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Histamine in two component system-mediated bacterial signaling

Dimitrios A. Kyriakidis[1], **Marina C. Theodorou**[1], **Ekaterini Tiligada**[2]

[1]Laboratory of Biochemistry, Department of Chemistry, Aristotle University of Thessaloniki, Greece,[2]Department of Pharmacology, Medical School University of Athens, Greece

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1. ABSTRACT

Histamine is a key mediator governing vital cellular processes in mammals beyond its decisive role in inflammation. Recent evidence implies additional actions in both eukaryotes and prokaryotes. Besides its function in host defense against bacterial infections, histamine elicits largely undefined actions in microorganisms that may contribute to bacteria–host interactions. Bacterial proliferation and adaptation are governed by sophisticated signal transduction networks, including the versatile two-component systems (TCSs) that comprise sensor histidine kinases and response regulators and rely on phosphotransfer mechanisms to exert their modulatory function. The AtoSC TCS regulates fundamental cellular processes such as short-chain fatty acid metabolism, poly-(R)-3-hydroxybutyrate (cPHB) biosynthesis and chemotaxis in *Escherichia coli*. The implication of exogenous histamine in the AtoSC-mediated cPHB biosynthesis and in *E. coli* chemotactic behavior is indicative of a putative function of histamine in bacterial physiology. The data raise questions on the significance of histamine actions in bacteria-host symbiosis, dysbiosis and pathogenicity as well as on the possible consequences upon therapeutic administration of histamine receptor-targeting agents and in particular ligands of the recently identified immunomodulatory H_4 receptor.

2. INTRODUCTION

Histamine (2- (4-imidazolyl)-ethylamine) is a short-acting biogenic amine with pleiotropic actions in mammals. Amongst others, histamine plays a decisive role in immune and inflammatory responses. Related studies focus largely on the mechanisms regulating its endogenous production and its actions in mammalian pathophysiology through binding to four histamine receptor subtypes (1). Beyond its vital role in mammalian pathophysiology, histamine seems to govern vital cellular processes in lower eukaryotes. For instance, histamine appears to induce the adaptive phenotype in the unicellular eukaryote *Saccharomyces cerevisiae* by yet undefined mechanisms possibly involving differential expression of heat shock proteins and tubulin (2). In prokaryotic physiology, the role of histamine has been largely disregarded. In *Escherichia coli* recent reports point to the implication histamine in biosynthetic pathways (3), in Ca^{2+}-mediated processes (4) and in the chemotactic phenotype (5).

It is now becoming clear that bacteria-host symbiosis extends beyond mere substrate exchange. The investigation of bidirectional signaling heralds a new era of understanding, the balance between health and disease. The involvement of histamine in microbe-host cross talk remains largely elusive, particularly regarding the potential

effects of the amine in microorganisms during symbiosis, virulence and dysbiosis. In this field, research is basically directed towards the key inflammatory mediator role of histamine contributing to the development and modulation of mammalian immune responses associated with bacterial infections (6-8). In addition, numerous studies consider the harmful effects of ingested histamine in food-borne illnesses, frequently associated with histamine-forming bacteria (9). The experimental data provide evidence for histamine synthesis by some bacteria (9-11) and the existence of membrane transporters driving histidine/histamine exchange (11, 12). Comparatively more species appear to have the potential to degrade the amine (13, 14). To date, histamine receptor homologues have not been identified in prokaryotic cells and the reports on the existence of proteins interacting with histamine in microorganisms are limited and inconclusive. This review aims to illustrate the possible contribution of histamine in bacterial biochemistry and physiology, thus providing insights into the possible modulatory properties of the amine during the vital microbe-host signaling.

3. HISTAMINE IN MAMMALIAN CELLULAR PHYSIOLOGY

3.1. Histamine metabolism

Histamine is synthesised from L-histidine through the catalytic activity of the rate-limiting enzyme histidine decarboxylase (HDC, EC 4.1.1.22) (15). Unlike other biogenic amines, histamine is not a direct inhibitor of its biosynthetic enzyme, *S*-α-fluoromethylhistidine being a selective and potent HDC suicide inhibitor (16).

Histamine can be degraded by oxidative deamination catalysed by the secreted enzyme diamine oxidase (DAO, histaminase, EC 1.4.3.22, previously EC 1.4.3.6), which converts it into imidazole acetic acid, a γ-aminobutyric acid $(GABA)_A$ receptor agonist or by ring methylation through the catabolic action of the cytosolic histamine N-methyltransferase (HNMT, EC 2.1.1.8) (17). In contrast to HNMT that is responsible for the inactivation of intracellular histamine, DAO, released from its binding sites in response to heparin, is important for the inactivation and scavenging of extracellular histamine thus terminating its action (17). DAO is inhibited by the non-selective inhibitor aminoguanidine, which also inhibits nitric oxide (NO) synthase (NOS, EC 1.14.13.39) that catalyses the production of the highly reactive free radical species NO (18). Although tissue- and species-specific differences have been reported, DAO levels and activity have been extensively implicated in the pathophysiology of a number of inflammatory and immunologically-mediated disorders (17, 18). In mammals, histamine is synthesized in several cell types of peripheral and central tissues and its release from repository cells is modulated by a variety of stimuli (19).

3.2. Histamine in physiology and pathophysiology

The classical source of histamine is the pluripotent heterogeneous mast cell, where it is stored in cytosolic granules and released to elicit its actions in a differential response to various immunological and non-immunological stimuli (19). These include allergens, mechanical and chemical stimuli, cold, ultra violet rays, endogenous polypeptides such as substance P and bradykinin, complement factors, food ingredients, infections and drugs (19). Non-mast cell histamine is derived from numerous sources, including the gastric enterochromaffin-like cells (20), haemopoietic cells, leukocytes, platelets (21) and histaminergic neurons of the tuberomamillary nucleus of the posterior hypothalamus that project all over the central nervous system (CNS) (22).

