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Suborno Jati [†], Sumana Mahata [†], Soumita Das, [Saurabh Chatterjee](#), [Sushil K. Mahata](#) ^{*§}

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Review

Catestatin: Antimicrobial Functions and Potential Therapeutics

Suborno Jati ^{1,†}, Sumana Mahata ^{2,†}, Soumita Das ³, Saurabh Chatterjee ⁴
and Sushil K. Mahata ^{1,5,6,*‡}

¹ Department of Chemistry and Biochemistry, University of California San Diego, La Jolla, CA, USA

² Department of Medicine, University of California San Diego, La Jolla, CA, USA

³ Department of Biomedical and Nutritional Science, University of Massachusetts-Lowell, Lowell, MA

⁴ Department of Medicine, University of California Irvine

⁵ VA San Diego Healthcare System, 3350 La Jolla Village Drive, San Diego, CA, USA

⁶ Metabolic Physiology & Ultrastructural Biology Laboratory, Department of Medicine, University of California, San Diego (0732), 9500 Gilman Drive, La Jolla, CA 92093-0732

* Correspondence: smahata@health.ucsd.edu; Tel.: +(858)-552-8585 (ext. 2637)

† With equal contribution.

‡ Dedicated to Marie Helene Metz-Boutigue for establishing catestatin as an antimicrobial and a cell permeable peptide.

Abstract: The Chromogranin A (CgA)-derived peptide Catestatin (CST: hCgA₃₅₂₋₃₇₂) is highly conserved (>90% in 90% species) in mammalian species. The highest-evolved primates show 58.8% similarity with the lowest-evolved monotremes. CST was initially identified as a physiological brake in catecholamine secretion by inhibiting nicotinic-cholinergic signaling. CST also inhibits desensitization of catecholamine secretion, indicating that CST can act both as a cholinergic antagonist (short-term) and as a cholinergic agonist (long-term). The long-term effect sustains catecholamine secretion during stressful situations. CST is now established as a pleiotropic hormone: it affects the cardiovascular system by lowering blood pressure and cardiac contractility, enhancing baroreflex sensitivity, increasing heart rate variability, and promoting angiogenesis; and it increases insulin sensitivity by reducing inflammation, inhibiting hepatic glucose production, attenuating endoplasmic reticulum stress, and inducing glycogen production. The present review will highlight the important direct and indirect effects of CST, CST₁₋₁₅ (aka cateslytin), D-CST₁₋₁₅ (where L-amino acids were changed to D-amino acids), and human variants of CST (Gly364Ser-CST and Pro370Leu-CST) on microbial growth inhibition and their potential as therapy for antibiotic-resistant pathogenic microbes.

Keywords: Chromogranin A; catestatin; gut microbiome; antimicrobial peptide; and cell permeable peptide

1. Introduction

Chromogranin A (CgA), the acidic and secretory proprotein [1–3], is proteolytically cleaved to generate several biologically important peptides including Catestatin (CST: hCgA₃₅₂₋₃₇₂) [4–12]. The 21 amino acid peptide CST was identified in 1997 as a physiologic brake in catecholamine secretion that acts by non-competitive inhibition of nicotinic-cholinergic signaling [5,13–17]. Initial studies were conducted in rat pheochromocytoma cells and primary cultures of bovine chromaffin cells with bovine CST (bCgA₃₄₄₋₃₆₄) [5]. In 1999, CST was shown to inhibit desensitization of catecholamine secretion [18]. CST blocks nicotinic desensitization of catecholamine release, which might sustain catecholamine release when there is increased sympathetic outflow, such as during stressful situations. Thus, CST can act both as an antagonist to nicotinic-cholinergic transmission (short-term) as well as a partial agonist to nicotinic-cholinergic receptor (long-term). Alanine substitution mutants of bovine CST revealed crucial roles for Arg³⁵¹, Arg³⁵³, and Arg³⁵⁸ in inhibiting nicotine-induced catecholamine secretion [19]. Further studies with bovine CST using serial single amino acid truncations or single residue substitution by alanine identified the N-terminal 15 amino acids (bCST₃₄₄₋₃₅₈) as crucial both for nicotine-induced catecholamine secretion and desensitization [14].

Subsequently, in 2003, the anti-adrenergic effects of CST were demonstrated in mice [20]. The substantial (63%) β -sheet structure of CST in a hydrophobic environment was revealed in circular dichroism studies [19]. Electrophysiological studies on the interaction between CST and several combinations of neuronal acetylcholine receptor (nAChR) subunits expressed in oocytes revealed CST as a potent and reversible blocker of the nAChR, without significant discrimination among different nAChR subtypes (α_7 , $\alpha_3\beta_4$, $\alpha_3\beta_2$, and $\alpha_4\beta_2$) tested [21]. The above studies were also shown by the molecular modeling of nAChRs and their interaction with CST [22]. Amongst the three natural variants of CST (Gly364Ser, Gly367Val, and Pro370Leu) in US population, Pro370Leu-CST showed the highest potency of inhibiting catecholamine secretion and desensitizing catecholamine secretion, followed by WT-CST and Gly364-Ser-CST [23–25].

