; Yoshimatsu, H. ; Masaki, T. ; Tsuda, K. Anti-obesity actions of mastication driven by histamine neurons in rats. *Exp Biol Med (Maywood).* **2003**, *228*, 1106-1110.

[21] Masaki, T.; Chiba, S.; Yoshimichi, G.; Yasuda, T.; Noguchi, H.; Kakuma, T.; Sakata, T.; Yoshimatsu, H. Neuronal histamine regulates food intake, adiposity, and uncoupling protein expression in agouti yellow (A(y)/a) obese mice. *Endocrinology.* **2003**, *144*, 2741-2748.

[22] Kasaoka, S.; Tsuboyama-Kasaoka, N.; Kawahara, Y.; Inoue, S.; Tsuji, M.; Ezaki, O.; Kato, H.; Tsuchiya, T.; Okuda, H.; Nakajima, S. Histidine supplementation suppresses food intake and fat accumulation in rats. *Nutrition* **2004**, *20*, 991-996.

[23] Yoshimatsu, H.; Chiba, S.; Tajima, D.; Akehi, Y.; Sakata, T. Histidine suppresses food intake through its conversion into neuronal histamine. *Exp Biol Med (Maywood).* **2002**, *227*, 63-68.

[24] Masaki, T.; Chiba, S.; Yasuda, T.; Noguchi, H.; Kakuma, T.; Watanabe, T.; Sakata, T.; Yoshimatsu, H. Involvement of Hypothalamic Histamine H_1-Receptor in the Regulation of Feeding Rhythm and Obesity. *Diabetes* **2004**, *53*, 2250-2260.

[25] Masaki, T.; Yoshimatsu, H.; Chiba, S.; Watanabe, T.; Sakata, T. Targeted disruption of histamine H1-receptor attenuates regulatory effects of leptin on feeding, adiposity, and UCP family in mice. *Diabetes.* **2001**, *50*, 385-391.

[26] Yasuda, T. ; Masaki, T. ; Sakata, T.; Yoshimatsu, H. Hypothalamic neuronal histamine regulates sympathetic nerve activity and expression of uncoupling protein 1 mRNA in brown adipose tissue in rats. *Neuroscience.* **2004**,*125*, 535-540.

[27] Masaki, T.; Yoshimatsu, H.; Chiba, S.; Watanabe, T.; Sakata, T. Central infusion of histamine reduces fat accumulation and upregulates UCP family in leptin-resistant obese mice. *Diabetes.* **2001**, 50, 376-384.

[28] Masaki, T.; Yoshimatsu, H. The hypothalamic H1 receptor: a novel therapeutic target for disrupting diurnal feeding rhythm and obesity. *Trends Pharmacol Sci.* **2006**, *27*, 279-284.

[29] Feldmann, H.M.; Golozoubova, V.; Cannon, B.; Nedergaard, J. UCP1 ablation induces obesity and abolishes diet-induced thermogenesis in mice exempt from thermal stress by living at thermoneutrality. *Cell Metab.* **2009**, *9*, 203-209.

[30] Masaki, T. ; Yoshimatsu, H. ; Sakata, T. Expression of rat uncoupling protein family mRNA levels by chronic treatment with thyroid hormone. *Int J Obes Relat Metab Disord.* **2000**, *24*. S162-164.

[31] Masaki, T.; Yoshimatsu, H.; Kakuma, T.; Chiba, S.; Hidaka, S.; Tajima, D.; Kurokawa, M.; Sakata, T. Induction of rat uncoupling protein-2 gene treated with tumour necrosis factor alpha *in vivo*. *Eur. J. Clin. Invest.* **1999**, *29*, 76-82.

[32] Masaki, T.; Yoshimatsu, H.; Chiba. S.; Sakata, T. Impaired response of UCP family to cold exposure in diabetic (db/db) mice. *Am. J. Physiol. Regul. Integr. Comp. Physiol.*, **2000**, *279*, R1305-1309.

[33] Barak, N. Betahistine: what's new on the agenda? *Expert Opin Investig Drugs.* **2008**,*17*,795-804.

[34] Barak, N.; Greenway, F.L.; Fujioka, K.; Aronne, L.J.; Kushner, R.F. Effect of histaminergic manipulation on weight in obese adults: a randomized placebo controlled trial. *Int J Obes (Lond).* **2008**, *32*, 1559-1565.

[35] Itoh, E.; Fujimiya, M.; Inui, A. Thioperamide, a histamine H3 receptor antagonist, powerfully suppresses peptide YY-induced food intake in rats. *Biol Psychiatry.***1999**, *45*, 475-481.

[36] Attoub, S.; Moizo, L.; Sobhani, I.; Laigneau, J.P.; Lewin, M.J.; Bado, A.The H3 receptor is involved in cholecystokinin inhibition of food intake in rats. *Life Sci.* **2001**, *69*, 469-478.

[37] Ishizuka, T.; Hatano, K.; Murotani, T.; Yamatodani, A. Comparison of the effect of an H(3)-inverse agonist on energy intake and hypothalamic histamine release in normal mice and leptin resistant mice with high fat diet-induced obesity.*Behav. Brain Res.* **2008**,*188*, 250-254.

[38] Pan, J.B.; Yao, B.B.; Miller, T.R.; Kroeger, P.E.; Bennani, Y.L.; Komater, V.A.; Esbenshade, T.A.; Hancock. A.A.; Decker, M.W.; Fox, G.B. Evidence for tolerance following repeated dosing in rats with ciproxifan, but not with A-304121. *Life Sci.*. **2006**,*79*,1366-1379.

[39] Jethwa, P.H.; Barrett, P.; Turnbull, Y.; Enright, R.A.; Warner, A.; Murphy, M.; Ebling, F.J. The role of histamine 3 receptors in the control of food intake in a seasonal model of obesity: the Siberian hamster. *Behav. Pharmacol.* **2009**,*20*,155-165.

[40] Yoshimoto, R.; Miyamoto, Y.; Shimamura, K.; Ishihara, A.; Takahashi, K.; Kotani, H.; Chen, A.S.; Chen, H.Y.; Macneil, D.J.; Kanatani, A.; Tokita, S. Therapeutic potential of histamine H3 receptor agonist for the treatment of obesity and diabetes mellitus. *Proc Natl Acad Sci U S A.* **2006**, *103*,13866-13671.

[41] Sindelar, D.K.; Shepperd, M.L.; Pickard. R.T.; Alexander-Chacko, J.; Dill M.J.; Cramer, J.W.; Smith, D.P.; Gadski, R. Central H3R activation by thioperamide does not affect energy balance. *Pharmacol. Biochem. Behav.*. **2004**, *78*, 275-283.

[42] Sander K, Kottke T, Stark H.Histamine H3 receptor antagonists go to clinics. *Biol. Pharm. Bull.* **2008**,31, 2163-2181.

[43] Celanire, S.; Wijtmans, M. ; Talaga, P. ; Leurs, R. ; de Esch, I.J. Keynote review: histamine H3 receptor antagonists reach out for the clinic.*Drug Discov Today.* **2005**,10,1613-1627.

[44] Tokita, S.; Takahashi, K.; Kotani, H. Recent advances in molecular pharmacology of the histamine systems: physiology and pharmacology of histamine H3 receptor: roles in feeding regulation and therapeutic potential for metabolic disorders. *J. Pharmacol. Sci.* **2006**,*101*,12-18.

[45] Hancock, A.A., Bennani, Y.L., Bush, E.N. *et al.* Antiobesity effects of A-331440, a novel non-imidazole histamine H_3 receptor antagonist. *Eur. J. Pharmacol.* **2004**, 487, 183–197.

[46] Hancock, A.A., Diehl, M.S., Fey, T.A. *et al.* Antiobesity evaluation of histamine H_3 receptor (H_3R) antagonist analogs of A-331440 with improved safety and efficacy. *Inflamm. Res.* **2005**, 54, S27–29.

[47] Malmlof, K.; Zaragoza, F.; Golozoubova, V.; Refsgaard, H.H.; Cremers, T.; Raun, K.; Wulff, B.S.; Johansen, P.B.; Westerink, B.; Rimvall, K. Influence of a selective histamine H3 receptor antagonist on hypothalamic neural activity, food intake and body weight. *Int. J. Obes. (Lond)* **2005**, *29*, 1402-1412.