Following its discovery 100 years ago (23), histamine has been one of the most studied substances in medicine for a century. It exerts a wide spectrum of activities, ranging from the well-established strong association with the pathophysiology of atopic diseases to neurotransmission (22). The pleiotropic regulatory properties of histamine in cellular events is elicited through binding to four subtypes of G-protein-coupled receptors (GPCRs), designated H_1, H_2, H_3 and H_4 (H_XR) that are differentially expressed in various tissues and cell types (1). Histamine receptor diversity is supported by pharmacological evidence and by the low protein sequence homology, which is suggestive of their evolution from different ancestral genes (24). In humans, the endogenous ligand shows low affinity for H_1Rs and H_2Rs, whereas its potency on the H_3R and H_4R is considerably higher. H_3Rs and H_4Rs are most closely related to each other and they have a closer phylogenetic relationship with peptide ligand GPCRs. Being remotely related to other biogenic amine receptors and to the H_1R and H_2R, the H_4R shows about 35% homology with the H_3R and even smaller with the classical pro-inflammatory H_1R or the H_2R (24).

Histamine actions on smooth muscle, vascular permeability and allergic responses are predominately H_1R-mediated processes that follow, largely but not exclusively, high-affinity binding of immunoglobulin E (IgE) to its specific receptor FcεRI. The consequent activation of mast cells and basophils causes degranulation and mediator release (25). In the gastric mucosa, enterochromaffin-like cell-derived histamine acts as a paracrine stimulant to control gastric acid secretion in response to hormonal and neural stimuli, basically *via* the H_2R (20, 26). In a mutual interaction network with other CNS transmitters, histamine exerts its central effects through H_1R, H_2R and H_3R signalling (22, 27). H_3Rs, whether presynaptic autoreceptors that inhibit the synthesis and release of histamine in the histaminergic neurones or postsynaptic heteroreceptors, are predominately distributed in the CNS and implicated in basic homeostatic and higher brain functions (22, 27). Finally, the recently identified H_4R controls eosinophil chemotaxis and selective mast cell recruitment, leading to amplification of histamine-mediated immune responses and eventually to chronic inflammation. Moreover, it modulates dendritic cell activation and helper T cell (T_H) differentiation and it is thus characterised as the immune system histamine receptor playing a key immunomodulatory role in atopic and inflammatory pathologies (8).

The human histaminergic system has proved to be a rich source of drugs over the last five decades with a

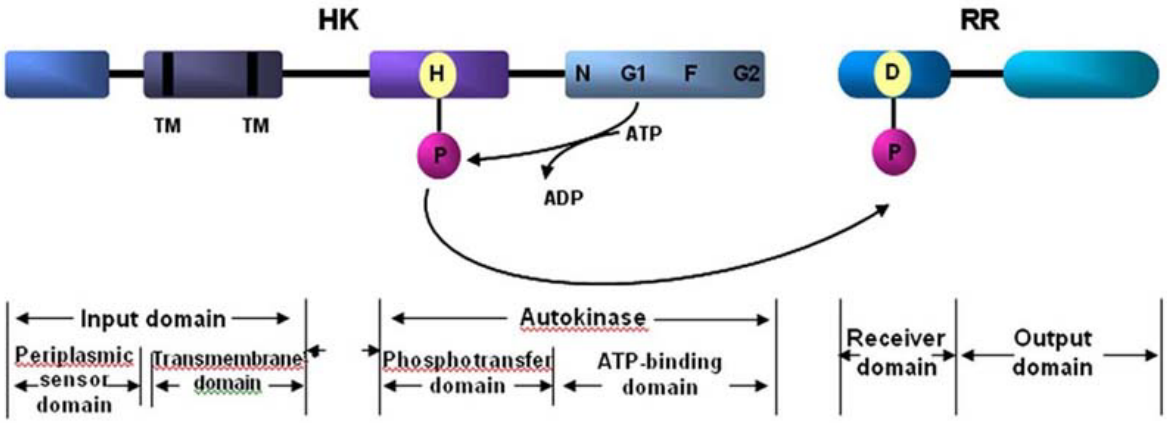

Figure 1. A typical histidine kinase (HK) monomer of the AtoSC two component system with a variable extracytoplasmic N-terminal sensing domain and a conserved cytoplasmic region. The latter comprises the dimerization and the C-terminal ATP-binding kinase domains and contains the phosphoacceptor His residue in the conserved H-box as well as four unique signature sequence N-, G1-, F- and G2-boxes. HAMP domain (H) is a linker between the input and autokinase. Response regulators (RR) consist of a conserved N-terminal receiver domain containing the site of phosphorylation in the conserved "acidic pocket" and a variable C-terminal output domain that elicits the output function (39, 40, 45). TM: transmembrane

number reaching blockbuster status. H_1R (commonly referred to as antihistamines) and H_2R antagonists are widely used in the treatment of allergy and gastrointestinal disorders, respectively (1). Despite the contribution of H_1R and H_2R in histamine-mediated neurotransmission, translational research has been directed towards the therapeutic potential of antagonists and inverse agonists targeting selectively the H_3R in dementias and psychotic or sleep disorders. However, no proof-of-concept for a H_3R (patho)physiological function has been reported so far (27, 28). Concerning the H_4R, even though the interpretation of preclinical testing is limited by species heterogeneity and the complex pharmacological profile of its ligands, the data offer an optimistic perspective for the therapeutic exploitation of H_4R ligands in inflammatory disorders such as allergy, asthma, chronic pruritus, arthritis, autoimmune diseases and pain (28).