The hypotensive effects of intravenous CST were first shown in rats in 1998 after activation of the sympathetic outflow by electrical stimulation. CST effects were shown to be blocked by a histamine H₁ receptor antagonist but not by blockade of the α - and β -adrenergic receptors [26]. In 2010, hand vein studies in humans also revealed the hypotensive effects of CST [27]. In 2005, the anti-hypertensive effects of CST were exhibited in a monogenetic model of rodent hypertension (CgA knockout mice) with excess plasma catecholamines [28]. Besides excess catecholamines, reactive oxygen species (ROS) were also implicated in the development of hypertension in CgA-KO mice [29]. The antihypertensive effects of CST were later determined in mice (polygenic model of hypertension) and spontaneously hypertensive rats (polygenic model of hypertension) in 2012 and 2014, respectively [30,31]. CST was also demonstrated to improve dampened baroreflex sensitivity [32] and dysregulated heart rate variability in CgA-KO mice [33]. Central effects of CST on regulation of arterial blood pressure include excitation of both the bulbospinal (glutamatergic) neurons in the rostral ventrolateral medulla (RVLM) and GABAergic neurons in the caudal ventrolateral medulla (CVLM). Loss and gain of function studies in CST knockout mice confirmed that CST is necessary and sufficient to regulate blood pressure [34]. The effects of natural variants of CST on blood pressure and autonomic nervous system have been described previously in a review article [35]. Several studies in Langendorff perfused heart preparations implicate CST as a cardioprotective peptide inhibiting both inotropy and lusitropy under basal and stimulated conditions [36–38]. CST was also indicated to provide comparable cardioprotection in isolated heart by pre-conditioning [39] and post-conditioning [40]. Plasma CST is diminished very early during development of hypertension [41], and the processing of CgA to CST is decreased in hypertensive patients [42]. Plasma CST is also low in black patients suffering from end-stage renal disease [43]. CST increases insulin sensitivity by decreasing infiltration of macrophages in the liver and the consequent inflammation [44], inhibiting hepatic glucose production [44], decreasing endoplasmic reticulum stress [45], and inducing glycogen production [46]. Although it is known that neurotransmitters released from parasympathetic (e.g., acetylcholine) and sympathetic nerve ending (e.g., norepinephrine) can bind with the acetylcholine receptors [47–51] and adrenergic receptors [52–56], respectively present on innate immune cells, the homeostatic regulation between these two systems is complex. CST, being an intrinsic regulator of neuroendocrine secretory system, can have both direct and indirect effects on the host-pathogen interactions. The goal of this review is to summarize the developing concept of the effect of CST as an antimicrobial and cell penetrating peptide.

2. Homology and non-synonymous single nucleotide polymorphisms of CST in mammals

2.1. Homology of CST in mammals

Sequence alignment of CST in 53 mammalian species belonging to 8 orders revealed >80% homology in 52 species except in Platypus (lowest in the mammalian phylogenetic tree) where the homology with the Primates (highest in the mammalian phylogenetic tree) was >58% (Figure 1), indicating that CST is highly conserved in mammals. The homology of individual amino acids is summarized in Figure 2.