[48] Malmlof, K.; Golozoubova, V.; Peschke, B.; Wulff, B.S.; Retsguhrd, H.; Johansen, P.B.; Cremers, T.; Rimvall, K. Increase of neuronal histamine in obese rats is associated with decreases in body weight and plasma triglycerides. *Obesity (Silver Spring)* **2006**, *14*, 2154-2162.

[49] Rimvall, K., Peschke, B., Cremers, T.I.F.H. Body weight lowering effects of the cinnamic amide, NNC-0038-0000-1202, a novel histamine H_3 receptor antagonist in obese rodents. *Abstract of the Eur. Histamine Res. Soc.* **2004**, *1*, 98.

[50] Barbier, A.J., Berridge, C., Dugovic, C. Acute wake-promoting actions of JNJ-5207852, a novel diamine-based H_3 antagonist. *Br. J. Pharmacol.* **2004**,143, 649–661.

[51] Cowart, M., Faghih, R., Curtis, M.P. (2-(2(R)-Methyl-pyrrolidine-1-yl)ethyl) benzofuran-5-yl)-benzonitrile (ABT-239) and related 2-aminoethylbenzofuran H_3 antagonists potently enhance cognition and attention. *J. Med. Chem.* **2005**, *48*, 38–55.

[52] Howland, R.H.Pharmacotherapy for psychotropic drug-related weight gain.*J Psychosoc Nurs Ment Health Serv.* **2008**;*46*:15-18.

[53] Tschoner, A.; Engl, J.; Laimer, M.; Kaser, S.; Rettenbacher, M.;

Fleischhacker, W.W.; Patsch, J.R.; Ebenbichler, C.F. Metabolic side effects of antipsychotic medication. *Int. J. Clin. Pract.*, **2007**, *61*,1356-1370.

[54] Correll, C.U. ; Malhotra, A.K. Pharmacogenetics of antipsychotic-induced weight gain.*Psychopharmacology (Berl).* **2004**,*174*, 477-489.

[55] Kim, S.F.; Huang, A.S.; Snowman, A.M.; Teuscher, C.; Snyder, S.H. Antipsychotic drug-induced weight gain mediated by histamine H1 receptor-linked activation of hypothalamic AMP-kinase. *Proc. Natl. Acad. Sci. U.S.A.* **2007**,*104*, 3456-3459.

[56] Han, M.; Deng, C.; Burne, T.H.; Newell, K.A.; Huang, X.F. Short- and long-term effects of antipsychotic drug treatment on weight gain and H1 receptor expression. *Psychoneuroendocrinology.* **2008**, *33*, 569-580.

CASE REPORT

Thrombopoietin and Thrombocytopenia in Anorexia Nervosa with Severe Liver Dysfunction

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Junko Moriya, MD, PhD
Shuji Inada, MD
Akira Akabayashi, MD, PhD

ABSTRACT

Objective/Method: Patients with anorexia nervosa (AN) display various physical complications. One such problem is thrombocytopenia. However, no studies have investigated links between AN and thrombopoietin (TPO), which is the primary regulator of megakaryocyte and platelet production produced mainly in the liver, although TPO has been recently reported to play a role in thrombocytopenia in liver diseases. We therefore clarified temporal relationships between platelet counts and TPO level in a woman with AN and severe liver dysfunction in whom platelet count decreased to 53 × 10^9/L.

Results: While international normalized ratio (INR) was low, serum TPO level was relatively low despite low platelet counts. After INR and liver enzymes improved in conjunction with improved nutritional status, a rapid increase in TPO was observed and platelet count began to rise.

Discussion: These findings thus suggest that decreased TPO production accompanying liver dysfunction may be related to thrombocytopenia besides myelosuppression in AN with malnutrition. © 2009 by Wiley Periodicals, Inc.

Keywords: thrombocytopenia; thrombopoitein; liver dysfunction; anorexia nervosa

(Int J Eat Disord 2010; 43:675–677)

Introduction

Various physical problems have been reported to occur in patients with anorexia nervosa (AN) because of malnutrition, including vitamin deficiency,[1] electrolyte disturbances, diminished bone mineral density, increased QT interval, cardiomyopathy, and liver dysfunction.[2,3]

Among these problems, thrombocytopenia is also known to occur in cases of low-body weight accompanied by AN.[2,4] In such cases, myelosuppression has been viewed as the main cause of thrombocytopenia.[5] To date, however, no studies have examined relationships between AN with acute liver dysfunction and thrombopoietin (TPO),[6] which is the primary regulator of megakaryocyte and platelet production produced mainly in the liver but also in the kidneys and bone marrow, although TPO has been recently reported to play a role in thrombocytopenia in liver diseases such as liver cirrhosis.[7] Furthermore, no studies have analyzed changes in TPO and platelet counts occurring during the recovery stage of severe liver dysfunction, even for other diseases.

We report herein the case of a patient who was affected by AN and presented with increased serum liver enzymes and thrombocytopenia, and discuss the possible influence of reduced TPO production by liver dysfunction on thrombocytopenia with a close examination of temporal changes in liver function, platelet counts, and TPO values.

Case Report

The patient was a 25-year-old woman with a 2-year history of restrictive-type AN who had been diagnosed according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV).[8] Premorbid body weight and body mass index (BMI) were 60.0 kg and 22.9 kg/m^2, respectively. Body weight and BMI at the time of hospitalization were 36.0 kg and 13.7 kg/m^2, respectively, and minimum body weight and BMI were 33.0 kg and 12.5 kg/m^2 on Day 17, respectively.

For 31 days after hospitalization, complete blood count, international normalized ratio (INR), and levels of aspartate aminotransferase, alanine ami-

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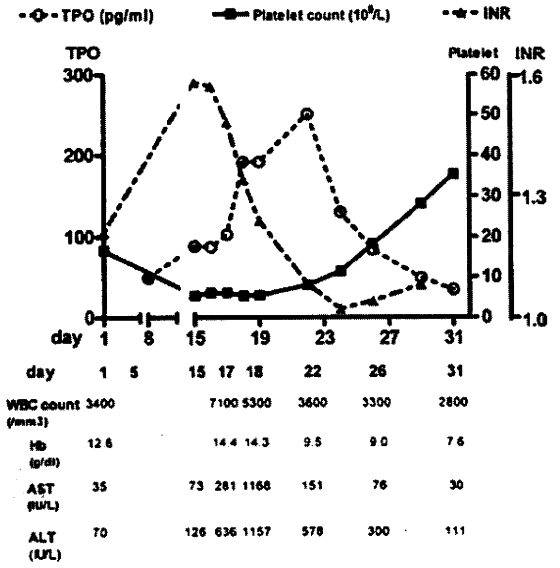
FIGURE 1. Thrombopoietin (TPO), platelet counts, and international normalized ratio (INR) during severe liver dysfunction and the recovery phase in a patient with anorexia nervosa (AN). TPO levels increased just after recovery of INR, on Day 18, whereas platelets remained low on days 15–17.



notransferase, and serum TPO were measured. TPO was measured using a Human Thrombopoietin ELISA kit (R&D Systems, Minneapolis, MN).

On admission, physical examination identified hypotension (88/50 mm Hg), bradycardia (48 beats/min), hypothermia, malasmus-like protein-energy malnutrition, and lanugo. Even after hospitalization, the patient continued to refuse to eat. By Day 15, platelet count had decreased to 53×10^9/L (normal, 155–365 $\times 10^9$/L). Concurrently, increased INR and serious liver dysfunction were noted. Despite low-platelet counts on Days 15–17, TPO level remained relatively low (see Fig. 1). Principal exogenous causes of acute liver failure such as hepatotropic virus, hepatotoxic drugs, alcohol, cocaine, and autoimmune hepatitis were excluded. On ultrasonography, although the left lobe of the liver was slightly shrunken, the gallbladder and biliary tree were found to be intact. Thrombosis was excluded by contrast-enhanced computed tomography. Because of the poor general clinical condition of the patient, liver biopsy was avoided.

From Day 15, the patient accepted gradual intravenous rehydration (1,000 mL/day) and nutritional rehabilitation with both enteral feeding using a nasogastric tube (energy intake, starting with 500 kcal, gradually increasing to 1,000 kcal with nutritional supplementation) and peripheral venous nutrition (77.5 g glucose per 1,000 mL water) with vitamins and minerals. Phosphate supplement was administrated first parenterally, then enterally after resumption of enteral feeding. At Day 19, oral nutrition was started with natural foods (1,200–1,900 kcal). When oral nutrition intake increased, parenteral support and tube feeding were gradually decreased.