4. HISTAMINE IN BACTERIAL PHYSIOLOGY AND ADAPTATION

Bacteria respond to the continuously changing conditions *via* multicomponent adaptive and protective networks involving alterations in gene expression, cell cycle progression, catalysis, protein–protein interactions and other modifications in cellular physiology (29). At the top of the bacterial signaling hierarchy, two-component systems (TCSs) that employ phosphorylation as the means of signal transduction affect these processes at several different levels (30). To date, no reports on the presence of TCSs in mammalian cells are available. Nevertheless, plants and lower eukaryotes such as yeasts make use of His-Asp phosphotransfer and multistep phosphorelay, albeit in a limited number of signaling pathways, to transmit stress signals (31, 32).

Among the numerous adaptive responses elicited through TCSs (33), the direct regulation and the intracellular distribution of the complexed poly-R-3-hydroxybutyrate (cPHB) biosynthesis has been demonstrated for the AtoSC TCS (34, 35). The abundantly naturally occurring cPHB, is a ubiquitous constituent of prokaryotic and eukaryotic cells that readily adheres to other molecules with valuable physiological functions, including Ca^{2+} homeostasis through the non-proteinaceous complexes of short-chain PHB-polyphosphate-Ca^{2+} acting as voltage-gated Ca^{2+} channels, competence for genetic transformation, protection of the complexed proteins from proteolysis and DNA organization (36, 37). Furthermore, biogenic amines appear to enable bacteria to survive and overcome host defense mechanisms, and in many occasions to elicit or arrest their pathogenic effects, often via TCS-regulated networks (6). The enterohemorrhagic *E. coli*, which is responsible for worldwide outbreaks of gastrointestinal manifestations, activates transcription of genes involved in intestinal lesions, such as the QseEF TCS, in response to signals originating from intestinal microflora and the host epinephrine and norepinephrine (38).

4.1. Bacterial two-component systems

TCSs usually comprise a homodimeric transmembrane sensor histidine kinase (HK) and a cytoplasmic cognate response regulator (RR) (39-41) (Figure 1). When the HK senses a signal, it triggers ATP-dependent *trans*-autophosphorylation on a conserved histidine residue in the autokinase domain. Following physical contact of the phosphorylated HK with the RR, the phosphoryl group is transferred, usually to an aspartate residue, thus modifying its conformation and eventually its biological properties as a DNA-binding transcriptional activator (41, 42). Some HKs may exhibit phosphatase activity towards their cognate RR as a supplementary means to regulate phosphorylation (43). Ultimate control of the RR output is accomplished by the level of RR phosphorylation determined by its intrinsic