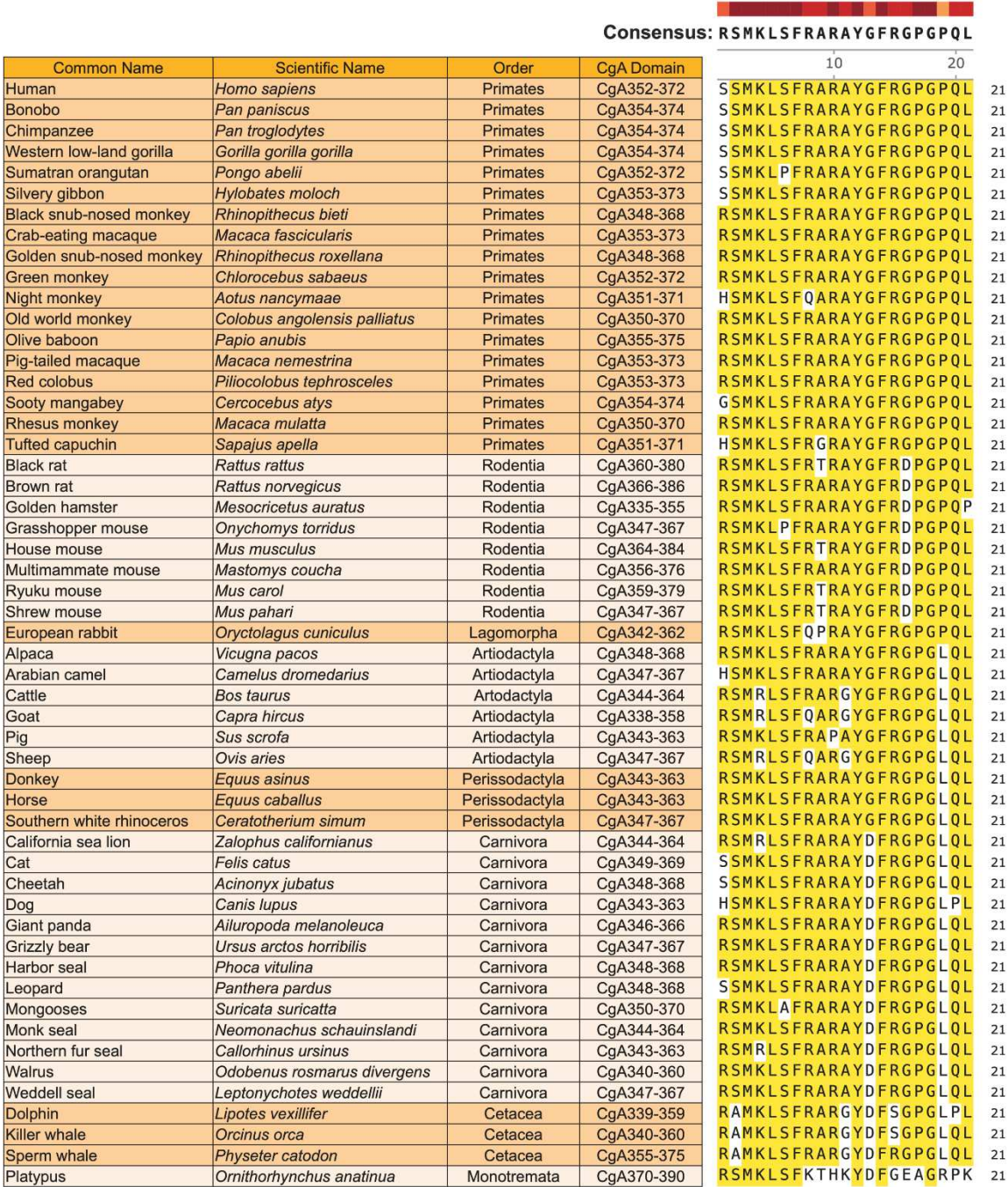


Fig. 1

Figure 1. Homology of CST sequence in 53 mammalian species belonging to 8 orders. CST sequences were aligned using the MUSCLE method provided by SnapGene software from the following mammalian species: human (*Homo sapiens*: NM_001275), bonobo (*Pan paniscus*: XP_008956465.1), chimpanzee (*Pan troglodytes*: PNI97600.1), western low-land gorilla (*Gorilla gorilla gorilla*: XM_019009788.2), Sumatran orangutan (*Pongo abelii*: XM_002825045.3), silvery gibbon (*Hylobates moloch*: XP_031990963.1), black snub-nosed monkey (*Rhinopithecus bieti*: XM_017857899.1), crab-eating macaque (*Macaca fascicularis*: XP_045252830.1), golden snub-nosed monkey (*Rhinopithecus roxellana*: XM_010384506.1), green monkey (*Chlorocebus sabaeus*: XM_007987644.2), night monkey (*Aotus nancymaae*: XM_012455409.1), old world monkey (*Colobus angolensis palliatus*: XM_011949380.1), olive baboon (*Papio Anubis*: XM_031667888.1), pig-tailed macaque (*Macaca nemestrina*: XM_011717182.1), red colobus (*Piliocolobus tephrosceles*: XM_023205512.3), Sooty mangabey (*Cercocebus atys*: XM_012083744.1), rhesus monkey (*Macaca mulatta*: NM_001278450.1), tufted capuchin (*Sapajus apella*: XM_032287580.1), black rat (*Rattus rattus*: XM_032908276.1), brown rat (*Rattus norvegicus*:

XM_032908276.1), golden hamster (*Mesocricetus auratus*: XM_005068386.4), grasshopper mouse (*Onychomys torridus*: XM_036206345.1), house mouse (*Mus musculus*: NM_007693.2), multimammate mouse (*Mastomys coucha*: XM_031357132.1), Ryuku mouse (*Mus caroli*: XM_021179357.1), Shrew mouse (*Mus pahari*: XM_021202342.2), European rabbit (*Oryctolagus cuniculus*: XM_051826432.1), alpaca (*Vicugna pacos*: XP_031534667.1), Arabian camel (*Camelus dromedarius*: XM_031454226.1), cattle (*Bos taurus*: NM_181005.2), goat (*Capra hircus*: XM_018066172.1), pig (*Sus scrofa*: NP_001157477.2), sheep (*Ovis aries*: XP_004018008.3), donkey (*Equus asinus*: XP_014687627.1), horse (*Equus caballus*: NP_001075283.2), southern white rhinoceros (*Ceratotherium simum*: XP_004434274.1), California sea lion (*Zalophus californianus*: XP_027424506.2), cat (*Felis catus*: XP_023111743.1), cheetah (*Acinonyx jubatus*: XP_026922275.1), dog (*Canis lupus*: XP_038528993.1), giant panda (*Ailuropoda melanoleuca*: XP_019660005.1), grizzly bear (*Ursus arctos horribilis*: XP_048075839.1), harbor seal (*Phoca vitulina*: XP_032261715.1), leopard (*Panthera pardus*: XP_019317643.2), mongooses (*Suricata suricatta*: XP_029807749.1), monk seal (*Neomonachus schauinslandi*: XP_021535325.1), Northern fur seal (*Callorhinus ursinus*: XP_025726236.1), walrus (*Odobenus rosmarus divergens*: XP_004394547.1), weddell-seal (*Leptonychotes weddellii*: XP_030873380.1), dolphin (*Lipotes vexillifer*: XP_007454783.1), killer whale (*Orcinus orca*: XP_004262400.1), sperm whale (*Physeter catodon*: XP_023986851.1), and platypus (*Ornithorhynchus anatinua*: XP_039767777.1). Yellow shows an amino acid match between species.

R	S	M	K	L	S	F
1 h352	2 h353	3 h354	4 h355	5 h356	6 h357	7 h358
73%	>94%	100%	>90%	100%	>92%	100%
R	A	R	A	Y	G	F
8 h359	9 h360	10 h361	11 h362	12 h363	13 h364	14 h365
>92%	>86%	>96%	>86%	100%	>66%	100%
R	G	P	G	P	Q	L
15 h366	16 h367	17 h368	18 h369	19 h370	20 h371	21 h372
>94%	>83%	>98%	100%	>58%	>94%	>96%

 Consensus sequence
 Amino Acid number
 Homology

Fig. 2

Figure 2. Homology of the individual amino acid in catestatin sequence in 53 mammalian species belonging to 7 orders.

2.2. Single nucleotide polymorphisms (SNPs) in the CST domain of mammals

Four non-synonymous SNPs have been identified in CST domain of CgA: Gly364Ser (US, Indian, and Japanese populations) [24,57,58], Gly367Val (only in Indian populations) [57], Pro370Leu (US and Indian populations) [24], and Arg374Gln (US populations only) [24]. Pro370Leu-CST has the

highest potency of inhibiting catecholamine secretion and desensitizing catecholamine secretion, followed by WT-CST and Gly364-Ser-CST [24]. The Gly364Ser variant was demonstrated to cause profound changes in parasympathetic and sympathetic activity including a ~2.4-fold increase in cardiac parasympathetic index and a ~26% decrease in cardiac sympathetic index in comparison to wild-type individuals [59]. This variant protects men from developing cardiovascular diseases compared to women [59].

