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Physiological Roles for Butyrylcholinesterase: A BChE-Ghrelin Axis

Stephen Brimijoin, Vicky Ping Chen, Yuan-Ping Pang, Liyi Geng, and Yang Gao

Department of Molecular Pharmacology and Experimental Therapeutics, Mayo Clinic, Rochester MN 55905, USA

Stephen Brimijoin: Brimijoin@mayo.edu; Vicky Ping Chen: Chen.vicky@mayo.edu; Yuan-Ping Pang: Pang@mayo.edu; Liyi Geng: Geng.liyi@mayo.edu; Yang Gao: Gao.yang@mayo.edu

Abstract

Butyrylcholinesterase (BChE) has long been regarded as an “orphan enzyme” with no specific physiological role other than to metabolize exogenous bioactive esters in the diet or in medicines. Human beings with genetic mutations that eliminate all BChE activity appear completely normal, and BChE-knockout mice have been described as “lacking a phenotype” except for faster weight gain on high-fat diets. However, our recent studies with viral gene transfer of BChE in mice reveal that BChE hydrolyses the so-called “hunger hormone,” ghrelin, at a rate which strongly affects the circulating levels of this peptide hormone. This action has important consequences for weight gain and fat metabolism. Surprisingly, it also impacts emotional behaviors such as aggression. Overexpression of BChE leads to low ghrelin levels in the blood stream and reduces aggression and social stress in mice. Under certain circumstances these combined effects contribute to increased life-span in group-housed animals. These findings may generalize to humans, as recent clinical studies by multiple investigators indicate that, among patients with severe cardiovascular disease, longevity correlates with increasing levels of plasma BChE activity.

Keywords

Butyrylcholinesterase; Ghrelin; Obesity; Aggression; Growth hormone secretagogue receptor

INTRODUCTION

Butyrylcholinesterase (BChE, E.C.3.1.1.8) is well recognized for its role in metabolizing bioactive esters in food and medications. It is best known for inactivating succinylcholine, a muscle relaxant used to facilitate abdominal surgery but endangers patients with “atypical BChE” that hydrolyzes it poorly. Although some BChE genetic variants are associated with elevated risk of cardiac death [1, 2] or early-onset Alzheimer’s disease [3], this enzyme was

Corresponding author: Stephen Brimijoin, Department of Molecular Pharmacology and Experimental Therapeutics, Mayo Clinic, 200 First Street SW, Rochester MN 55905, USA, Telephone: +1 507 2848165, Fax: +1 507 28449111, Brimijoin@mayo.edu.

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not known to play a direct role in mammalian physiology. But in 2004, De Vriese reported that BChE is capable of hydrolyzing the acylated peptide known as “ghrelin,” which stimulates hunger and food-seeking [4]. This deacylation reaction cleaves the octanoyl group essential for ghrelin activity at the growth hormone secretagogue receptor, “GHSR1a,” which drives growth hormone release from the pituitary gland [5, 6]. The importance of the finding was underappreciated at the time, for two likely reasons. First, the reaction seemed too slow for physiological impact. Second, the small size of BChE’s active site pocket made it hard to see how the enzyme could accommodate a substrate more than an order of magnitude larger than butyrylcholine.

BChE is a ghrelin hydrolase

Our own views of BChE’s catalytic interactions with ghrelin changed very recently, after accidentally observing that mice with high blood levels of BChE generated by viral gene transfer showed dose-dependent reductions in plasma ghrelin. Thus, after a moderate viral dose (e.g., 10^{10} particles per mouse), there was a marginal decline ($\sim 10\%$). A 10-fold higher dose caused a $\sim 50\%$ decline, and a 100-fold higher dose reduced ghrelin levels 90% or more. These effects arose within ten days and lasted for as long as high BChE levels were sustained (months to years). In fact, ghrelin is an unusual peptide hormone with a biological activity that requires octanoylation of its Ser3 residue [5, 7]. BChE, an esterase with wide substrate specificity, does cleave this ester bond and transforms ghrelin into desacyl-ghrelin, which is inactive at GHSR1a although it may have other physiological targets [8, 9]. Because gene transfer of irrelevant luciferase did not alter plasma ghrelin, it seemed likely that the effects of high BChE were specific. To test that conclusion we gave vector-treated mice an i.p. injection of the selective BChE inhibitor, iso-OMPA. This treatment returned ghrelin levels to near normal for 12–24 hr in mice with excess BChE [10]. Furthermore we observed that plasma ghrelin levels in untreated, BChE-null C57BL/6 mice were consistently 40% higher than in wild type animals of the same strain [10].