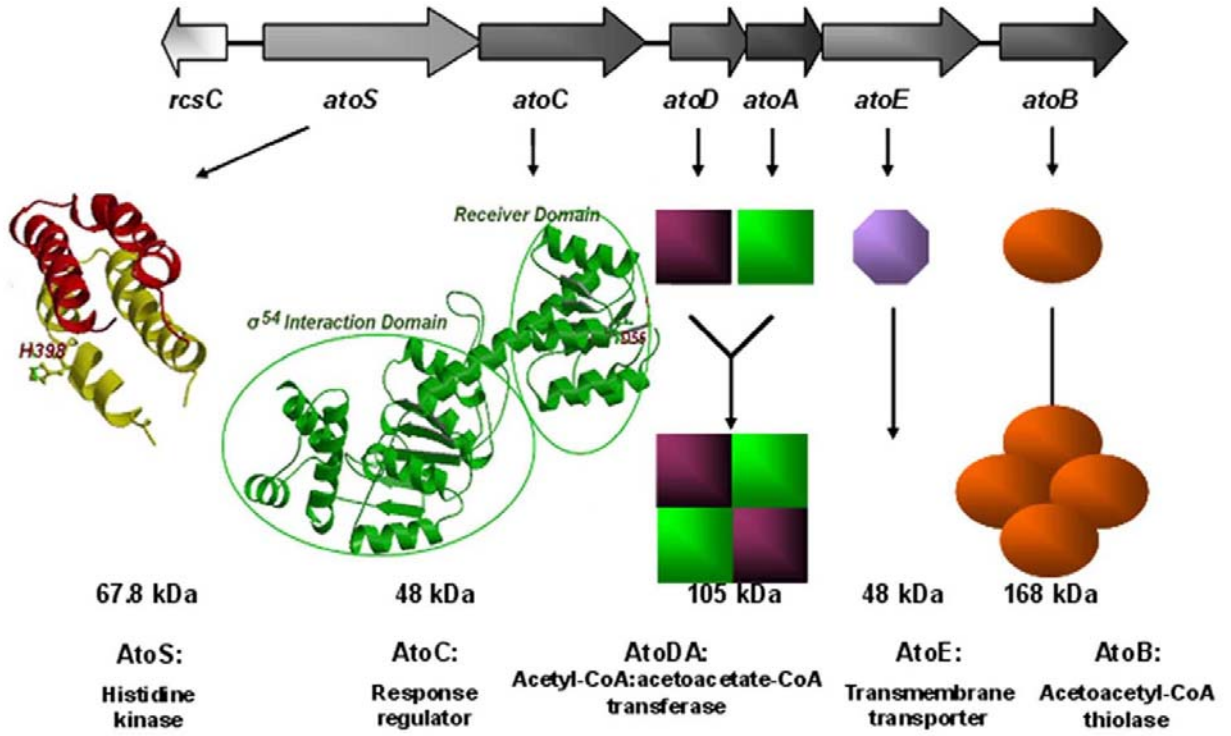

Figure 2. Transcriptional direction of the *atoS-atoC* and *atoDAEB* locus of *E. coli* K-12 genome and the encoded proteins. The sizes of *atoS, atoC* and *atoDAEB* genes and their intergenic regions are to scale in the linear linkage map. The protein molecular weights are indicated in kDa. Ribbon representation of the 3D model of a region of AtoC (aa:7–381, in green) which forms complex with the potential dimerization domain of AtoS (aa: 382–449, in yellow and red) (58). The four-α helix bundle structural motif was proposed by molecular modeling for AtoS dimerization/phosphoacceptor domain. The AtoC receiver domain, containing a central β-sheet of five parallel β-strands flanked by five α-helices, is linked to the σ^{54} interaction domain *via* an extended α-helical linker and communicates functionally with the ATPase region containing Walker A and Walker B motifs (58). *AtoD* and *atoA* genes encode for the α- and β-subunit of acetyl-CoA:acetoacetyl-CoA transferase (EC 2.8.3.8), *atoE* for the membrane-bound short-chain fatty acid transporter and *atoB* for acetoacetyl-CoA thiolase or thiolase II (EC 2.3.1.9).

autophosphatase activity and additional influencing factors (40).

Genome sequencing revealed that most bacteria possess numerous TCSs, with the number of systems increasing with the genome size and the complexity of the lifestyle of the organism (44). Classification attempts by numerous criteria denote the vast diversity of RRs that include almost all known types of DNA-binding domains (45) and the versatility of HKs. A phylogenetic analysis of 336 HKs in the genomes of 22 Bacteria and 4 Achaea assigned HKs to five major types (46).

More complicated multilayered networks of TCSs also exist and may play a role in bacterial virulence (41, 47) and bacterial-mammalian cell symbiosis (48). In this case, different signals can be channeled to the same regulatory pathway activating the phosphorylation of a RR by additional HKs to its cognate, each responding to a different signal, as exemplified by the sporulation processes of Gram-positive pathogens (49). The transcriptional regulation of a TCS by another TCS is exemplified by the multiple regulatory TCS networks implicated in bacterial pathogenesis and symbiosis (50). The plasticity of some of these sophisticated systems may contribute to strain-specific cellular processes leading to the acquisition of distinct features and phenotypes, particularly in pathogens (51).

The widespread distribution of TCSs in microorganisms but apparently not in animals including humans (52), as well as their association with bacterial evolution (53) reflect their pivotal role in adaptive mechanisms, symbiosis and pathogenicity (42), thus placing TCSs among the attractive targets for the development of selective and more beneficial antimicrobial therapeutic approaches (54). The multiple regulatory networks of signal transduction have not been fully identified in a range of microorganisms, including symbiotic and potentially pathogenic bacteria such as *Escherichia coli.* As an example, the elucidation of the mechanisms underlying the actions of the TCS AtoSC (30) and its involvement in regulatory pathogenetic mechanisms and pro-inflammatory signals, could lead to a new perspective on the symbiotic and pathogenic behavior of bacteria.

4.1.1. The AtoSC two-component system in *E. coli*

Among the 32 encoded TCSs in *Escherichia coli,* the vital orchestration of cellular economics under

circumstances that might have potentially deleterious impact on their survival and wellbeing (33, 55) is attributed to the AtoSC system (30). The AtoSC TCS consists of the AtoS sensor HK and the AtoC RR. In the *E. coli* genome the *atoS* and *atoC* genes are located upstream of the *ato* operon genes *atoD, atoA, atoE* and *atoB* (*atoDAEB*) that encode proteins involved in short-chain fatty acid (SCFA) metabolism (Figure 2) (56). AtoS is a transmembrane homodimer and comprises an N-terminal periplasmic ligand-binding region, a kinase domain containing the phosphorylation His398 residue in a conserved H-box, as well as a functional G2-box in the transmitter region, critical for ATP-binding (57). AtoC is a member of the NtrC-NifA family of σ^{54}-RNA polymerase transcriptional activators possessing intrinsic ATPase activity and requiring binding to enhancer-like element for the induction of the promoter (58, 59). AtoC consists of an N-terminal receiver domain, a central AAA^{+} ATPase region and a DNA-binding region (58). Two putative phosphorylation residues have been identified for AtoC. In addition to the receiver domain Asp55 residue in the conserved "acidic pocket", a potential second independent phosphorylation target has been identified at His73 residue within an unexpected H-box consensus sequence common to homodimeric HKs (58, 60). Upon induction, AtoS is autophosphorylated to His398 (57) followed by the phosphotransfer to Asp55 and His73 of AtoC by protein-protein interaction (60). The first established downstream target of AtoSC is the transcriptional activation of the *atoDAEB* operon (60) encoding for proteins involved in SCFA catabolism (61) (Figure 2). The phosphorylated AtoC binds to the *atoDAEB* operon promoter at an inverted palindromic repeat (59), it is oligomerized and activated (58), subsequently regulating a number of cellular processes (30).

It is of interest that the RR AtoC possesses a second function as a post-translational regulator. The *atoC* gene also encodes antizyme, a polyamine-inducible endogenous non-competitive protein inhibitor of ornithine decarboxylase (ODC, L-ornithine carboxylyase, EC 4.1.1.17) that catalyzes the conversion of ornithine to putrescine in the first rate-limiting step of polyamine biosynthesis (62, 63).

The regulation of SCFA catabolism through *atoDAEB* is an essential function of the symbiotic gastrointestinal flora that digests unutilized energy substrates in favor of the host (48). In addition, AtoSC participates in many other processes including the biosynthesis and intracellular distribution of cPHB (4, 34, 35), aminoglycoside antibiotics sensitivity, cross-regulation with the EnvZ-OmpR TCS, flagella synthesis and chemotaxis (5, 33, 55, 64).