3. Catestatin and innate immunity

The first indication for the role of CST in innate immunity came from a study in rats where intravenous administration of CST was shown to reduce pressor responses by electrical stimulation [26]. The hypotensive effect of CST was revealed to be mediated at least in part by profuse histamine release (by ~21-fold) and action at the H₁ receptor [26]. The *in vivo* studies were later confirmed in peritoneal and pleural mast cells where CST caused dose-dependent release of histamine utilizing signaling pathways established for wasp venom peptide mastoparan and other amphiphilic cationic neuropeptides (the peptidergic pathway) [60]. This pathway is in sharp contrast to the nicotinic-cholinergic pathway used by CST to induce catecholamine secretion from chromaffin cells [5]. Subsequent studies uncover the following: (i) release of immunoreactive CST-containing peptides from human stimulated polymorphonuclear neutrophils [61]; (ii) detection of CST in mouse peritoneal macrophages by Western blots [39]; (iii) detection of CST in human monocytes and monocyte-derived macrophages by Western blots [62]; (iv) blockade of lipopolysaccharide (LPS)-induced increase in expression of tumor necrosis factor alpha (TNF- α) [62]; (v) decreased expression of proinflammatory cytokines by CST in plasma and heart [39]; (vi) inhibition of infiltration of macrophages in obese liver [44]; (vii) degranulation of primary mast cells from human peripheral blood [63] and (viii) low plasma CST in fatal COVID-19 patients [64]. These findings implicate CST as an immunomodulatory peptide. Since, receptor-ligand interactions are an essential driver of host-immune response [65], it is important to examine if CST can bind with a receptor on immune cells and regulate their polarization and function in host defense.

4. Antibacterial effects of CST

4.1. Inhibition of bacterial growth by CST

Metz-Boutigue's group was the first to demonstrate the antibacterial activity of CST. Her group used bCST₃₄₄₋₃₅₈ (coining the term cateslytin to describe this antibacterial effect) to reveal inhibition of growth of the Gram-positive and Gram-negative bacteria [61]. The minimal inhibitory concentrations (MICs) of CST (bCgA₃₄₄₋₃₅₈, hCgA₃₅₂₋₃₇₂, Gly364Ser-CST and Pro370Leu-CST) for Gram-positive bacteria (*Micrococcus luteus*, *Bacillus megaterium*, Group A *Streptococcus*, *S. aureus* ATCC 25923, *S. aureus* ATCC 49775, *S. aureus* S1 MRSA, *S. aureus* S1 MSSA, and *S. aureus* DmprF) range from 0.8 μ M to >100 μ M (Figure 3) [61,66]. The minimal concentration with 100% inhibition (MIC₁₀₀) for Gram-positive bacteria range from 2 μ M to >100 μ M of 2 μ M. The MIC of CST was higher (8 μ M to 50 μ M) for Gram-negative bacteria (*Escherichia coli* D22, *E. coli* 029, and *Pseudomonas aeruginosa*) compared to Gram-positive bacteria (Figure 3). Likewise, the MIC₁₀₀ of CST was higher (15 μ M to 150 μ M) for Gram-negative bacteria compared to Gram-positive bacteria (Figure 3). The higher MIC and MIC₁₀₀ values of CST for Gram-negative bacteria are consistent with the presence of extra outer membrane containing LPS [67,68]. Besides the extra-thick cell membrane, Gram-negative bacteria release exotoxins like tetanus [69,70] and cholera toxins [71] that make worse prognosis.

Bacterial species	WT-CST bCgA ₃₄₄₋₃₅₈ MIC (μM)	WT-CST bCgA ₃₄₄₋₃₅₈ MIC ₁₀₀ (μM)	WT-CST hCgA ₃₅₂₋₃₇₂ MIC (μM)	WT-CST hCgA ₃₅₂₋₃₇₂ MIC ₁₀₀ (μM)	G364S-CST hCgA ₃₅₂₋₃₇₂ MIC (μM)	G364S-CST hCgA ₃₅₂₋₃₇₂ MIC ₁₀₀ (μM)	P370L-CST hCgA ₃₅₂₋₃₇₂ MIC (μM)	P370L-CST hCgA ₃₅₂₋₃₇₂ MIC ₁₀₀ (μM)
Gram-positive bacteria								
<i>Micrococcus luteus</i>	0.8	2	5	15	1	2	2	10
<i>Bacillus megaterium</i>	0.8	2	-	-	-	-	-	-
Group A <i>Streptococcus</i>			75	75		30		30-50
<i>Staphylococcus aureus</i> ATCC 25923	40		>100	>100	>100	>100		
<i>Staphylococcus aureus</i> ATCC 49775	37		125					
<i>Staphylococcus aureus</i> S1 (MRSA)	37		130					
<i>Staphylococcus aureus</i> S1 (MSSA)	45		150					
<i>Staphylococcus aureus</i> ΔmprF			20	30	5-10	10	5	5
Gram-negative bacteria								
<i>Escherichia coli</i> D22	8	15	15	150	10	40	20	100
<i>Escherichia coli</i> O29			30	30	20	20-30	10	5-10
<i>Pseudomonas aeruginosa</i>			50	50				

Fig. 3

Figure 3. Effects of wild-type (WT)-CST and natural human variants of CST (Gly364Ser and Pro370Leu) on the growth of Gram-positive and Gram-negative bacteria showing minimal inhibitory concentration (MIC) and lethal concentration (MIC₁₀₀) of CST.