The summarized findings left little doubt that BChE is a regulator of circulating ghrelin, but did not explain how the enzyme can deacylate such a large substrate. We addressed that issue by molecular dynamics simulations of ghrelin and BChE. These showed most of the peptide backbone excluded from the active site, but the crucial ester bond was in an orientation conducive to hydrolysis. In fact, the consensus structure [10] had ghrelin’s carbonyl ester carbon positioned closer to the catalytic serine hydroxyl than was previously seen with the equivalent atoms in BChE-cocaine simulations [11].

Further studies using commercial immunoassays for ghrelin and desacyl-ghrelin yielded identical rates for the disappearance of intact peptide and the appearance of its breakdown product, confirming the original findings of ghrelin hydrolysis by BChE. Similar results were obtained by quantitative mass spectrometry in collaboration with Schopfer et al, [12], and again with a new assay developed to track ^3H -ghrelin deacylation by quantitative transfer of free octanoic acid from aqueous media into toluene [13]. Although BChE hydrolyzes ghrelin less efficiently than smaller substrates, with a K_m of $3.6 \pm 0.3 \mu\text{M}$ and k_{cat} of $2.2 \pm 0.1 \text{ min}^{-1}$ it can exert a strong influence on circulating levels of ghrelin. BChE is highly concentrated in the amygdala, hypothalamus, and pituitary gland [14, 15], where

ghrelin and its receptor are prominently localized [16]. This spatial arrangement may facilitate a central BChE-ghrelin regulatory circuit that impacts emotional behaviors. In short, past and present observations provide good grounds for concluding that BChE has evolved in part to serve as a natural ghrelin hydrolase. The next logical issue is to determine fully how it affects ghrelin-driven events in live organisms.

Physiological role of BChE

It is now reasonable to ask this question: does BChE serve as an important ghrelin modulator or is its hydrolytic activity a mere curiosity? Existing data support the idea that BChE does impact ghrelin-driven events. In 2008, Lockridge's group reported that BChE^{-/-} S129 mice showed excessive weight gain on a high fat diet under parameters that did not promote obesity in mice with normal BChE expression [17]. That same year we found excess weight gain in rats given daily exposures to low doses of chlorpyrifos [18]. This irreversible organophosphate inhibitor impacts BChE more readily than acetylcholinesterase [19]. We have now repeated Lockridge's finding in a second BChE^{-/-} mouse strain (C57BL/6) and also have shown that a BChE gene transfer can restore resistance to obesity in genetically BChE-deficient mice (unpublished data). These observations are in line with the idea that ghrelin arouses hunger and stimulates eating, and that BChE's ability to deacylate ghrelin contributes to the regulation of these phenomena. Oddly, however, neither we nor Lockridge saw increased *food consumption* in BChE-null animals. Other apparent paradoxes have come to light as well. For example, plasma ghrelin levels in obese BChE^{-/-} mice and humans are actually lower than in lean individuals [20]. One possible reason is that ghrelin as a hormone is influenced by many factors, only one of which is diet. We hypothesize that it may affect fat deposition more directly via actions within the adipocyte, yet to be discovered. In fact, although ghrelin is a documented regulator of food intake and energy metabolism, its essential function is still obscure. For example, eliminating the gene encoding the ghrelin peptide or its activating enzyme, ghrelin octanoyl acyl transferase (GOAT), does not seem to produce any severe phenotype in mice, such as altered body weight, length, and composition, or even a change in daily food intake [21–24]. Thus, the BChE-ghrelin axis now appears far more complex than was originally envisioned, and the intertwined roles of BChE and ghrelin in obesity progression clearly deserve intensive further investigation.