INR subsequently improved in conjunction with improved nutritional status resulting from tube feeding. With the return of liver function from Days 18–22, a rapid increase in TPO was observed and platelet count began to rise. TPO values then decreased with the rise in platelet count (see Fig. 1).

Discussion

In AN, malnutrition has been reported to cause thrombocytopenia as along with liver dysfunction. For example, thrombocytopenia was seen at the peak level of liver enzymes in a previous case report, whereas the mechanisms underlying thrombocytopenia were not discussed.[3]

This report describes temporal changes in liver enzyme levels, platelet counts, and TPO values in a patient with restrictive-type AN who developed liver dysfunction and thrombocytopenia. We have also reported that TPO values did not increase despite thrombocytopenia during liver dysfunction, although TPO level increases under normal conditions when platelet count decreases. TPO values increased soon after the recovery of liver function, and then platelet count began to rise.

TPO values have previously been reported to not increase even with a drop in platelets accompanying severe liver failure,[9] as seen in this report. However, previous studies have not investigated temporal changes in TPO values during both severe liver dysfunction and recovery. In contrast, this report examined detailed time-series data for TPO and platelet counts during severe liver dysfunction and recovery. Interestingly, prompt restoration (within 24 h) of TPO production accompanied the recovery of liver function.

In addition, subsequent gradual increases in platelet count after improvement of TPO production may provide further insights into the physiological role of hepatic TPO when severe liver dysfunction such as hepatic cirrhosis is present. The findings also suggest the possibility that decreased TPO production accompanying liver dysfunction is related to lowered platelet counts in AN patients with malnutrition, along with myelosuppression.

In this report, liver enzymes rose to over 1,000 IU/L. In this patient with AN, acute liver dysfunction was not due to alcohol, hepatotoxic drug intake, or infection due to hepatotropic viruses. The increase in liver enzymes might thus be attributable to malnutrition and liver hypoperfusion, as suggested by previous studies,[3,10] supported by the observation that rapid recovery occurred within a few days of hydration and nutritional treatment.

In conclusion, reductions in hepatic TPO may play a significant role in thrombocytopenia in AN patients with acute severe liver dysfunction.

References

1. Winston AP, Jamieson CP, Madira W, Gatward NM, Palmer RL. Prevalence of thiamin deficiency in anorexia nervosa. Int J Eat Disord 2000;28:451–454.
2. Becker AE, Grinspoon SK, Klibanski A, Herzog DB. Eating disorders. N Engl J Med 1999;340:1092–1098.
3. de Caprio C, Alfano A, Senatore I, Zarrella L, Pasanisi F, Contaldo F. Severe acute liver damage in anorexia nervosa: Two case reports. Nutrition 2006;22:572–575.
4. Hütter G, Ganepola S, Hoffmann WK. The hematology of anorexia nervosa. Int J Eat Disord 2009;42:293–300.
5. Abella E, Feliu E, Granada I, Milla F, Orioi A, Ribera JM, et al. Bone marrow changes in anorexia nervosa are correlated with the amount of weight loss and not with other clinical findings. Am J Clin Pathol 2002;118:582–588.
6. Kaushansky K. Lineage-specific hematopoietic growth factors. N Engl J Med 2006;354:2034–2045.
7. Afdhal N, McHutchison J, Brown R, Jacobson T, Manns M, Poordad F, et al. Thrombocytopenia associated with chronic liver disease. J Hepatol 2008;48:1000–1007.
8. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Washington, DC: American Psychiatric Association, 1994.
9. Schiødt FV, Balko J, Schilsky M, Harrison ME, Thornton A, Lee WM, et al. Thrombopoietin in acute liver failure. Hepatology 2003;37:558–561.
10. di Pascoli L, Lion A, Milazzo D, Caregaro L. Acute liver damage in anorexia nervosa. Int J Eat Disord 2004;36:114–117.

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Review Article

Ghrelin and Functional Dyspepsia

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The majority of patients with dyspepsia have no identifiable cause of their disease, leading to a diagnosis of functional dyspepsia (FD). While a number of different factors affect gut activity, components of the nervous and endocrine systems are essential for normal gut function. Communication between the brain and gut occurs via direct neural connections or endocrine signaling events. Ghrelin, a peptide produced by the stomach, affects gastric motility/emptying and secretion, suggesting it may play a pathophysiological role in FD. It is also possible that the functional abnormalities in FD may affect ghrelin production in the stomach. Plasma ghrelin levels are reported to be altered in FD, correlating with FD symptom score. Furthermore, some patients with FD suffer from anorexia with body-weight loss. As ghrelin increases gastric emptying and promotes feeding, ghrelin therapy may be a new approach to the treatment of FD.

1. Introduction

Dyspepsia is associated with a variety of organic and functional disorders. The organic causes of dyspeptic symptoms include peptic ulcers, cholelithiasis, reflux disease, and malignancy. In patients initially presenting with dyspepsia, approximately 33% to 50% have an underlying organic disease [1]. Routine clinical evaluation and procedures do not reveal the cause of symptoms in the majority of patients with dyspepsia. If symptoms persist for more than three months with symptom onset of at least six months prior to the diagnosis, affected patients are diagnosed with functional dyspepsia (FD).

Despite an absence of organic disease in patients with FD, abnormalities in gastric emptying, dysregulation of gastroduodenal motility, and visceral hypersensitivity are often associated with FD. As ghrelin affects gastric motility/emptying [2–7] and secretion [8, 9], this peptide may play a pathophysiological role in FD. It is also possible that the functional abnormalities in FD may affect the production of ghrelin by the stomach. Indeed, plasma ghrelin levels are reported to be altered in FD [10, 11], frequently correlating with FD symptom score [11, 12]. Some patients with FD also suffer from anorexia with significant weight loss, frequently leading to diagnosis of eating disorders. As yet, no treatment guidelines for patients with FD or eating disorders have been established. Given its role triggering eating behaviors, ghrelin might be an appropriate treatment for FD, potentially improving food intake by influencing gastric emptying and motility. In this article, we discuss FD and the potential role of ghrelin in this disease.

2. Functional Dyspepsia

Functional dyspepsia (FD), a functional gastroduodenal disorder (FGDD) [13, 14] and one of the functional gastrointestinal disorders (FGIDs) [15], was previously known as nonulcer dyspepsia (NUD), essential dyspepsia, or idiopathic dyspepsia [16, 17]. The original Rome I criteria, which established the classification and diagnosis of FD in 1994 [18], have since been updated twice as Rome II in 2000 [19] and Rome III in 2006 [15].

The Rome II (Table 1) [19] defines FD as persistent or recurrent pain or discomfort centered in the upper abdomen. Discomfort refers to a subjective, negative feeling

Table 1: Diagnostic criteria and classification of FD in Rome II.

Diagnostic criteria
At least 12 weeks, which need not be consecutive, in the preceding 12 months of
(1) Persistent or recurrent symptoms (pain or discomfort centered in the upper abdomen)
(2) No evidence of organic disease (including at upper endoscopy) that is likely to explain the symptoms
(3) No evidence that dyspepsia is exclusively relieved by defecation or associated with the onset of a change in stool frequency or stool form (i.e., not irritable bowel).
Classification
(B1a) Ulcer-like dyspepsia
Pain centered in the upper abdomen is the predominant (most bothersome) symptom.
(B1b) Dysmotility-like dyspepsia
An unpleasant or troublesome nonpainful sensation (discomfort) centered in the upper abdomen is the predominant symptom; this sensation may be characterized by or associated with upper abdominal fullness, early satiety, bloating, or nausea.
(B1c) Unspecified (nonspecific) dyspepsia
Symptomatic patients whose symptoms do not fulfill the criteria for ulcer-like or dysmotility-like dyspepsia.

Table 2: Dyspeptic symptoms defined by Rome III. This table is adopted by permission from Elsevier Limited [13, 15].

Symptom	Definition
Postprandial fullness	An unpleasant sensation akin to the prolonged persistence of food in the stomach
Early satiation	A feeling that the stomach is overfilled soon after starting to eat. This feeling is out of proportion to the size of the meal and results in the patient being unable to finish the meal
Epigastric pain	Pain located between the umbilicus and sternum in the midline of the torso. The pain is a subjective and unpleasant feeling, but difficult to describe. Some patients may describe feelings of tissue damage or chest pain
Epigastric burning	Pain located in the epigastrium that has a burning quality, but does not radiate to the chest

Table 3: Rome III criteria for functional gastroduodenal disorders. This table is adopted by permission from Elsevier Limited [13].