4.2. Interaction of CST with the bacterial wall

While Gram-positive bacteria contain only the cytoplasmic membrane that surrounds the cell, Gram-negative bacteria contain an additional LPS-containing thick outer membrane [67,68]. Furthermore, the peptidoglycan layer on the outer side of the cytoplasmic membrane is much thicker in Gram-positive bacteria compared to Gram-negative bacteria [72,73]. In addition, the LPS in Gram-positive bacteria are lipoteichoic acids that are embedded in the cytoplasmic membrane [74]. In contrast, in Gram-negative bacteria, the LPS forms the major lipid component of the outer leaflet of the outer membrane [74]. Although the membranes in both groups possess phosphate groups and are negatively charged, the Gram-negative bacteria in general have a higher content of the zwitterionic phospholipid is phosphatidylethanolamine than Gram-positive bacteria [74–77]. The predominant anionic lipids in bacterial membranes are phosphatidylglycerol and cardiolipin [78–80]. Metz-Boutigue's group has shown that cateslytin (bCgA₃₄₄₋₃₅₈) is unstructured in solution but is converted to an antiparallel β -structure and forms aggregates at the surface of negatively charged bacterial membranes [81]. As for catecholamine secretion [14], arginine residues were found to be crucial for binding to negatively charged lipids [81,82]. They proposed that the phase boundary defects caused by zones of different rigidity and thickness lead to permeability induction and peptide crossing through the bacterial membrane [81]. That CST penetrates through the bacterial wall was shown by measuring the optical density of the released β -galactosidase from ML-35p [66]. Electron microscopical studies of *E. coli* ML-35p confirmed that CST rapidly disrupts the *E. coli* membrane with visible membrane blebbing compared to untreated cells within 10 minutes [66].

4.3. CST as a potential therapy for bacterial diseases

The antimicrobial peptides (AMPs) derived from CgA display antimicrobial activities by lytic effects at micromolar range against Gram-positive bacteria, filamentous fungi, and yeasts. Interestingly, Catestatin-derived peptides can kill superbugs and more particularly *S. aureus* [83]. Considering the actions of CST on *E. coli*, it could be useful as a therapeutic target for the Gram-negative bacteria cause many serious infections, including Cholera [84], *E. coli* infection [85], Plague [86], *Campylobacter* [87], Legionnaire's disease [88], Salmonella [89], Klebsiella [90], *Pseudomonas* [91], Tularemia [92], and Typhoid fever [93] and microbes associated with drug resistance [94–97], CST might be used as a therapeutic target for the above diseases.

5. Antifungal and antiyeast effects of CST

5.1. Inhibition of growth of fungus and yeast by CST

Fungal infections are common on the surface of skin, nails, or mucous membranes (superficial or mucocutaneous), underneath skin (subcutaneous), or in the lungs, brain, or heart (deep infection). Deep fungal infections include Histoplasmosis [98,99], Coccidioidomycosis (Valley fever) [100,101], Blastomycosis [102,103], Aspergillosis [104,105], Candidal urinary tract infection [106,107], invasive candidiasis [108,109], *Pneumocystis pneumonia* [110,111], Mucormycosis [112,113], and Cryptococcosis [114,115]. It is becoming increasingly evident that resistance to antifungal therapy is on the rise [116,117], which calls for the development alternative therapy for these infections. Host-defense peptides are emerging as new promising candidates to counteract antifungal resistance [118]. To this end, Metz-Boutigue’s group tested the effects of CST on the growth of fungus and yeasts. They found MIC values of CST or its human variants ranging from 0.2 μ M to 75 μ M against a host of fungal species (*Neurospora crassa*, *Aspergillus fumigatus*, *A. niger*, *Nectria haematococca*, *Fusarium culmorum*, *F. oxysporum*, *Trichophyton mentagrophytes*, and *T. rubrum*) [61,66] (Figure 3). The MIC₁₀₀ values of CST or its human variants against the above fungal species ranged from 0.8 μ M to 100 μ M [61,66] (Figure 4). CST and its human variants also displayed similar inhibitory effects on the growth of yeasts with MIC ranged from 1.2 μ M to >240 μ M (Figure 4) [61,66]. The MIC₁₀₀ of CST and its variants against the above yeasts ranged from 6 μ M to 75 μ M [61,66] (Figure 5). Similar to the effects of retro-inverso (RI)-CST on catecholamine secretion [30], D-CST (L-amino acids were replaced by D-amino acids) exhibited comparable inhibitory effects on the growth of yeast compared to L-CST with MIC ranged from 2 μ M to 9.6 μ M [119]. D-CST was also uncovered to be resistant to proteolytic digestion [83,119,120]. Like L-CST, D-CST can also be used to develop therapies for drug-resistant microbial infection [121].

Phylum Fungal species	WT-CST bCgA ₃₄₄₋₃₅₈ MIC (μ M)	WT-CST bCgA ₃₄₄₋₃₅₈ MIC ₁₀₀ (μ M)	WT-CST hCgA ₃₅₂₋₃₇₂ MIC (μ M)	WT-CST hCgA ₃₅₂₋₃₇₂ MIC ₁₀₀ (μ M)	G364S-CST hCgA ₃₅₂₋₃₇₂ MIC (μ M)	G364S-CST hCgA ₃₅₂₋₃₇₂ MIC ₁₀₀ (μ M)	P370L-CST hCgA ₃₅₂₋₃₇₂ MIC (μ M)	P370L-CST hCgA ₃₅₂₋₃₇₂ MIC ₁₀₀ (μ M)
Ascomycota								
<i>Neurospora crassa</i>	1.2	3.2	20	50	3	5	3	10
<i>Aspergillus fumigatus</i>	10	80	20-80	30	10-20	80	10-20	100
<i>Aspergillus niger</i>			20	30	20	30	10	20
<i>Nectria haematococca</i>	0.2	0.8						
<i>Fusarium culmorum</i>	2	8						
<i>Fusarium oxysporum</i>	6	10						
<i>Trichophyton mentagrophytes</i>	4	20						
<i>Trichophyton rubrum</i>			75	75	20		30	

Fig. 4

Figure 4. Effects of WT-CST and natural human variants of CST (Gly364Ser and Pro370Leu) on the growth of fungal species showing MIC and MIC₁₀₀ of CST.