4.2. Histamine modulation of AtoSC signaling

Both histamine anabolic and catabolic pathways have been identified in prokaryotic organisms. Studies on bacterial HDC have shown that pyridoxal phosphate-dependent HDCs are encountered in Gram-negative species including the nosocomial pathogen *Enterobacter aerogenes* but apparently not the commensal and potential pathogenic *E. coli* (10). Pyruvoyl-dependent HDCs are associated with Gram-positive bacteria including some lactic acid bacteria and staphylococci (9). Regarding the potential for amine degradation, this does not seem to be associated with the capability of amine formation in microorganisms. Inactivation of biogenic amines can be achieved by amine oxidases catalysing the oxidative deamination of primary amines to aldehydes, hydrogen peroxide and ammonia (13). The crystal structure of histamine dehydrogenase isolated from *Nocardioides simplex*, catalyzing the oxidative deamination of histamine to imidazole acetaldehyde has been described recently (14). Even though histamine metabolic pathways have not been identified in *E. coli* so far, exogenous histamine has been reported to stimulate proliferation and biomass accumulation during the late lag and early exponential growth phases of *E. coli* K-12 strain in a nonlinear concentration-dependent fashion (65). Additionally, exogenous histamine has been implicated in the AtoSC-regulated cPHB biosynthesis (3). This may possibly have consequences for *E. coli* symbiosis in humans, particularly regarding bacterial chemotactic response and adherence in the induction of infection and during the inflammatory response.

4.2.1. Histamine involvement in cPHB biosynthesis

AtoSC-mediated signal transduction has been associated with acetoacetate (34), spermidine (35) or intermediate metabolic compounds of the SCFA catabolic pathway (66). Interestingly, AtoSC responds to pro-inflammatory mediators, such as histamine (3) and platelet activating factor (Theodorou *et al.,* unpublished data), as well as to the basic polyamine compound 48/80 (C48/80) (3), most likely in an extracellular Ca2+-dependent manner (4). Histamine elicited a suppressive effect on cPHB biosynthesis, in contrast to C48/80 that induced cPHB biosynthesis in AtoSC-expressing but not in Δ*atoSC E. coli.* Histamine was able to counteract this action of C48/80, irrespective of the time of amine addition during bacterial growth (3). In addition to the inhibition of cPHB biosynthesis, the selective histamine-induced activation of *atoC* but not of the *atoDAEB* operon (3) points to multiple effects of this biologically important amine in prokaryotic cells.

The implication of Ca2+ as a signal in a wide variety of cellular processes affecting the physiology and pathogenesis is now becoming evident for bacteria where cytosolic Ca2+ levels are tightly controlled by mechanisms involving plasma membrane transporters (67). Indeed, extracellular Ca2+ was able to modulate both histamine and C48/80 effects on cPHB biosynthesis under the control of AtoSC (4). Along this line of research, the polycationic C48/80 was shown to disrupt membrane permeability in *E. coli* and to increase Ca2+ efflux (69). Recent studies revealed a modulatory role of extracellular Ca2+ on cPHB regulation by AtoSC TCS and AtoSC-mediated Ca2+ variations through influx systems, generated by differential effects of the Ca2+-channels blockers in *E. coli* (4). The Ca2+-dependent induction of cPHB biosynthesis by histamine in AtoSC-overproducing cells provides strong