B			Functional gastroduodenal disorders
	B1		Functional dyspepsia (for application in clinical practice but not otherwise useful)
		B1a	Postprandial distress syndrome
		B1b	Epigastric pain syndrome
	B2		Belching disorders
		B2a	Aerophagia
		B2b	Unspecified excessive belching
	B3		Nausea and vomiting disorders
		B3a	Chronic idiopathic nausea
		B3b	Functional vomiting
		B3c	Cyclic vomiting syndrome
	B4		Rumination syndrome in adults

characterized by or associated with non-painful symptoms such as upper abdominal fullness, early satiety, bloating, or nausea. For a diagnosis, symptoms must have persisted or recurred for at least 12 weeks over a 12-month period. A dyspepsia subgroup classification was also proposed for research purposes, based on the predominant (most bothersome) symptom, (a) ulcer-like dyspepsia features pain (from mild to severe) as the predominant symptom, while (b) dysmotility-like dyspepsia exhibits discomfort (not pain) as the predominant symptom.

The Rome III system radically reformulated the classification of FD (Table 2) [14]. The description of symptoms centered in the upper abdominal area was refined by the Committee to pain in the precise epigastric region, while other key symptoms (early satiety and fullness) must be meal-related. According to Rome III, discomfort was abandoned as a key concept, replaced by post-prandial fullness and early satiety. The Rome III criteria moved away from subcategorization using the predominant symptom (dysmotility-like and ulcer-like dyspepsia of Rome II), although similar entities, (a) postprandial distress syndrome and (b) epigastric pain syndrome, are subsumed under the FD section (Table 3). The Committee recognized that there are no one symptoms present in the majority of patients previously labeled with a diagnosis of FD. The time course for diagnosis was made less restrictive for all functional disorders; diagnosis was acceptable for symptoms originating six, not 12, months prior to diagnosis when currently active (i.e., meet criteria) for at least three months [13]. For research purposes, the term FD was abandoned in favor of a new classification system described in Table 3.

Although the etiology of FD remains unclear, a number of factors may play a role in the development of symptoms [1] (Table 4). Visceral hypersensitivity is thought to be critical in causing FD by enhancing perception and processing of gastrointestinal neural inputs [20]. In a study of experimentally induced gut distention, the majority of patients with FD developed greater discomfort than matched healthy controls. As increased gut sensitivity may affect gut motility, acid secretion, and gastric distension, hypersensitivity may

Table 4: Postulated mechanisms leading to the development of dyspeptic symptoms in patients with functional dyspepsia. This table is adopted by permission from Elsevier Limited [1].

Visceral hypersensitivity
(a) Increased perception of distention
(b) Impaired or altered perception of acid
(c) Visceral hypersensitivity secondary to chronic inflammation
Motility disorders
(a) Postprandial antral hypomotility
(b) Reduced relaxation of the gastric fundus
(c) Decreased or impaired gastric emptying
(d) Changes of the gastric electric rhythm
(e) Gastro-esophageal reflux
(f) Duodeno-gastric reflux
Changes in acid secretion
Hyperacidity
Helicobacter pylori infection
Stress
Psychological disorders and abnormalities
Genetic predisposition

underlie many of the symptoms of FD. Patients with FD often have concomitant GI motility disorders and psychiatric illnesses. Whether these disorders are an epiphenomenon or related to the underlying disease remains unclear. Symptom development and exacerbation of FD are often linked to stressful life events, causing the patient to seek medical help at that time. Thus, patients seeking care for FD symptoms are more likely to have active life stressors than those who remain undiagnosed, leading to bias in the sample population. External stressors may also affect intestinal function, which in connection with visceral hypersensitivity, may lead to increased symptom perception.

3. Relationship of Ghrelin to the GI Tract and Feeding Behaviors

Neural and hormonal communication between the gut and the brain modulate appetite, feeding, and digestion [21, 22]. In the integrated gut-brain-energy axis, gastrointestinal (GI) motility, gastric acid secretion, digestion, and defecation are coordinated with appetite, satiation, and metabolism. Both organic and functional GI disorders are associated with alterations of the physiologic factors regulating the gut-brain-energy axis.

Multiple hormones are secreted by the gut and adipose tissues during feeding, digestion, and fasting, each of which can profoundly affect the GI tract [22]. A subset of these hormones directly affects secretory function along the GI tract (e.g., gastrin stimulates acid secretion by parietal cells); major sites of hormone action also include enteric and vagal neurons, the area postrema (AP) within the medulla, and the hypothalamic arcuate nucleus (HAN). The AP and the median eminence, which has a close relationship with the HAN, have greatly reduced or absent blood-brain barriers. Impulses from the AP travel along nerve projections to the adjacent nucleus tractus solitarius (NTS) and higher regions of the brain, while those from the HAN do to other parts of the hypothalamus. Several hormones can cross the blood-brain barrier, including those with specific transporters such as leptin, insulin, and ghrelin [23]. Hormones released from the gut act on both the enteric nervous system (ENS) to contribute to the migrating motor complex (MMC) cycle and the CNS to promote the gradual re-establishment of appetite. The plasma concentrations of leptin and glucagon-like peptide 1 (GLP1) are low during fasting, while those of ghrelin and orexin are high. Significant research has focused on hormones whose plasma concentrations increase during fasting, as it is hypothesized that these hormones strongly affect hunger and energy expenditure. In addition to systemic effects, fasting-associated hormones also strongly affect a myriad of GI functions, possibly preparing the GI tract for food reception. Such a role has been proposed for ghrelin, the first orexigenic hormone identified that is produced in and released from the stomach. Ghrelin has a well-established role in increasing appetite and food intake [24, 25] and in stimulating gastric emptying and acid secretion [26, 27]; these functions are mediated, at least in-part, via vagal nerve pathways [9, 28]. The details concerning relationship of ghrelin to the GI tract function and food intake are also described in several manuscripts of this special issue (see, e.g., "Ghrelin's effect on hypothalamic neurons", "Ghrelin-NPY axis", "Gastric ghrelin and leptin", "Motilin and ghrelin in the dog," and "Ghrelin and stress in GI tract").

4. Plasma Concentrations of Ghrelin in FD

The gut and brain are highly integrated, communicating bidirectionally through neural and hormonal pathways [29]. Psychosocial factors can significantly influence digestive function, symptom perception, disease presentation, and outcome. Functional GI disorders, in return, can alter the physiologic factors regulating digestion and feeding [22].

The circulating levels of hormones related to appetite regulation are altered in dyspeptic disorders. Patients with dysmotility-like dyspepsia have higher serum concentrations of leptin, which is associated with gastritis and *H. pylori* infection [30]. Given that leptin is produced within the stomach to activate vagal-nerve terminals, reduce appetite, and increase mucin secretion, leptin may have a protective role in the upper gut during states of injury [22]. Plasma ghrelin levels in patients with FD are, however, controversial. While the total ghrelin levels were reported to be significantly higher in patients with FD (32 dysmotility-like and 7 ulcer-like FD patients) [31], they were significantly lower in patients with dysmotility-like FD [10, 32]. Concerning the active ghrelin levels, they were decreased in patients with postprandial fullness and/or early satiation defined by the Rome III classification [33], whereas similar between dysmotility-like FD patients and healthy controls [10]. The reason for discrepancy in plasma ghrelin levels remains uncertain, warranting further investigation.