Yeast species	WT-L-CST bCgA ₃₄₄₋₃₅₈ MIC (μ M)	WT-L-CST bCgA ₃₄₄₋₃₅₈ MIC ₁₀₀ (μ M)	WT-D-CST bCgA ₃₄₄₋₃₅₈ MIC (μ M)	WT-L-CST bCgA ₃₄₄₋₃₅₄ MIC (μ M)	WT-CST hCgA ₃₅₂₋₃₇₂ MIC (μ M)	WT-CST hCgA ₃₅₂₋₃₇₂ MIC ₁₀₀ (μ M)	G364S-CST hCgA ₃₅₂₋₃₇₂ MIC ₁₀₀ (μ M)	P370L-CST hCgA ₃₅₂₋₃₇₂ MIC ₁₀₀ (μ M)
<i>Candida albicans</i> ATCC 14053						50-75	30	30
<i>Candida albicans</i>	1.2	8						
<i>Candida albicans</i> "S"	7.9		5.5	30	>240			
<i>Candida albicans</i> "R"	9.6		9.6	50	>240			
<i>Candida tropicalis</i>	1.8	10						
<i>Candida tropicalis</i> "S"	9.8		8.1	50	>240			
<i>Candida tropicalis</i> "R"	2.0		2.0	20	>240			
<i>Candida glabrata</i>	8	30						
<i>Candida glabrata</i> "S"	38.2	13.4						
<i>Candida glabrata</i> "R"	61.4	15.0		>100	>240			
<i>Candida neoformans</i>	1.4	6		>100	>240			

Fig. 5

Figure 5. Effects of WT-CST and natural human variants of CST (Gly364Ser and Pro370Leu) on the growth of yeast species showing MIC and MIC₁₀₀ of CST.

5.2. Mechanisms underlying the antifungal and antiyeast activities of CST

Metz-Boutigue’s group used confocal laser microscopy to analyze the interaction of the synthetic rhodamine-labeled cateslytin (bCgA_{344-358R}) with fungal (*A. fumigatus*) and yeast (*C. albicans*) membranes [61]. Rhodaminated cateslytin (1 µM) was detected in the inner compartment after 2 min of incubation, implicating rapid and efficient penetration through the cell wall [61]. Using time-lapse videomicroscopy of fungal growth, they have shown that rhodaminated cateslytin blocked the growth and development of nascent fungus [61]. Penetration of rhodaminated cateslytin takes place at both ends of the small fungi (three cells and expressing a slow growth rate) as compared to larger fungi with a higher growth rate where penetration takes place at one end [61]. Sequence homology of the well-known cell-permeable peptide penetratin with CST representing 7 mammalian orders (Primates, Rodentia, Artiodactyla, Perissodactyla, Carnivora, Cetacea and Monotremata) revealed 63.64% to 75% similarity, which should qualify CST as a cell-permeable peptide (Figure 6).

Common Name		Scientific Name	Order	Sequence	Identity	Similarity
Penetratin				RQIKIW FQNRR		
Consensus mammalian CST				RSMLSFRA R	40%	70%
Human	<i>Homo sapiens</i>	Primates		MKLSFRA R	37.5%	75%
House mouse	<i>Mus musculus</i>	Rodentia		RSMLSLFRT R	40%	70%
Cattle	<i>Bos taurus</i>	Artiodactyla		RSMLSLFRA R	30%	70%
Pig	<i>Sus scrofa</i>	Artiodactyla		RSMLSLFR	37.5%	75%
Horse	<i>Equus caballus</i>	Perissodactyla		RSMLSLFRA R	40%	70%
Walrus	<i>Odobanus rosmarus divergens</i>	Carnivora		RSMLSLFRA R	40%	70%
Killer whale	<i>Orcinus orca</i>	Cetacea		RAMKLSFRA R	40%	70%
Platypus	<i>Ornithorhynchus anatinua</i>	Monotremata		RSMLSLFKTHK	27.27%	63.64%
Identical: Black; Similar: Blue; Not Similar: Red						

Fig. 6

Figure 6. Homology between cell permeable peptide penetratin and CST in 7 mammalian orders.

6. CST regulation of gut microbiota

6.1. Microbiomes in colonic mucosa versus feces

Recent studies have identified a larger role of gut microbiota in gut-immune homeostasis and in intestinal pathology. The human intestinal microbiota is dominated by five phyla: Bacillota (aka Firmicutes), Bacteroidota, Actinomycetota (aka Actinobacteria), Pseudomonadota (aka Proteobacteri), and Verrucomicrobiota [122]. In contrast, the intestinal microbiota of mice is dominated by four phyla: Bacillota, Bacteroidota, Defferibacterota, and Pseudomonadota [123], where the phylum Defferibacterota is in high abundance and the phyla Actinomycetota and Verrucomicrobiota are in low abundance compared to humans. In human adults, more than 80% of the species belong to just two phyla: Gram-negative Bacteriodota and Gram-positive Bacillota (aka Firmicutes). In mouse colonic mucosa samples, 19 phyla were identified [124]. The high-abundant (≥1%) phyla included Bacillota, Bacteroidota, Defferibacterota, and Pseudomonadota [124] (Figure 7). The low-abundant (<1%) phyla included the following: Actinomycetota (aka Actinobacteria), Parcubacteria (aka OD1), Saccharibacteria (aka TM7), Omnitrophota (aka OP3), Acidobacteriota, Armatimonadota, Chlamydiae, Chlorobiota, Cyanobacteria, Fibrobacterota, Mycoplasmatota (aka Tenericutes), Lentisphaerota, Planctomycetota, Spirochaetes, and Verrucomicrobiota) [124] (Figure 7). Although CST failed to alter bacterial populations in the four high-abundant phyla, it altered colonic mucosa-associated bacterial community composition at lower taxonomic levels. Thus, CST showed a positive association with Orders including Bacteroidales, Clostridiales, and YS2; Families