Emotional behaviors represent another complex arena in which BChE can exert a major impact by deacylating ghrelin. Our awareness of this link was prompted by cage-side observations revealing that group-housed male Balb/c mice accumulated fewer bite wounds over time if they and their cage mates had ever received BChE gene transfer. As time continued, the BChE vector recipients outlived the untreated or luciferase vector treated controls (Fig 1). These observations were not made under conditions that met standards for unbiased analysis of mouse longevity, and they were certainly influenced by ongoing cage-fighting and unequal housing conditions. Thus they have no claim to be definitive, but they strongly indicate that administration of BChE vector can alleviate psychosocial stress.

For quantitative determinations of aggressive behaviors we turned to Klaus Miczek's rigorous "resident-intruder paradigm." This model actively provokes aggression in a host

male (residing in a cage where he had mated with a female), when another male is introduced [25]. Bites and fights were videotaped and scored by a blinded observer. Under this procedure a distinctly different behavior pattern emerged between mice that had undergone BChE gene transfer versus those that had not [10]. The chief difference was in the rate at which aggressive acts per session rose during repeated daily encounters. The rise in aggression was fastest in untreated mice or mice given a different vector that did not decrease circulating levels of ghrelin (Fig 2A), i.e., vector encoding luciferase or a mutated version of BChE (CocH-6 T) that readily hydrolyzes cocaine but has poor catalytic efficiency with ghrelin [10]. The impact was all the more surprising because ghrelin had not been recognized as a factor in aggression although widely known to affect fear and anxiety [26]. Therefore we used the same model to test the effect of sustaining modestly elevated ghrelin levels by means of double gene transfer with cDNA encoding a) ghrelin peptide and b) its activator enzyme, GOAT. This combined treatment did raise aggression scores, but not when BChE gene transfer was added to prevent the rise in plasma ghrelin (Fig 2B).

In these aggression experiments untreated mice could all be induced to fight, although the rate of onset and intensity of that outcome differed between the two tested strains (Balb/c > C57BL/6). Inbred mice show large strain differences in aggressive behaviors and stress responses. This fact must be considered carefully when interpreting outcomes, especially in purely observational studies. Shortly after our aggression data were published, however, Chatonnet's group released a study focused on cognitive function in BChE-knockout and wild type mice [27]. Their report included a statement that they were "unable to confirm" our observations on mouse aggression. This wording suggested a divergent view. However, in private exchanges the senior author clarified the intended meaning, which was simply that their experiments had not been designed to assess such behavior. Thus there is no conflict. Meanwhile we acknowledge that experiments have yet to be performed to test the impact of high BChE levels on aggression in *females*, an important remaining issue.

Complex impact of ghrelin and BChE in emotional behaviors

Clearly, emotional behaviors in rodents must be evaluated with care. The mechanism by which ghrelin affects mood-related behaviors has not yet been fully elucidated. There is general agreement that ghrelin levels rise in response to various stressors, but two opposite models for ghrelin actions in stress responses are under debate. One is based on the concept that ghrelin is in itself a stressor, while the other views ghrelin as calming under stressful conditions. In any event there is fair agreement that ghrelin strongly affects "perceived stress," which can then influence a wide range of responses. The complexity of the underlying neural circuitry is further enhanced by special features of GHSR1a. GHSR1a is a G protein-coupled receptor mainly expressed in the hypothalamus and pituitary [28]. It has unusually high constitutive activity that contributes to downstream signaling and physiological processes [29]. Thus, even in the total absence of ligand, GHSR1a receptors show significant signaling, substantial inactivation, and unusually high levels of internalization [30]. This curious behavior has contributed to controversy over the true impact of ghrelin in regard to emotion. Prominent neurobehavioral scientists have reached diametrically opposite conclusions from studies of anxiety and fear in rodents. In 2006, Donahue et al reported that growth hormone, which is released in response to ghrelin

receptor activation, rises after exposure to stress [31]. That finding linked ghrelin to stress, but it did not indicate whether the hormonal response was a conveyer or a reliever of stress. Soon afterward, mouse experiments from Eric Nestler's group [32] and rat experiments from an Australian team [33] linked ghrelin to reduced behavioral signs of chronic and acute stress. On the other hand, in rat models of post-traumatic stress disorder, K.A. Goosens and coworkers found that ghrelin administration *enhanced* fear and anxiety [34].