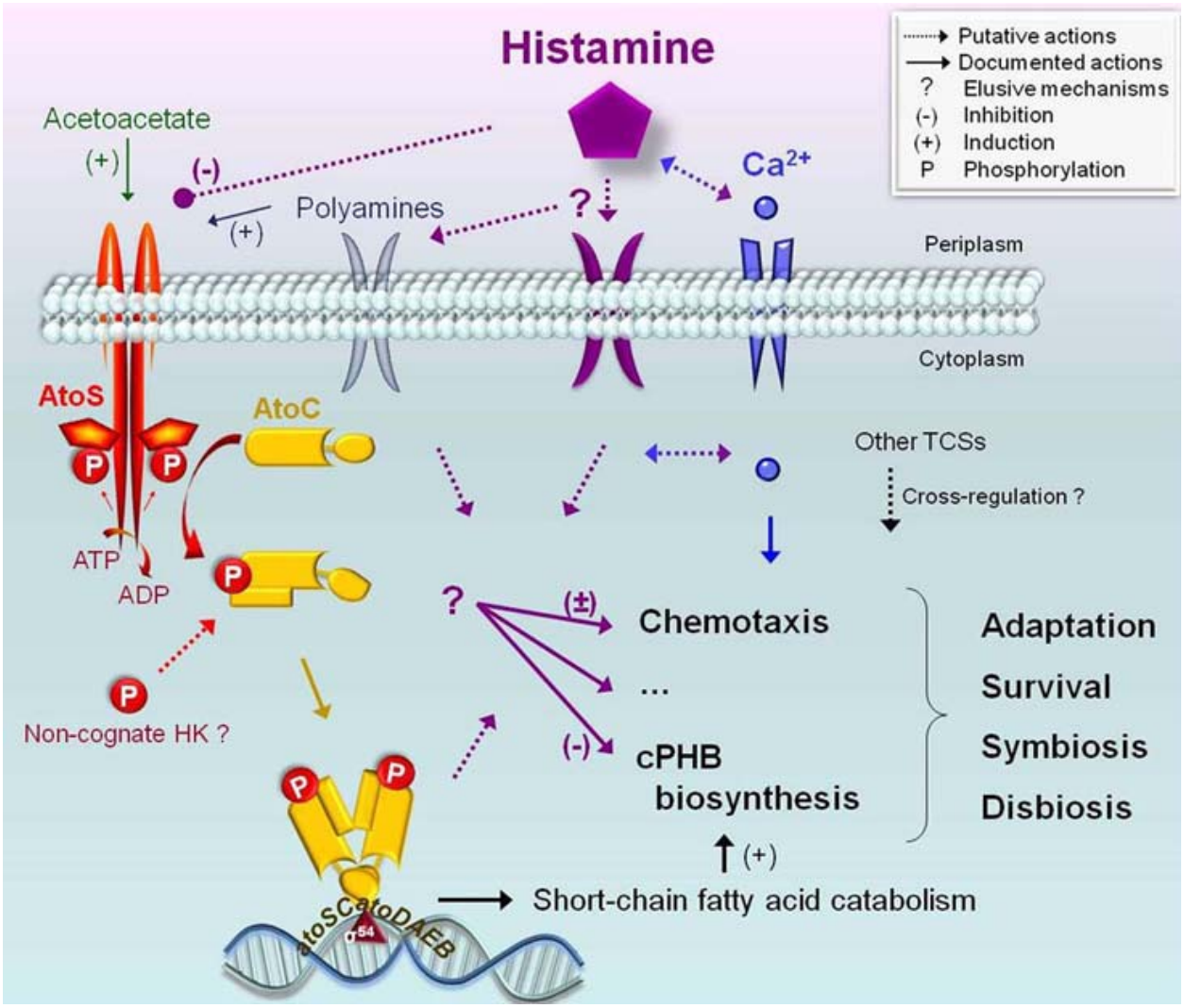

Figure 3. Histamine-induced AtoSC two-component system regulates pivotal cellular processes in *E. coli.* The established AtoSC signaling is induced by acetoacetate, spermidine or other amine analogs. They act as signals for homodimeric AtoS sensor histidine kinase (HK) autophosphorylation at His398, followed by phosphoryl group transfer to Asp55 and/or possibly to the His73 residue of the AtoC response regulator. The activated oligomerized AtoC binds to the promoter of the *atoDAEB* operon and induces its transcription *via* the action of σ^{54}-RNA polymerase holoenzyme, leading to short-chain fatty acids' catabolism and activation of the complexed poly- (R)-3-hydroxybutyrate (cPHB) biosynthetic pathway. The functional AtoSC system affects also *E. coli* chemotactic behavior and some other related adaptive responses. Ca^{2+} affects the AtoSC-mediated responses. Histamine, modulates the AtoSC signaling towards its downsteram effects, either acting on an *E. coli* membrane-bound yet undefined receptor or it entering the cell through the polyamine transport system. Subsequently, it elicits a suppressive action on the AtoSC-mediated cPHB biosynthesis and alters the chemotactic behavior of *E. coli*, while it demonstrates no effect on the *atoDAEB* operon. Ca^{2+} is engaged in interplay with histamine either at the periplasm or intracellularly, thus modifying histamine effects. The cross-regulation involving AtoSC system and other TCSs deserve consideration for the understanding of *E. coli* symbiosis and adaptation.

indications for the participation of the AtoSC TCS on the bacterial gene regulation by pro-inflammatory signals.

Histamine and polyamines seem to be at the interface of AtoSC signaling. The *potIHGF* putrescine ABC transport system, the *potBCAD* spermidine/putrescine ABC transport system and the putrescine/ornithine antiporter encoded by *potE* operate in *E. coli* (69). Polyamines and synthetic polyamine analogs can induce *atoC* transcription resulting in increased AtoC accumulation and subsequent inhibition of ODC activity, with putrescine and the non-natural diamine diaminopropane being the most potent, activating neither the *ato* operon promoter nor *atoS* (35, 70). Likewise, C48/80 showed some tendency to suppress *atoC* expression and it was unable to induce any significant alterations to *atoDAEB* (3). Growing evidence implicates a metabolic interplay between histamine and polyamines (71) among

numerous other interactions. Due to their cationic nature, both histamine and polyamines are able to bind DNA (72). However, research on their cross-talk at the level of gene expression or metabolism remains limited. Indirect indications have been provided by the histamine effects on *atoDAEB* expression and cPHB biosynthesis that are opposite to those observed with spermidine (3). Moreover, the H_1R antagonist chlorpheniramine, a 1,4 diamine, binds to nucleic acids and elicits effects on protein synthesis and ODC translation (71).

The existing literature does not provide evidence to support any suggestion regarding the specificity of the histamine effects on AtoSC signaling in *E. coli*. Therefore, histamine may act on yet unidentified cellular targets or/and it may elicit its actions *via* direct or indirect non-specific interaction (s) with structurally related membrane or cytoplasmic components (Figure 3). Candidates include members of the basic amino acid/polyamine antiporter family that may mediate downsteam signaling, such as PotE and the histidine/histamine exchanger HdcP which has been detected in *Lactobacillus hilgardii* but was shown to have no affinity for exogenous histamine (11). The pH-dependent putative histidine/histamine antiporter HdcT, which takes histidine into the cytoplasm and histamine out of the cell, was characterized recently in the opportunistic pathogen *Photobacterium damselae* subsp. *damselae* (formally *P. histaminum*) by sequence alignment and comparison of predicted transmembrane domains (12) using information on the putrescine/ornithine antiporter PotE of *E. coli (*69).

Additional hypotheses on putative histamine targets cannot be excluded at present. Further to the well-established histamine binding to GPCRs, information on histamine interaction with soluble receptors is provided by the identification of histamine-binding proteins (HBPs), which are members of the lipocalins secreted by hematophagous arthropods in order to scavenge biogenic amines and consequently to modulate the host inflammatory defense (73). Besides membrane receptors, sporadic reports suggested that histamine may bind to intracellular sites, designated as H_{IC}, which are associated with cytochrome P_{450} implicated in drug and other xenobiotic metabolism in mammals (74). However, concrete evidence on H_{IC} functionality remains unclear. Undoubtedly, the identification of cellular components able to sense and/or bind histamine would provide valuable information regarding the selectivity of the reported effects of histamine in *E. coli*.