including Chitinophagaceae, Clostridiaceae, Coriobacteriaceae, Pseudomonadaceae, Rikenellaceae, and Ruminococcaceae; and Genera *Bifidobacterium* and *Stenotrophomonas* [124]. Fecal samples identified 10 phyla including the high-abundant ($\geq 1\%$) Bacillota, Bacteroidota, Pseudomonadota, and Deferribacterota and low-abundant ($< 1\%$) Actinomycetota, Cyanobacteria, Fibrobacterota, Saccharibacteria, Mycoplasmatota and Verrucomicrobiota [124]. The relative abundance of Bacteroidota was observed to increase significantly after CST treatment. In contrast, CST was learned to cause a marked decrease in Bacillota population. Like mucosal samples, fecal samples disclosed positive associations with the Class Alpharotobacteria; Orders including Bacteroidales, RF32, and YS2; and genera *Prevotella*, *Bacteroides*, *Ovatus*, *Parabacteroidesdistarosis*, *Parabacteroides*, and *Dorea* (Figure 7). *Bacteroides* and *Parabacteroides* species, representing ~25% of the colonic microbiota, transform simple and complex sugars into volatile short-chain fatty acids (SCFAs) such as acetate, butyrate, and propionate [125–127], which are absorbed in colon as a nutrient [128–130]. Besides colonic nutrients, SCFAs are well established for their roles in accelerating gut transit time via release of serotonin [131–134]. SCFAs also release glucagon-like peptide 1 (GLP1) from the enteroendocrine L-cells [135–138] and improve insulin sensitivity [139–141]. *Bacteroides thetaiotaomicron* produces significant amounts of glycosylhydrolases, which prevent obesity [142]. Other *Bacteroides* species are also reported to prevent obesity and increase insulin sensitivity [143–146]. Furthermore, *Bacteroides fragilis* produces zwitterionic polysaccharide, which activates CD4⁺ T cells to produce interleukin 10 (IL-10). IL-10 plays crucial roles in preventing abscess formation and other unchecked inflammatory responses [142,147,148]. Negative association of CST was reported for the Class Clostrida, Families Bacteroidaceae and Ruminococcaceae, and Genera *Adlercreutzia* and *Allobaculum* [124]. Interestingly, the functional correlation between different CST mutants across species and their respective microbiota remains elusive. It is important to decipher the effect of different CST mutant on microbial diversity between species.

	WT Mucosal samples	WT+Sal Fecal samples	WT+CST Fecal samples	CST-KO+Sal Fecal samples	CST-KO+CST Fecal samples	WT+FMT-CST-KO Fecal samples	CST-KO+FMT-WT Fecal samples
Major Phyla ($>1\%$)	Bacillota (aka Firmicutes)	Bacillota	Bacillota ↓	Bacillota	Bacillota ↓↓	Bacillota	Bacillota
	Bacteroidota	Bacteroidota	Bacteroidota ↑↑	Bacteroidota	Bacteroidota ↑	Bacteroidota ↑	Bacteroidota ↓
	Deferribacterota	Deferribacterota	Deferribacterota	Deferribacterota	Deferribacterota	Deferribacterota	Deferribacterota
	Pseudomonadota (aka Proteobacteria)	Pseudomonadota	Pseudomonadota ↑	Pseudomonadota	Pseudomonadota ↑	Pseudomonadota	Pseudomonadota
Minor Phyla ($<1\%$)	Actinomycetota (aka Actinobacteria)	Actinomycetota	Actinomycetota	Actinomycetota	Actinomycetota	Actinomycetota ↑	Actinomycetota
	Parcubacteria (aka OD1)	Parcubacteria	Parcubacteria ↑	Parcubacteria	Parcubacteria	Parcubacteria ↑	Parcubacteria
	Saccharibacteria (aka TM7)	Saccharibacteria			Saccharibacteria	Saccharibacteria	Saccharibacteria
		Campylobacterota	Campylobacterota	Campylobacterota	Campylobacterota	Campylobacterota	Campylobacterota
	Cyanobacteria	Cyanobacteria	Cyanobacteria	Cyanobacteria	Cyanobacteria	Cyanobacteria	Cyanobacteria
		Desulfobacterota	Desulfobacterota ↑	Desulfobacterota	Desulfobacterota	Desulfobacterota	Desulfobacterota
	Fibrobacterota	Fibrobacterota			Fibrobacterota	Fibrobacterota	Fibrobacterota
	Mycoplasmatota (aka Tenericutes)	Mycoplasmatota			Mycoplasmatota	Mycoplasmatota	Mycoplasmatota
	Verrucomicrobiota	Verrucomicrobiota	Verrucomicrobiota	Verrucomicrobiota ↓	Verrucomicrobiota ↑↑	Verrucomicrobiota ↓	Verrucomicrobiota

Fig. 7

Figure 7. Abundance of bacterial species in mucosal and fecal samples in WT and CST-KO mice in presence or absence of CST as well as after fecal microbial transplant. Green arrows indicate CST effects; red arrows indicate FMT effects.

6.2. Microbiomes in CST knockout (CST-KO) mice and inflammation

CST knockout (CST-KO) mice were generated in 2018 and are: insulin-resistant on a normal chow diet [44], hyperadrenergic [39], hypertensive [39], and with a leaky gut [149]. The microbiome in CST-KO mice was unearthed to be quite different in composition than its WT littermates [149]. Microbial richness, assessed by the number of amplicon sequence variants (ASVs) and ACE (abundance-based Coverage Estimator) index revealed a significant decrease in CST-KO compared to WT mice [150]. The most prominent observation was the higher ratio of Bacillota to Bacteroidota,

which was opposite to the decreased ratio observed in WT mice intrarectally infused with CST [124] (Figure 7). The ratio of Bacillota to Bacteroidota plays crucial roles in regulation of obesity and metabolic syndrome [151,152]. Thus, the ratio of Bacillota to Bacteroidota in adults increases as BMI increased [153]. Considering these reports, it remains to be seen if this change in microbiota can promote host defense against enteric pathogens like *Salmonella*. Furthermore, Verrucomicrobiota population was very low in CST-KO mice, which indicates low levels of *Akkermansia* species. Since *Akkermansia muciniphila* modulates obesity by regulating metabolism and energy homeostasis to improve insulin sensitivity and glucose homeostasis [154], low Verrucomicrobiota population contributes to the insulin resistance reported for CST-KO mice [44].