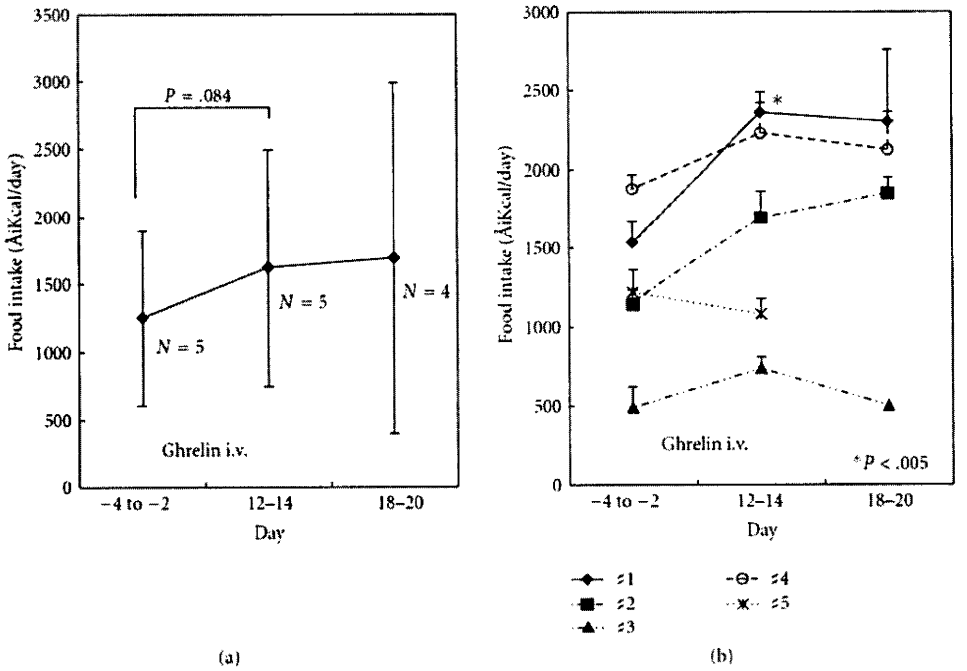

FIGURE 1: Daily food intake was measured before ghrelin injection (days −4 to −2), at the completion of treatment (days 12 to 14), and one week after injection (days 18 to 20) in five subjects who completed two weeks of ghrelin treatment. (a) Mean and 95% confidence interval (CI) for five subjects; (b) three-day means and SD of daily food intake for each subject.

In terms of pathogenetic implication of these alterations in plasma ghrelin levels, the relationship with gastric emptying time in these patients was investigated. Significant correlation between the active ghrelin levels and the T_{max} value [33] and delayed gastric empyting in the majority of patients with abnormally low total ghrelin levels [32] were observed. In addition, elevations in the acylated form of ghrelin (active ghrelin) were significantly associated with subjective symptom score in FD patients [12]. Increased ghrelin concentrations are also seen in patients with duodenal and gastric ulcers, suggesting a possible relationship to mucosal injury [34].

5. Ghrelin Administration to Patients with FD

The therapies currently available for the treatment of dyspepsia, and for FD specifically, target the underlying hypothesized pathophysiology, including increased gastric acid sensitivity, delayed gastric emptying, and *H. pylori* infection. Only a small proportion of patients, however, experiences symptomatic relief using these treatments [35]. New treatment modalities targeting impaired gastric accommodation, visceral hypersensitivity, and central nervous system dysfunction are currently under development.

In dysmotility-type FD, which comprises the largest subset of patients, abnormalities in gastrointestinal motility and sensitivity are thought to underlie the development of symptoms. Some patients with FD suffer from anorexia with weight loss, frequently leading to diagnosis with eating disorders. No treatment guidelines for patients with FD or eating disorders have been established. As ghrelin increases gastric emptying [2–6] and promotes feeding [36, 37], we investigated the ability of repeated ghrelin administrations to increase appetite and food intake in patients with FD [38]. We administered ghrelin by intravenous infusion (3 μg/kg) twice a day before breakfast and dinner for two weeks to five patients. Ghrelin administration tended to increase daily food intake by approximately 30% in comparison to levels before and after completion of treatment, although this difference did not reach statistical significance (P = .084) (Figure 1(a)). Increases in food intake were maintained even one week after treatment (days 18–20). Although the precise mechanism is not known, the acute effects of ghrelin on gastric function may lead to sequential improvements in gastric mucosa and/or function. In addition, improvement in food intake may result from decreased anxiety or increased confidence concerning food intake in these patients. On an individual basis, food intake increased in four of the five subjects tested, decreasing in Patient #5 (Figure 1(b)). Food intake in Patient #1 was significantly elevated at the end of ghrelin treatment (days 12–14) from levels observed before treatment (P < .005). Hunger sensation was significantly elevated following a drip infusion (P < .0001). No severe adverse effects were observed. These results support the therapeutic potential of ghrelin in patients with FD. Additional studies, including larger placebo-controlled trials, will be necessary to confirm the usefulness of ghrelin in FD treatment.

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References

[1] H. D. Allescher, "Functional dyspepsia—a multicausal disease and its therapy," *Phytomedicine*, vol. 13, supplement 5, pp. 2–11, 2006.

[2] A. Asakawa, A. Inui, T. Kaga, et al., "Ghrelin is an appetite-stimulatory signal from stomach with structural resemblance to motilin," *Gastroenterology*, vol. 120, no. 2, pp. 337–345, 2001.

[3] F. Levin, T. Edholm, P. T. Schmidt, et al., "Ghrelin stimulates gastric emptying and hunger in normal-weight humans," *Journal of Clinical Endocrinology and Metabolism*, vol. 91, no. 9, pp. 3296–3302, 2006.

[4] C. D. R. Murray, N. M. Martin, M. Patterson, et al., "Ghrelin enhances gastric emptying in diabetic gastroparesis: a double blind, placebo controlled, crossover study," *Gut*, vol. 54, no. 12, pp. 1693–1698, 2005.

[5] J. Tack, I. Depoortere, R. Bisschops, et al., "Influence of ghrelin on interdigestive gastrointestinal motility in humans," *Gut*, vol. 55, no. 3, pp. 327–333, 2006.

[6] M. Binn, C. Albert, A. Gougeon, et al., "Ghrelin gastrokinetic action in patients with neurogenic gastroparesis," *Peptides*, vol. 27, no. 7, pp. 1603–1606, 2006.

[7] J. Tack, I. Depoortere, R. Bisschops, K. Verbeke, J. Janssens, and T. Peeters, "Influence of ghrelin on gastric emptying and meal-related symptoms in idiopathic gastroparesis," *Alimentary Pharmacology and Therapeutics*, vol. 22, no. 9, pp. 847–853, 2005.

[8] M. Mori, H. Suzuki, T. Masaoka, et al., "Intravenous ghrelin administration enhances gastric acid secretion—evaluation using wireless pH capsule," *Alimentary Pharmacology and Therapeutics*, vol. 24, supplement 4, pp. 96–103, 2006.

[9] Y. Masuda, T. Tanaka, N. Inomata, et al., "Ghrelin stimulates gastric acid secretion and motility in rats," *Biochemical and Biophysical Research Communications*, vol. 276, no. 3, pp. 905–908, 2000.

[10] K.-I. Takamori, Y. Mizuta, F. Takeshima, et al., "Relation among plasma ghrelin level, gastric emptying, and psychologic condition in patients with functional dyspepsia," *Journal of Clinical Gastroenterology*, vol. 41, no. 5, pp. 477–483, 2007.

[11] T. Nishizawa, H. Suzuki, Y. Nomoto, et al., "Enhanced plasma ghrelin levels in patients with functional dyspepsia," *Alimentary Pharmacology and Therapeutics*, vol. 24, supplement 4, pp. 104–110, 2006.

[12] T. Shinomiya, M. Fukunaga, T. Akamizu, et al., "Plasma acylated ghrelin levels correlate with subjective symptoms of functional dyspepsia in female patients," *Scandinavian Journal of Gastroenterology*, vol. 40, no. 6, pp. 648–653, 2005.

[13] J. Tack, N. J. Talley, M. Camilleri, et al., "Functional gastroduodenal disorders," *Gastroenterology*, vol. 130, no. 5, pp. 1466–1479, 2006.

[14] N. J. Talley, K. Ruff, X. Jiang, and H. K. Jung, "The Rome III classification of dyspepsia: will it help research?" *Digestive Diseases*, vol. 26, no. 3, pp. 203–209, 2008.

[15] D. A. Drossman, "The functional gastrointestinal disorders and the Rome III process," *Gastroenterology*, vol. 130, no. 5, pp. 1377–1390, 2006.

[16] W. G. Thompson, "Nonulcer dyspepsia," *Canadian Medical Association Journal*, vol. 130, no. 5, pp. 565–569, 1984.

[17] N. J. Talley, "Non-ulcer dyspepsia: myths and realities," *Alimentary Pharmacology and Therapeutics*, vol. 5, supplement 1, pp. 145–162, 1991.

[18] D. A. Drossman, J. E. Richter, N. J. Talley, E. Corazziari, W. G. Thompson, and W. E. Whitehead, *Functional Gastrointestinal Disorders*, Little Brown, Boston, Mass, USA, 1994.

[19] N. J. Talley, V. Stanghellini, R. C. Heading, K. L. Koch, J. R. Malagelada, and G. N. J. Tytgat, "Functional gastroduodenal disorders," *Gut*, vol. 45, supplement 2, pp. 37–42, 1999.