4.2.2. Histamine involvement in motility and chemotaxis

Similarly to other motile bacteria *E. coli* responds to a number of agents including aminoacids, hydrocarbons, metabolites and drugs by suitable flagella movement, thus adapting to environmental conditions through motility and chemotaxis (75). Around 50 genes constitute the flagellar regulon in *E. coli*, which is regulated *via* yet poorly defined mechanisms in response to environmental cues that involve a number of transcriptional regulators and cross-regulatory TCS networks (76, 77). For instance, chemotactic adaptation that is regulated by CheAY TCS signaling involves movement towards chemoattractive agents or away of chemorepellents (78, 79). AtoSC has been implicated in *E. coli* chemotactic processes, since its genomic locus deletion triggered gene expression alterations, resulting to reduced flagella synthesis and different motility phenotypes (55). Evidence also comes from recent data revealing the AtoSC contribution in the regulation of *E. coli* motility and chemotaxis in an inducer-dependent manner (5). An illustrative example is the biphasic histamine-induced alterations in the motility and chemotactic phenotypes of AtoSC-expressing bacteria. At low concentrations exogenous histamine enhanced motility, while higher concentrations inhibited *E. coli* motility (5).

5. HISTAMINE IN VIRULENCE AND PATHOGENICITY

Bacteria are able to sense a wide range of micro-environmental stimuli including xenobiotics and host signals. Changes in microenvironmental conditions, such as oxidative stress, may lead to alterations in normally dormant bacterial genes that are sufficient to induce virulence determinants and thus to confer pathogenic phenotypes to otherwise non-infectious bacteria, including the widely used laboratory strain *E. coli* K12 (80).

The bidirectional histamine-mediated communication between microorganisms and mammalian cells (Figure 4), which may control susceptibility to allergy and infections remains inadequately understood. Besides the typically symbiotic relationship, commensal microbes of the normal human intestinal flora seem to have an orchestrator function in the development of dysbiosis. Subsequently, extra-intestinal diseases may be triggered or the risk of developing pathologies could be modified, including urinary tract infections, peritonitis and autoimmune disorders such as inflammatory bowel disease **(**81). Histamine modulates the defense against *E. coli* infection in experimental peritonitis (6), while bacterial endotoxins, such as lipopolysaccharides differentially alter histamine levels in mammalian tissues (8). Moreover, alpha-hemolysin-producing *E. coli* induces the release of histamine and pro-inflammatory cytokines from mast cells which may link innate and adaptive immunity in bacterial infections (7). Hemolysin secretion is related to bacterial iron metabolism and is regulated differently among *E. coli* strains (82). Interestingly, Gram-negative bacteria utilize histamine to constitute the iron-sequestering siderophores which are implicated in their survival and protection against host defense mechanisms (83).

Bacteria are not metabolically inert. The most common example of the symbiotic relationship between human hosts and intestinal microbes is that of colonic bacteria-dependent butyrate production, the main fuel source for colonocytes stimulating the proliferation and differentiation of epithelial cells in the gut (84). Histamine and the mast cell degranulator C48/80 have been implicated in the AtoSC-regulated cPHB biosynthesis which may be have significant consequences for *E. coli* symbiosis in

