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REVIEW

Pharmacological potential of biogenic amine–polyamine interactions beyond neurotransmission

F Sánchez-Jiménez[1,2], M V Ruiz-Pérez[1], J L Urdiales[1,2] and M A Medina[1,2]

[1]*Departamento de Biología Molecular y Bioquímica, Facultad de Ciencias, Campus de Teatinos, Universidad de Málaga, Málaga, Spain, and* [2]*Centro de Investigación en Red de Enfermedades Raras (CIBERER), Valencia, Spain*

Correspondence
Francisca Sánchez-Jiménez, Departamento de Biología Molecular y Bioquímica, Facultad de Ciencias, Campus de Teatinos, Universidad de Málaga, Málaga 29071, Spain. E-mail: kika@uma.es

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Histamine, serotonin and dopamine are biogenic amines involved in intercellular communication with multiple effects on human pathophysiology. They are products of two highly homologous enzymes, histidine decarboxylase and L-aromatic amino acid decarboxylase, and transmit their signals through different receptors and signal transduction mechanisms. Polyamines derived from ornithine (putrescine, spermidine and spermine) are mainly involved in intracellular effects related to cell proliferation and death mechanisms. This review summarizes structural and functional evidence for interactions between components of all these amine metabolic and signalling networks (decarboxylases, transporters, oxidases, receptors etc.) at cellular and tissue levels, distinct from nervous and neuroendocrine systems, where the crosstalk among these amine-related components can also have important pathophysiological consequences. The discussion highlights aspects that could help to predict and discuss the effects of intervention strategies.

LINKED ARTICLES
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Abbreviations
CYP, cytochrome P450; DAO, diamine oxidase; DDC, dopamine decarboxylase; DFMO, difluoromethyl ornithine; HDC, histidine decarboxylase; MATE1, multidrug and toxin extrusion transporter-1; ODC, ornithine decarboxylase; SAM, S-adenosyl methionine; sVMATs, vesicular monoamine transporters

The aim of the present review

Integration of biological information can reveal new properties and features that could contribute to progress in the characterization of complex systems; this is a fundamental principle of systems biology (Kitano, 2002). A human being can be considered as a system composed of different subsystems specialized in certain functions: interchange with the environment, defence, internal coordination (metabolic homeostasis, motor and cognitive capacities) and reproduction.

Biogenic amines and polyamines have relevant roles in all of these human functions, but the topic is too extensive to be the subject of a single review. Excellent reviews have been published recently on the pharmacological potential of biogenic amines (and related compounds) in neurotransmission (Nuutinen and Panula, 2010; Lin *et al.*, 2011; Lodge and Grace, 2011; Sharp and Cowen, 2011; Tiligada *et al.*, 2011; Deneris and Wyler, 2012; Fleck *et al.*, 2012; and others within this volume).

In the present work, we focus our attention on a set of small physiological subsystems beyond neurotransmission, where components related to cationic amino acids, dopamine and serotonin are present and can interact (Figure 1). Here, we also discuss the potential consequences of these metabolic connections for pharmacology, as well as pointing out some important gaps of information that require further basic research in order to generate useful translational information.

General biochemical and physiological features of biogenic amines and polyamines

Biogenic amines are produced by α-decarboxylation of amino acids. Most amino acid decarboxylases are pyridoxal phosphate-dependent enzymes with several pyruvoyl-

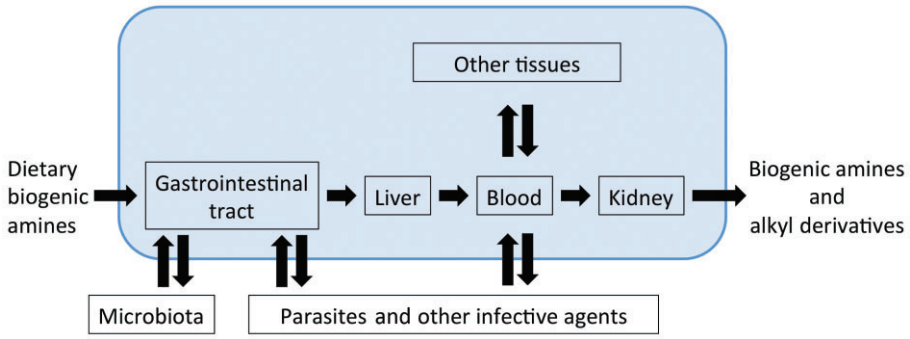

Figure 1

Schematic representation of the different scenarios of amine and amine analogues interactions in humans.