[20] F. Mearin, M. Cucala, F. Azpiroz, and J.-R. Malagelada, "The origin of symptoms on the brain-gut axis in functional dyspepsia," *Gastroenterology*, vol. 101, no. 4, pp. 999–1006, 1991.

[21] G. A. Bray, "Afferent signals regulating food intake," *Proceedings of the Nutrition Society*, vol. 59, no. 3, pp. 373–384, 2000.

[22] G. J. Sanger and K. Lee, "Hormones of the gut-brain axis as targets for the treatment of upper gastrointestinal disorders," *Nature Reviews Drug Discovery*, vol. 7, no. 3, pp. 241–254, 2008.

[23] W. A. Banks, "The blood-brain barrier as a regulatory interface in the gut-brain axes," *Physiology and Behavior*, vol. 89, no. 4, pp. 472–476, 2006.

[24] D. E. Cummings, "Ghrelin and the short- and long-term regulation of appetite and body weight," *Physiology and Behavior*, vol. 89, no. 1, pp. 71–84, 2006.

[25] A. M. Wren and S. R. Bloom, "Gut hormones and appetite control," *Gastroenterology*, vol. 132, no. 6, pp. 2116–2130, 2007.

[26] T. L. Peeters, "Central and peripheral mechanisms by which ghrelin regulates gut motility," *Journal of Physiology and Pharmacology*, vol. 54, supplement 4, pp. 95–103, 2003.

[27] K. Yakabi, J. Kawashima, and S. Kato, "Ghrelin and gastric acid secretion," *World Journal of Gastroenterology*, vol. 14, no. 41, pp. 6334–6338, 2008.

[28] Y. Date, N. Murakami, K. Toshinai, et al., "The role of the gastric afferent vagal nerve in ghrelin-induced feeding and growth hormone secretion in rats," *Gastroenterology*, vol. 123, no. 4, pp. 1120–1128, 2002.

[29] M. P. Jones, J. B. Dilley, D. Drossman, and M. D. Crowell, "Brain-gut connections in functional GI disorders: anatomic and physiologic relationships," *Neurogastroenterology and Motility*, vol. 18, no. 2, pp. 91–103, 2006.

[30] K. B. Lankarani, M. Moghadami, M. Masoumpoor, B. Geramizadeh, and G. R. Omrani, "Serum leptin level in patients with functional dyspepsia," *Digestive and Liver Disease*, vol. 36, no. 11, pp. 717–721, 2004.

[31] A. Lanzini, P. Magni, M. L. Petroni, et al., "Circulating ghrelin level is increased in coeliac disease as in functional dyspepsia and reverts to normal during gluten-free diet," *Alimentary Pharmacology and Therapeutics*, vol. 23, no. 7, pp. 907–913, 2006.

[32] K. J. Lee, D. Y. Cha, S. J. Cheon, M. Yeo, and S. W. Cho, "Plasma ghrelin levels and their relationship with gastric emptying in patients with dysmotility-like functional dyspepsia," *Digestion*, vol. 80, no. 1, pp. 58–63, 2009.

[33] T. Shindo, S. Futagami, T. Hiratsuka, et al., "Comparison of gastric emptying and plasma ghrelin levels in patients with functional dyspepsia and non-erosive reflux disease," *Digestion*, vol. 79, no. 2, pp. 65–72, 2009.

[34] H. Suzuki, T. Nishizawa, and T. Hibi, "Therapeutic strategies for functional dyspepsia and the introduction of the Rome III classification," *Journal of Gastroenterology*, vol. 41, no. 6, pp. 513–523, 2006.

[35] F. Cremonini, S. Delgado-Aros, and N. J. Talley, "Functional dyspepsia: drugs for new (and old) therapeutic targets," *Best Practice and Research Clinical Gastroenterology*, vol. 18, no. 4, pp. 717–733, 2004.

[36] A. M. Wren, L. J. Seal, M. A. Cohen, et al., "Ghrelin enhances appetite and increases food intake in humans," *Journal of Clinical Endocrinology and Metabolism*, vol. 86, no. 12, pp. 5992–5995, 2001.

[37] T. Akamizu, K. Takaya, T. Irako, et al., "Pharmacokinetics, safety, and endocrine and appetite effects of ghrelin administration in young healthy subjects," *European Journal of Endocrinology*, vol. 150, no. 4, pp. 447–455, 2004.

[38] T. Akamizu, H. Iwakura, H. Ariyasu, et al., "Repeated administration of ghrelin to patients with functional dyspepsia: its effects on food intake and appetite," *European Journal of Endocrinology*, vol. 158, no. 4, pp. 491–498, 2008.

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摂食障害の合併症と治療

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はじめに

厚生労働省調査研究班の最後の疫学調査は1992年に全国の300床以上の病院を対象にアンケート方式で行われた。神経性食欲不振症(anorexia nervosa: AN)と神経性大食症(bulimia nervosa: BN)の推定患者数は10～29歳の女性10万人に対してそれぞれ29.3人と6.7人となり，臨床現場からは過小評価ではないかと危惧された。一方，京都市の女子中学生から大学生を対象に自己記入式の摂食態度調査表による調査では，1982年から2002年の20年間に摂食障害患者数は増加しており，ANは200～600人に1人，BNは50～350人に1人という高い有病率が得られた。

患者数の増加とともに患者の年齢の幅が広がっている。小児発症例では，成長期の栄養障害は身体，精神，社会的発達に障害を残す。30歳以上や結婚や出産後の発病や再発も増加しており，慢性遷延化して社会復帰できずに経済的な問題を抱える。また，骨粗鬆症，腎不全などの内科的合併症やうつ病などの精神疾患併存症によって医療費負担の増大と，自立生活の困難さが社会問題化している。

シンポジウムでは摂食障害の合併症と身体的治療について概説したので，本稿では要約して紹介したい。

Ⅰ. 神経性大食症の合併症と治療

(1) 疾患の概略

本邦にはまだ診断基準がない。自分では抑制できない発作的なむちゃ食いを繰り返す疾患である。体重は正常範囲か肥満である。過食中は何も考えないという開放感ゆえに止められない。脳が甘くて脂っこい食品を快と感じることが報告されており，低カロリー食品では代用できない。過食発作は夜に多く，疲れたときや暇なときに起こりやすく，習慣になると毎日，毎食後にも起こる。一方，自分の体型や体重に異常なこだわりがあり，過食後，自己嘔吐や下剤乱用で体重の増加を抑える(図1)。過食後は後悔や自責の念にさいなまれ，強い抑うつに襲われ，就学・就労できなくなったり，万引きや自傷行為をしたりすることがある。境界性人格障害，アルコールや薬物依存を合併することもある。患者の本音は過食だけを止めてやせを維持することで，内面への自己評価が低いため，やせにのみ価値を見出すという認知のゆがみが強化され，目標体重は達成困難なほど低い。過食中はつらいことを考えないで済むというメリットに加えて，アルコールや薬物依存

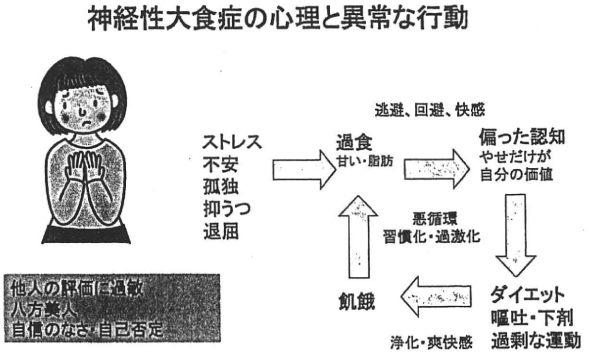

図1 神経性大食症の過食と排出行為の悪循環

や自傷行為などの問題行動を抑止している。

(2) 身体的合併症

正常体重のため低栄養による異常は少ない。自己嘔吐例では唾液腺の腫脹や手甲の吐きだこを認め，電解質異常（低 Na, Cl, K 血症），脱水，腎不全，偽性バーター症候群，不整脈，逆流性食道炎などを認める。