6.3. Alteration of diversity and composition of the microbiota in the CST-KO after supplementation with CST.

Decreased ASVs and ACE indices in CST-KO mice were restored after supplementation with CST for 15 days [150]. Like richness scores, supplementation of CST-KO mice with CST increased the diversity index as assessed by Shanon's *H* and inverted Simpson's index [150]. At the phylum level, CST was testified to decrease Bacillota phylum and increase Bacteroidota, Patescibacteria, Desulfobacterota, and Proteobacteria in both CST-KO and WT mice [150]. Low bacteria levels in Verrucomicrobiota phylum in CST-KO mice were markedly increased in CST-supplemented CST-KO mice. CST was also described to decrease abundance of *Staphylococcus* and *Turicibacter* in both WT and CST-KO mice. In contrast, CST increased *Alistipes*, *Akkermansia*, and *Roseburia* genera only in CST-KO mice [150]. *A. muciniphila*, a mucin-degrading bacterium, is a member of Verrucomicrobiota, which use mucin as a carbon, nitrogen, and energy source [155,156]. Murine studies show a causative role for *A. muciniphila* in lowering body fat mass, improving glucose homeostasis, decreasing adipose tissue inflammation, and increasing gut integrity [157–159]. Human studies show a negative correlation between *A. muciniphila* abundance and being overweight, being obese, having untreated type 2 diabetes mellitus, and having hypertension [160–166].

6.4. Restoration of microbial dysbiosis in CST-KO mice after fecal microbial transplant (FMT) from WT donor mice

FMT, first tested in 1958 to modify the human microbiome and consequently ameliorate fulminant pseudomembranous enterocolitis [167], has become established as an effective therapeutic modality in the treatment of antibiotic-refractory recurrent *Clostridium difficile* colitis with a success rate of up to 95% [168–172]. Subsequently, FMT was tested for the treatment of constipation, irritable bowel syndrome, and inflammatory bowel disease [173–177]. As discussed above, CST-KO mice are associated with an altered gut microbiota composition and richness. WT mice that received FMT from the CST-KO mice were shown to encompass a reduction of Clostridia and *Akkermansia* [178], which are linked to metabolic disorders and insulin resistance [179,180]. Furthermore, WT^{FMT-CST-KO} mice exhibit a marked increase in the Proteobacteria population, which are associated with active inflammatory bowel disease (IBD) states [181,182]. Of note, CST-KO mice are insulin-resistant on normal chow diet [44]. In contrast, CST-KO that received FMT from the WT mice (CST-KO^{FMT-WT}) showed an increase in richness, a notable reduction of *Staphylococcus*, and an increase in the butyrate-producing *Intestinimonas* [178] (Figure 7). *I. butyriciproducens* produces butyrate from not only sugars but also lysine and even glycated lysine [183]. Butyrate, taken up directly by colonocytes, serves as a direct source of energy and directly contributes to a healthy gut. In addition, butyrate as a signaling molecule affects many factors such as satiety, secretion of hormones, and glucose metabolism [184–186]. Of note, reduced levels of butyrate are strongly associated with IBD and metabolic disorders [187,188]. Further, butyrate has shown promise in restoring gut barrier integrity [189] and modulating regulatory T cell function by inhibiting histone deacetylase [190–192] though the former role is understudied. Butyrate modulation of certain serine proteases [193,194] would be a promising therapeutic target in future studies.

7. Conclusions

Alignment of CST sequences from 53 mammalian species belonging to eight orders revealed that CST sequence is highly conserved (>90% in 90% species) in mammals: Five (23.8%) amino acids (M³, L⁵, F⁷, F¹⁴, and G¹⁸) are 100% conserved; nine (42.8%) amino acids (S², K⁴, S⁶, R⁸, R¹⁰, R¹⁵, P¹⁷, Q²⁰ and L²¹) are 90-96% conserved; and three (14.28%) amino acids (A⁹, A¹¹, and G¹⁶), are >80% conserved. The least conserved sequences are G¹³ (>66%) and P¹⁹ (>58%), where human variants of CST were reported for G¹³ (G¹³S) and P¹⁹ (P¹⁹L), indicating that natural selection pressures still exist on those two amino acids [195–198]. Existing literature (expression of CST in innate immune cells, inhibition of macrophage infiltration in tissues, decreased expression of pro-inflammatory cytokines by CST, and low plasma CST in fatal COVID-19 patients) implicate CST as an immunomodulatory peptide. Prominent effects of CST in low micromolar range on inhibition of growth of Gram-positive and Gram-negative bacteria, fungi, and yeast establish CST as an antimicrobial peptide. Penetration of CST (pI 12.03-12.48) in bacteria, fungus, yeast, and neutrophils, coupled with 70-75% homology with cell penetrating peptide Penetratin (pI 12.62) rightfully qualify CST as a member of the cell permeable peptide. Increased ratio of Bacilotta to Bacteroidota, together with low levels of Verrucomicrobiota (e.g., *Akkermansia* spp) in CST-KO mice, not only explains insulin resistance in CST-KO mice but also implicates that CST is necessary for the maintenance of insulin sensitivity. Decreased ratio of Bacilotta to Bacteroidota coupled with increased abundance of Verrucomicrobiota after supplementation of CST-KO mice with CST confirm that CST is necessary and sufficient to increase insulin sensitivity by modulating gut microbiota. Decreased population of *Akkermansia* and increased population of Proteobacteria in WT^{FMT-CST-KO} coupled with increased population of butyrate producing *Intestimonas* in CST-KO^{FMT-WT} further substantiates regulation of obesity and insulin resistance by CST [44] via regulation of gut microbial population [150,178].

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