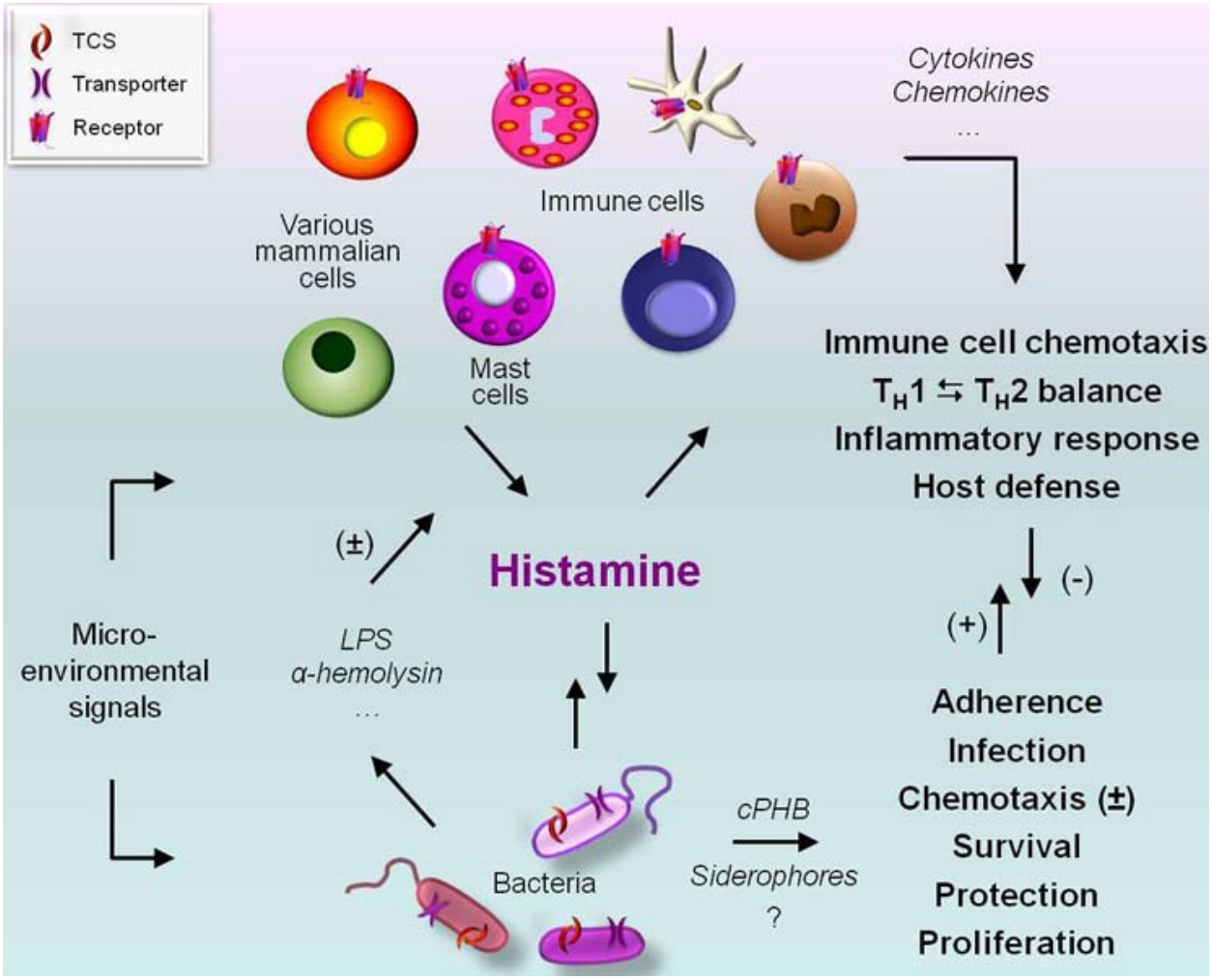

Figure 4. Bidirectional histamine-mediated communication between microorganisms and mammalian cells. Histamine is mainly synthesized and released from mast cells, additional sources including other types of mammalian cells as well as symbiotic microorganisms. In addition to regulating the host defense and inflammatory responses, mainly through immune cell chemotaxis, histamine modulates bacterial responses by acting on largely undefined bacterial targets (see text for details). cPHB: complexed poly-R-3-hydroxybutyrate, LPS: lipopolysaccharide, TCS: two component system, T_H: helper T-cell.

humans, particularly regarding bacterial chemotactic response and adherence in the induction of infection and during the inflammatory response (3). Additionally, the outer membrane protein P5 of the Gram-negative opportunistic pathogen *Haemophilus influenzae*, commonly linked with otitis media, chronic bronchitis and other mucosal infections has been shown to associate with cPHB (85). cPHB is present in a wide variety of tissues, such as the eye where histamine is abundant, and is implicated in diseases including atherosclerosis, diabetes and possibly glaucoma (86). Therefore, it would be interesting to explore the possible indirect involvement of histamine in the development of host pathologies by modifying cPHB production in microbes (Figure 4).

Although limited, the reports on the actions of histamine on potential pathogens provide the lead for the investigation of the underlying mechanisms and urge the exploration of yet undefined functional properties of histamine, a host-derived pro-inflammatory component, on symbiotic and/or infectious microorganisms, beyond the commonly investigated histamine receptor-mediated effects on host pathophysiology (1).

6. CONLUSION AND FUTURE PERSPECTIVES

The coordination of sophisticated molecular interactions that shape the conversion of extracellular information into exploitable intracellular signals in bacteria is a vital ongoing research area. Exposure of novel transmission signals in bacterial adaptation, survival and proliferation exemplified by the *E. coli* ATOSC TCS would improve the perspectives for their potential exploitation in health and disease. The bidirectional histamine-mediated communication between mammalian cells and microorganisms of the human intestinal flora, such as the *E. coli* may play a role in developing pathologies, including amongst others disorders such as colitis and inflammatory

bowel disease. The complexity of leukocyte immune surveillance, trafficking and recruitment and the plethora of different effects exerted by histamine through a repertoire of four receptor subtypes make hard to predict the overall effect of histamine in immune system-mediated conditions at present. The potential of H_4R ligands' therapeutic exploitation in inflammatory disorders strongly points to the H_4R as a novel target for the pharmacological modulation of histamine-transferred immune signals. The identification of bacterial TCS interplay with inflammatory mediators including histamine that may underlie bacteria-host communication is an attractive challenge in this field of research.

7. ACKNOWLEDGEMENTS

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Abbreviations: *atoSC*$^{+}$: genetic locus encoding the AtoS and AtoC proteins: AcAc: acetoacetate; cPHB: complexed poly- (R)-3-hydroxybutyrate; (Ca^{2+})e: concentrations of extracellular Ca^{2+}; C48/80: compound 48/80; GI: gastrointestinal; HI: histamine; HK: histidine kinase; RR: response regulator; SPD: spermidine; SCFA: short-chain fatty acid; TCS: two-component system, HDC: histidine decarboxylase, H_XR: histamine H_X receptor, PTX: pertussis toxin GPCR: G-protein-coupled receptor, DAO: diamine oxidase, GABA: γ-aminobutyric acid, HNMT: histamine N-methyltransferase, NO: nitric oxide, NOS: NO synthase high-affinity binding of IgE: immunoglobulin E, FcεRI: immunoglobulin E receptor, T_H: helper T-cell, CNS: central nervous system, ODC: ornithine decarboxylase, H_{IC}: histamine intracellular site, HBP: histamine-binding protein

Key Words AtoSC, C48/80 AtoSC, Chemotaxis; Histamine AtoSC, cPHB, Two-Component System, Symbiosis AtoSC, Pathogenesis, Review

Send correspondence to: Dimitrios A. Kyriakidis, Laboratory of Biochemistry, Department of Chemistry, Aristotle University of Thessaloniki, 54124 Thessaloniki, GREECE, Tel: 30 2310997771, Fax: 30 2310997689, E-mail: kyr@chem.auth.gr

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