A plausible explanation for these divergent outcomes can be constructed on the premise that ghrelin-induced release of *growth hormone* is an effective anti-stress response, but acute pulses of ghrelin and long-term elevations generate opposite effects. Thus, a sudden rise in ghrelin will stimulate functionally sensitized GHSR1a to release growth hormone, but chronically high ghrelin levels will weaken the response of GSHR1a receptors to subsequent pulses of the same peptide and, in turn, reduce growth hormone release. This seemingly contradictory behavior could be explained by the unusually high sensitivity of GSHR1a to desensitization and its unique propensity to self-activate in the absence of ligand [35, 36]. Preliminary results from our lab, designed to examine growth hormone release in response to a synthetic GHSR1a agonist, appear to support this concept (not shown).

Other factors add even further complexity to the task of gaining a comprehensive understanding of ghrelin's role in modulating aggression and other emotional behaviors. One such factor is the des-acylated peptide, lacking the octanoyl ester. There is a consensus that desacyl-ghrelin (DAG) does not interact productively with GHSR1a, but the literature suggests that DAG has one or more target receptors that remain to be clearly identified and linked to emotional states and behavioral outcomes [37]. Preliminary results from our ongoing studies are consistent with that interpretation and, specifically, they do not exclude the possibility that high levels of circulating DAG generated by BChE's action on the parent peptide might exert anti-aggressive effects through a separate receptor.

Conclusion

The findings summarized in this brief review highlight the fact that the BChE-ghrelin axis is one complex component in an intricate regulatory system composed of numerous known and unknown receptors, enzymes, neural circuits, and biological processes. It is obvious that ghrelin affects a wide array of physiological functions and pathological states including insulin release [38], adiposity [39], energy homeostasis [40], and the development and progression of several types of cancers [41]. Apart from these, ghrelin is also involved in psychosocial states, memory and learning [42]. From our perspective, BChE looks to be a key regulator of ghrelin in the peripheral circulation with widespread impacts, as suggested in the graphics of Figure 3. It now seems likely that intelligent manipulations of BChE, by any of various methods including gene transfer and nanoparticle delivery, might eventually prove to have therapeutic value in an array of metabolic and psychosocial disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

- BChE is a hydrolase that modulates ghrelin in the blood stream.
- BChE alters the impact of ghrelin on its growth hormone secretagogue receptor.
- Manipulating the BChE-ghrelin axis may alleviate obesity, anxiety, and aggression.

Fig 1.

Unpublished findings from long-term daily observations of group-housed male mice (32 pooled controls and 30 mice transduced at six weeks with adeno-associated virus (AAV) or helper dependent virus vector encoding mutated mouse BChE, “mBChE mut”). Plasma BChE levels in the vectors treated group were ~100-fold above normal and were sustained for the following 2 years. Initially, mice were housed 5 per cage, until signs of fighting arose (4 to 5 months), when they moved to single cage housing. The varied housing conditions prevent a definitive judgment of true lifespan although ANOVA showed a significant main effect of treatment (controls vs pooled vector-treated groups): $F_{1,60} = 13.64$, $P < 0.001$. No post-hoc testing was performed.

Fig 2.

Bite scores in confrontations between a resident male mouse and a male intruder [10]. **A.** 3-month Balb/c with AAV-luciferase vector ($n = 18$) versus mBChE mutant vector-treated ($n = 7$); AAV-Coch-6 ΔT treated mice ($n = 14$). **B.** AAV-luciferase treated 3-month C57BL/6 wild type ($n = 9$) versus same age C57BL/6 treated simultaneously with AAV vectors encoding cDNA for ghrelin and GOAT ($n = 6$); and same-age mice treated triply, with vectors for ghrelin, GOAT, and mBChE mutant ($n = 9$). * $p < 0.05$; *** $p < 0.001$; n.s., not significant.

Fig 3.

The BChE-ghrelin axis. Ghrelin is predominantly produced by the stomach and secreted into the blood stream. It crosses the blood brain barrier and affects growth hormone release from the pituitary gland, impacting appetite, stress responses, insulin sensitivity and even life span. Ghrelin is also produced, stored, and released in specific brain loci. In the hypothalamus it activates circuits that regulate hunger and body temperature. In the amygdala it affects emotions including fear, anxiety, and aggression. BChE in liver, plasma, and brain can hydrolyze ghrelin and transform it into its inactive desacyl form. This regulatory pathway appears to be physiologically important.