(3) 治療

過食を消失させるよりコントロールすること，目標体重を標準体重の 85％以上に適正化させることから始まる。過食は嘔吐や下剤乱用による身体的飢餓によっても惹起されることを認識させる。飢餓を予防する食生活(適切なエネルギーと栄養素を摂取，嘔吐や下剤乱用を減少）を薦め，過食しやすい環境や生活パターン（食べ物が多い，夜型の生活）を修正する。食事日誌にその日の出来事や摂食の時間や内容を記入して，抑うつ，不安，孤独，退屈，ストレスが過食の引き金になっていることに気付かせ，費やしている金額や時間を徐々に減らすプログラムを作成する[1]。

ストレスと受け取りやすい認知の偏りを修正しながら，コーピングスキルの向上をはかる。本人が受け取るストレスを減らし，ストレスを適切な方法で解決する行動パターンを学ばせる。認知行動療法や，近年，対人関係療法の有効性が報告され[2]，selective serotonin reuptake inhibitor などの抗うつ薬もある程度有効である。グループ療法も行われる。

Ⅱ.――神経性食欲不振症の合併症と治療―

(1) 疾患の概略

対処困難な状況になるとやせたい気持ちになることが本症の本質である。発病の契機は半数がダイエットである。食事制限や過剰な運動にかまけているといやな現実に直面することから逃れられ，やせると不快でつらいことに鈍感になれる。この擬似安心感ゆえにますますやせようと努力して治療しようとはしない。また，年齢相応の負担が軽減され，周囲の配慮を得られるというメリットがある。

小食の一方で，思考や行動は食に関することばかりになる。料理番組や料理雑誌を食い入るように見て，スーパーやデパート地下の食品売り場をうろつき，有名で高価な食品に執着し，母親に摂食を強制し，栄養科や調理師を志望する。これらは飢餓による代償性の食への執着で生体の合目的反応である。ついには食欲に負けてむちゃ食いが始まると，やせを維持するために自己嘔吐や下剤・利尿剤の乱用をする。生活すべてが食に振り回され，集中力や判断力が低下し，情緒や社会性や人格も変化する。これらは，飢餓にともなう精神症状で飢餓症候群という。健康人の飢餓実験でも，本症に似た心理行動異常が出現することが明らかにされている[3]。家庭や医療現場でのトラブルの多くは異常行動が原因である。しかし，これらは低栄養状態を改善しない限り軽快しない。

(2) 身体的合併症

症状や検査異常のほとんどは栄養不良の影響である[4]。低血圧，徐脈，低体温は生体の省エネである。厚生労働省精神・神経疾患研究班（前主任研究者：国立国際医療センター国府台病院心療内科 石川俊男先生，現主任研究者：大阪市立医科大学精神神経科 切池信夫先生）は 2007 年度に摂食障害救急患者治療マニュアルを作成し，救急搬入時診察や身体面管理のポイントをまとめた（表 1)。重篤な合併症とその対処を概略した (表 2)。

多くの合併症は栄養状態が改善し排出行為が止まれば回復するが，後遺症になるものがある。成長期の 15 歳以下で発症した患者では背の伸びが止まる。患者の約 50％で骨のカルシウム量(骨密度)の低下を認める[5]。低下は迅速であるが，回復は遅く，AN が治癒しても骨密度は正常域に達しないことがある。体重と月経を回復させることが一番の治療法で，女性ホルモン治療は超低体重者のみで効果がある。ビタミン D3 やビタミン K2 は骨密度低下を阻止できる。女性ホルモンの回復も体重に比例する。月経は標準体重の最低でも 85％以上に回復して最短でも 6 ヵ月後に再来する。標準体重の 85％以上に回

表1 救急で見られる症状と疾患

症状	疾患	要因
意識障害・痙攣	低血糖昏睡	
	電解質異常	低ナトリウム血症，低カリウム血症，低リン血症
	ウエルニッケ脳症	ビタミンB1欠乏
	悪性症候群	
	急性薬物中毒	
	糖尿病の合併症	インスリン過剰投与，ケトアシドーシス
腹部・消化器症状	急性胃拡張	
	上腸間膜動脈症候群	
	逆流性食道炎	自己誘発性嘔吐
	食道破裂	自己誘発性嘔吐
	マロリー・ワイス症候群	自己誘発性嘔吐
	急性膵炎	大食
	下剤乱用症候群	
	便秘	
呼吸器症状	誤嚥性肺炎	自己誘発性嘔吐
	結核・非結核性抗酸菌症	
	気胸，縦隔気腫	やせ，自己誘発性嘔吐
循環器症状	起立性低血圧	やせ
	心電図異常，不整脈	低栄養，電解質異常
	心不全	低栄養，低リン血症，低セレン血症
	タコツボ型心筋症	低血糖
腎・泌尿器症状	腎不全	脱水，横紋筋融解症，低カリウム血症（偽性バーター症候群）
	尿管結石	
筋・骨格筋症状	筋力低下	横紋筋融解症，低カリウム血症
	テタニー	低カリウム血症，低カルシウム血症，低マグネシウム血症
	骨折	骨粗鬆症，身体能力低下による転倒
	神経麻痺	脂肪組織の減少によって圧迫で発症

復し，心理的にも安定し，挙児を希望する無月経の患者では排卵誘発治療は行うことが可能で，異常出産，児の体重や健康度は健常群と差がない。妊娠中の母体の低体重や低栄養は流早産，低体重児，未熟児，帝王切開の合併率を高くする。

(3) 治療

① 内科的緊急入院の適応と労作制限

難治性疾患克服研究事業（前主任研究者：日本医科大学生理学 芝崎保先生，現主任研究者：東京医科歯科大学 小川佳宏先生）では，2007年度に神経性食欲不振症プライマリケア・ガイドライン(15歳以上を対象）を作成し，一般医向けに合併症の評価，緊急の内科的入院の適応，体重に応じた労作制限の目安，栄養療法，後遺症対策をまとめた。この背景には，摂食障害患者数の増加と摂食障害の身体管理の特殊性がある。① 標準体重の60％以下のやせ，② 全身衰弱（起立，階段昇降が困難），③ 重篤な検査異常や合併症（低血糖性昏睡，低カリウム血症，不整脈，腎不全，横紋筋融解症，感染症），④ 著しいやせはないものの1ヵ月に5kg以上の体重減少があり消耗が激しく，絶食に近い摂食量の減少が続いている場合は内科的緊急入院の適応である。やせにもかかわらず過活動で，就学・就労や競技スポーツへの参加を強く希望し，転倒の危険があっても制止を守らないことが多い。やせの程度に応じた活動制限を指示する（表3)。体重だけでなく異常検査値の程度も考慮して判断すべきである。一方，小児ANでは身体症状を訴え，やせ願望が明らかでないことが多く，子ども家庭総合研究事業（主任研究員：慶応大学医学部小児科 渡辺久子先生）では思春期やせ症の予防と早期発見のために冊子を作成し，プライマリケアの普及に努めている。日本小児心身医学会は2009年に小児の神経性無食欲症診療ガイドラインを出版している[6]。

