Prolonged treatment with glycerophosphocholine, an acetylcholine precursor, does not disclose the potentiating effect of cholinesterase inhibitors on GHRH-induced somatotroph secretion in anorexia nervosa


*Division of Psychiatry, Department of Neurosciences, **Division of Endocrinology, Department of Internal Medicine, University of Turin, Turin, Italy

ABSTRACT. Unlike normal subjects, in patients with anorexia nervosa (AN) the GH response to GHRH is refractory to the increasing and inhibitory effect of cholinergic agonists and antagonists, respectively. This cholinergic impairment could reflect malnutrition-induced exhaustion of acetylcholine (Ach) precursors. We studied whether treatment with glycerophosphocholine (GLY), an Ach precursor, could disclose the potentiating effect of pyridostigmine (PD) on the GH response to GHRH in AN. In 6 young women with AN (AW) we studied the GH response to iv GHRH (1.0 μg/kg) alone and combined with oral PD (120 mg) before and after 1 month of oral treatment with GLY (400 mg thrice daily). Eight age-matched normal women (NW) were studied as controls. Before GLY, basal GH levels in AW were higher (p<0.05) than in NW. The GH response to GHRH in AW was higher (p<0.05) than in NW. PD failed to modify the GHRH-induced GH rise in AW, while it enhanced it in NW (p<0.05). One month treatment with GLY in AW did not modify the GH response to GHRH either alone or combined with PD. This study shows the existence of a derangement in the cholinergic control of somatotroph function in AN and indicates that treatment with Ach precursors does not exert any effect on this impairment. This could reflect primary alterations of cholinergic neurons, though the effectiveness of more prolonged treatment and/or higher doses of cholinergic precursors needs to be verified.

INTRODUCTION

Today, it is still unclear whether a defective nutritional state leading to peripheral GH resistance or a primary hypothalamic dysfunction is responsible for GH hypersecretion in anorexia nervosa (AN) (1-3). GH hypersecretion could be partially explained by the peripheral GH resistance leading to reduced IGF-I synthesis and release which, in turn, leads to the reduction of the negative IGF-I feedback effect (1-4). However, the evidence that a low dose of recombinant human IGF-I inhibits but does not normalize spontaneous and GHRH-stimulated GH secretion in AN points to the existence of a defective hypothalamic control of GH release in this condition (5). Several abnormalities in the neural control of GH secretion in AN support this hypothesis (6-14). Previous studies showed that the blockade of cholinergic muscarinic receptors by pirenzepine abolishes the GH response to GHRH in normal subjects (15) while it only blunts the exaggerated somatotroph responsiveness to the neurohormone in patients with AN (10, 11). Other studies showed that pretreatment with pyridostigmine (PD), a cholinesterase inhibitor which potentiates the GH response to GHRH in normal subjects, fails to increase the GHRH-induced GH rise in patients with AN (12). As the stimulatory influence of acetylcholine (Ach) on GH secretion is thought to be mediated by the inhibition of hypothalamic somatostatin (15-21), these findings led to hypothesize the existence of an hypothalamic cholinergic hyperactivity in AN, leading to a reduced somatostatinergic
tone. Later on, further studies (12) cast doubt on the existence of a reduced somatostatinergic activity in AN. In fact, unlike PD, arginine potentiated the GH response to GHRH in patients with AN as well as in normal subjects (12). As arginine, like PD, is thought to act via the inhibition of hypothalamic somatostatin (22), these findings indicate that the activity of somatostatinergic neurons is probably preserved in AN. Thus, we hypothesized that the failure of cholinergic agonists to potentiate GH release in AN may be due to a primitive reduced, rather than increased, activity of the central cholinergic system. This impairment could be associated with a malnutrition-induced exhaustion of Ach precursors. In fact, there is evidence that nervous tissue cannot synthesize choline, which is ultimately derived from diet and delivered to neurons through the blood stream (23). Therefore, a reduced choline intake could influence the synthesis of Ach and thus reduce neurotransmitter availability in the central nervous system (CNS). To this regard, a normal availability of Ach in the CNS seems to be crucial for the cholinergic effects on GH secretion, as only cholinesterase inhibitors, but not direct cholinergic agonists, have been shown to stimulate GH secretion both in animals and in humans (24-26).

In order to evaluate whether the cholinergic impairment in the control of GH secretion in AN could reflect malnutrition-induced exhaustion of Ach precursors, we studied the effect of PD on the somatotroph responsiveness to GHRH before and after a prolonged treatment with glycerophosphocholine (GLY), an Ach precursor, in patients with AN. This latter cholinergic compound has previously been demonstrated to enhance Ach availability and release at CNS in patients with Alzheimer’s disease (23), a condition characterized by a marked impairment of cholinergic neurons (27).

MATERIALS AND METHODS

Six young women with AN (AW) (age, mean±SE, 25.4±5.3 yr; BMI 14.6±1.5 kg/m²) were recruited for this study. All AW met the diagnostic criteria for AN according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM IV) (28) and were in the acute phase of the illness. None of them had a clinical history of depression or evidence of other diseases. None had received drugs for at least one month before the study.

Eight healthy young women (NW) (age, mean±SE, 22.0±1.8 yr; BMI 21.1±1.8 kg/m²) in their early follicular phase were studied as controls. They were selected from a group of medical students and working paramedics. None of them had either received drugs for at least one month before the study or was assuming oral contraceptives. They did not report any history of eating disorders or significant weight loss over the past year. All AW and NW gave their written informed consent to partici-