② 栄養療法

低体重に比例して内科的合併症や後遺症は増加し，飢餓による精神症状[10]や脳機能の低下がある状

表2　重篤な合併症と治療

重篤な合併症	病態の説明と治療
低血糖性昏睡	標準体重の50%以下の患者の60%に既往を認める。食事時間が遅れたり，長時間の絶食後，特に早朝に起こりやすい。低血糖時でも頻脈，発汗，空腹感はない。記銘力障害やろれつがまわらないなどで気づかれる。インスリン分泌能は低下しているので，糖の大量急速投与ではむしろ高血糖を誘発する。20%ブドウ糖液20～40 mlをゆっくり静脈内投与する。また，グリコーゲン貯蔵がないため，経口摂取するまでは7.5～10%糖液の持続点滴を行う。低血糖昏睡時に心電図異常やタコツボ心筋症の合併をみることがある。
低カリウム血症	下剤・利尿剤乱用によってカリウムが失われる。自己嘔吐で胃酸のHイオンが失われることによるアルカローシスで尿中K排泄が増加する。さらに循環血漿量の減少によってレニン-アルドステロン系が刺激されて，Kの腎からの排泄は増加する。低カリウム血症は筋力低下，イレウス，不整脈，横紋筋融解症，腎不全の原因になる。2.5 mEq/L以下は経静脈性にKを投与し，速度は10 mEq/hr以下，総量40 mEq/日で，カリウム製剤を摂取させる。
低ナトリウム血症	下剤・利尿剤乱用によってナトリウムは失われる。また，胃液，胆汁，膵液，のNa濃度は高いので，大量・頻回の嘔吐では低ナトリウム血症が起こりうる。循環血漿量の減少を伴う。低血圧，脱力感や筋力低下を認める。生理食塩水による補液を行う。補正速度は1～2 mEq/L/hrを超えないようにして，重篤な臨床症状が少ない125 mEq/Lを目標にし，central pontine myelinolysisの併発を予防する。その後は経口で食塩を投与してゆっくり補正する。心因性多飲症の場合は水制限，furosemideの静脈内投与，3%食塩水50 mlの点滴静脈内投与を行う。
その他の電解質異常	大量・頻回の嘔吐や下剤の乱用者，慢性アルコール症の合併者では，低カリウム，低ナトリウム血症に加えて，低マグネシウム血症やマグネシウム不足に伴う低カルシウム血症が起こりうる。血清Mg　1 mg/dl以下の場合はリン酸を含まない輸液製剤にコンクライトMgや補正用硫酸Mg液を加えて点滴する。
腎不全	脱水，低K血症による腎機能障害，横紋筋融解症，偽性バーター症候群による。腎前性腎不全や腎性腎不全への進行などある。一時的な透析を必要とすることもある。
マロリー・ワイス症候群	自己嘔吐によって逆流性食道炎やマロリー・ワイス症候群を合併する。
下剤乱用症候群	カタル性大腸や嘔気が出現する。内視鏡検査では大腸は正常の粘膜ひだを失い，メラニン色素が沈着し，びらん，潰瘍，出血を認める。
上腸間膜動脈症候群	内臓脂肪の減少によって大動脈からの上腸間膜動脈の起始角が狭まり，間を通過する十二指腸が圧迫されて慢性イレウス状態になる。下垂した胃に大量に食物や水分が入ると，十二指腸をさらに圧迫してイレウスが増悪する。大量の胆汁色の嘔吐が起こる。内臓下垂でもたれや腹痛を訴える患者には大食させない。食後は右側甲臥位にさせる。体重を増加させ，脂肪量を増やす。
タコツボ心筋症	急性心筋梗塞と同様の心筋由来酵素の上昇と心電図異常を呈するものの，冠動脈造影では狭窄を認めず，予後の良い心筋症とみなされている。超音波検査で心尖部のakinesisと心基部の代償性のhyperkinesisが認められる。低血糖昏睡に併発することがある。
抗酸菌，真菌感染症	やせに伴うサイトカインの増加が代償性に作用して，一般にウイルス感染に罹患しにくい。しかし，慢性の低栄養は結核，非結核性抗酸菌，深在性真菌感染症の易感染性をもたらすことを再認識すべきである。
急性唾腺症	自己誘発性嘔吐の常習者では唾液腺が腫れていることが多い。急に中止すると，唾液腺は自然に縮小することもあるが，一方，さらに腫大して発熱，唾液腺の疼痛と圧痛，炎症反応を伴うことがある。消炎鎮痛剤を投与する。
Refeeding症候群	摂食，経腸，経静脈性栄養などのいずれの栄養法に限らず，急速に栄養状態が改善している時期に起こりうる。再栄養時に細胞内にカリウムやリンが移動し，リン酸が急速に消費されることによって，低カリウム血症や低リン血症が起こりうる。低リン血症による心不全は死因になりうる。再栄養後2週間目に多い。血清Pのモニターを行い，低下時には燐酸2K製剤で補充する。
ウェルニッケ・コルサコフ症候群	ビタミンB1の欠乏による。点滴などで糖を補う場合はビタミンB1も投与する。
事故	体力と筋力低下，注意力や判断力の低下により，転倒，転落，歩行や自転車乗車時の交通事故がある。脳挫傷や骨折を合併する。

態では心理的治療は奏功しないので，栄養療法が優先される。

強力な心身治療の枠を設定できる入院治療を除いて，やせによって免れている現実の問題への対処能力が回復するまでは，健康体重まで一気に戻すことは困難で，段階的に体重増加を図るしかない。方法は，インパクトのある治療動機の発掘と体重増加を拒む要因の排除である[7]。

動機を持たせるために心理教育的アプローチを行う（資料は日本摂食障害学会 www.jsed.org の「摂食障害の理解と治療」でダウンロード可能）。患者は知的レベルは高いが，体重，食欲，栄養の基本的知識

表3 やせの程度による身体状況と活動制限の目安（15歳以上）〔神経性食欲不振症プライマリケア・ガイドラインより抜粋，改変〕

標準体重%	身長158 cm	身体状況	活動制限
55未満	29.3 kg	低血糖昏睡など重症の内科的合併症が多い	入院による栄養療法の絶対適応
55～65	29.3～34.6 kg	摂食だけで体重増加に困難がある。機敏な動作ができず，最低限の日常生活にも支障がある	入院による栄養療法が適切
65～70	34.6～37.2 kg	軽労作の日常生活にも支障がある	自宅療養が望ましい
70～75	37.2～39.9 kg	軽労作の日常生活は可能	制限つき就学・就労の許可，重労作体育禁止
75以上	39.9 kg～	通常の日常生活は可能，低身長や骨粗鬆症阻止	就学・就労の許可，競技スポーツの許可
80以上	42.6 kg	80%が本症の診断基準	
85以上	45.2 kg	月経再来の可能性あり	

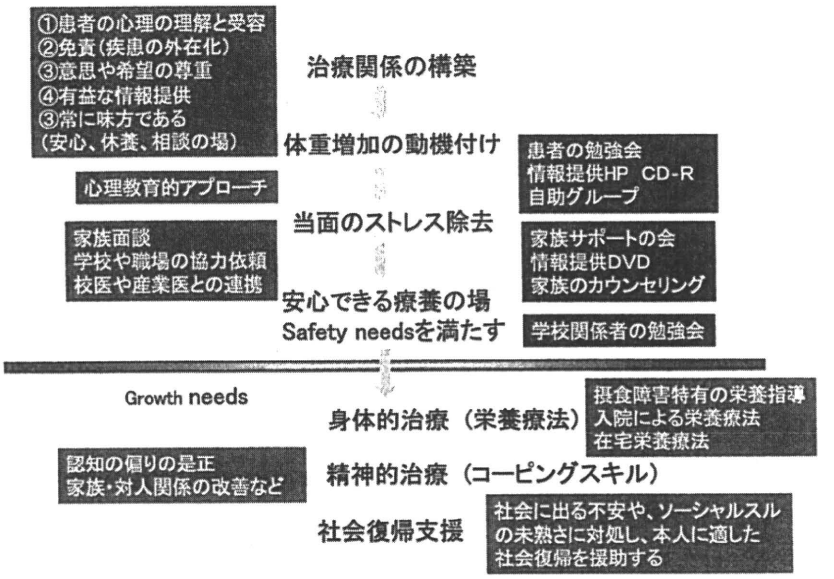

図2 神経性食欲不振症の治療の概略

さえ知らない。やせはストレスの誤った回避で現実逃避や疾病利得があることなど丁寧に教育する。困った食行動は自分が悪いのではなく，疾患のせいであると知ると安心する。また，過食や精神症状は栄養状態がよくならない限り改善しないことも認識させる。患者は体重増加によるメリットがやせのメリット上回ると自覚したときのみ栄養療法を受け入れるので，「通学したい，修学旅行に行きたい，身長を伸ばしたい，入院したくない」などの現実的な利益を治療動機にする。たとえ，治療意欲を持っても，療養環境が不適切では意欲も萎える。体重回復するといじめられる学校にいかなければいけない，などの体重増加をはばむ当面の要因があれば，この解決が急がれる。家庭が安心して療養できる場になること，当面の大きな心理ストレスがないことが早期回復の条件で，家族（情報提供DVD：「拒食症の家族教室」2巻はhttp://www3.grips.ac.jp/~eatfamilyから購入可能）や学校・職場の協力を得る[8]。これらが満たされない限り，栄養療法も心理的治療も進展しない（図2）。

患者は受け入れられる体重の設定を持っており，栄養素やメニューにもこだわりが強いので，最初から栄養バランスの良い三食を摂取することは外来患者にはハードルが高い。体重1 kgを維持するエネルギーは49 kcalで健康人より高い[9]。好物を取り入れて可能な限り1日三食で摂取エネルギーを必要エネルギーに近づける。カロリーが明示された宅配便やレトルト食品，高カロリー流動食も利用する。本人の食事態度を否定せずに良い点を支持しながら，改善点をアドバイスし，「体が温かくなった，早く歩ける」などの自覚症状や，検査所見の改善をフィードバックして良い食行動を強化する。