dependent exceptions, such as histidine decarboxylase (HDC) of Gram-positive bacteria (Huynh and Snell, 1985) and arginine decarboxylase of hyperthermophilic methanogen bacteria (Graham *et al.*, 2002). For human physiology, the most important amino acid-derived biogenic amines are those synthesized from cationic L-amino acids (putrescine from ornithine and histamine from histidine), from aromatic L-amino acids (serotonin from tryptophan, and dopamine, noradrenaline and adrenaline from tyrosine) and from glutamate (GABA) (Figure 2). An aminopropyl group derived from decarboxylated S-adenosyl methionine has to be added to putrescine to produce spermidine and another one to spermidine to produce spermine. Figure 2 summarizes the amine metabolic pathways in mammalian cells. Other biogenic amines such as cadaverine (decarboxylation product of lysine) and agmatine (decarboxylation product of arginine), present in the human body, mainly come from our diet or are produced by gut microbiota. Recent reviews provide a synthesis of the interspecies differences in biogenic amine metabolism and polyamine metabolism (Heby *et al.*, 2007; Landete *et al.*, 2008; Michael, 2011), which yield opportunities for specific intervention.

Most biogenic amines and polyamines are degraded by flavin-dependent or copper-dependent amino oxidases; for example, MAOs, MAO-A and MAO-B (Mitchell, 2008; Wang *et al.*, 2012), and diamine oxidase (DAO)/histaminidase, polyamine oxidases (McGrath *et al.*, 2009; Stevanato *et al.*, 2011) respectively. Amine oxidases are located in different cellular levels (from extracellular to mitochondrial locations, globally referred to as reaction 18 in Figure 2) (Edmondson *et al.*, 2009). Methylation or acetylation steps can precede the action of oxidases. Accumulation of some amine degradation products, such as aldehydes and reactive oxygen species (ROS), can become toxic (Sinigaglia *et al.*, 2012). Therefore, amine oxidases are well-established pharmacological targets, especially for neuroprotection and cardioprotection (Bortolato *et al.*, 2008; Edmondson *et al.*, 2009; Bolasco *et al.*, 2010).

All amines are important signal transducers in mammalian physiology. Nevertheless, the major roles of polyamines (spermidine and spermine) are carried out inside the polyamine-producing cells, as they bind to chromatin and RNAs and are essential to maintain macromolecular synthesis and cell viability (Ruiz-Chica *et al.*, 2001; Medina *et al.*, 2003). Polyamine metabolism is very robust and strictly regulated, as both lack and excess of polyamine levels can be lethal for cells (Rodríguez-Caso *et al.*, 2006). On the other hand, the other monoamines and diamines (histamine, serotonin, dopamine and their derivatives and GABA) are mainly involved in highly complex cell–cell communication networks. The involvement of histamine and serotonin in immune responses is well known (Chodaczek *et al.*, 2009; Schneider *et al.*, 2010). They are all considered neurotransmitters. These intercellular communication processes elicited by biogenic amines involve a numerous family of GPCRs, which have conserved rhodopsin-like structures (Katritch *et al.*, 2012). In spite of the common structural features of the receptors, many questions remain to be answered about the signal transduction pathways of a given biogenic amine in the different mammalian/human cell types under different circumstances. Different arrangements of the polypeptide subunits of the G proteins and other associated macromolecules can even occur in a same cell type, leading to different intracellular effects depending on the stage of development and differentiation, concomitant external stimuli or metabolic status (Ferrada *et al.*, 2009; Moreno *et al.*, 2011). This complexity is in agreement with the 'pleiotropy' of these compounds driven by evolution to transmit information among different cell types, tissues and organs.

Biogenic mono-, di- and polyamines can also be transported through different biological membranes by common transport systems, such as the organic cation transporters 2 and 3 – SLC22A2/A3 – and the vesicular monoamine transporters – VMATs/SLC18 (Schütz *et al.*, 1998; Ogasawara *et al.*, 2006)]. Information on cell-specific expression of these and other amine-related proteins can be obtained from Gene Expression Atlas database (Kapushesky *et al.*, 2010) and/or from BioGPS database (Wu *et al.*, 2012). As these transporters are also responsible for the uptake and efflux of other metabolites and drugs; the amines can compete among themselves and with many other drugs, with physiological consequences (Ciarimboli, 2011). Recent reviews have been published on this issue, taking into account the tissue-dependent expression patterns of these transporters in the small intestine, liver, kidney (Müller and Fromm, 2011) and lung (Bosquillon, 2010). In addition, histamine and histamine analogues and polyamines can interfere with two mammalian polyamine-related transport systems: ornithine/arginine transport

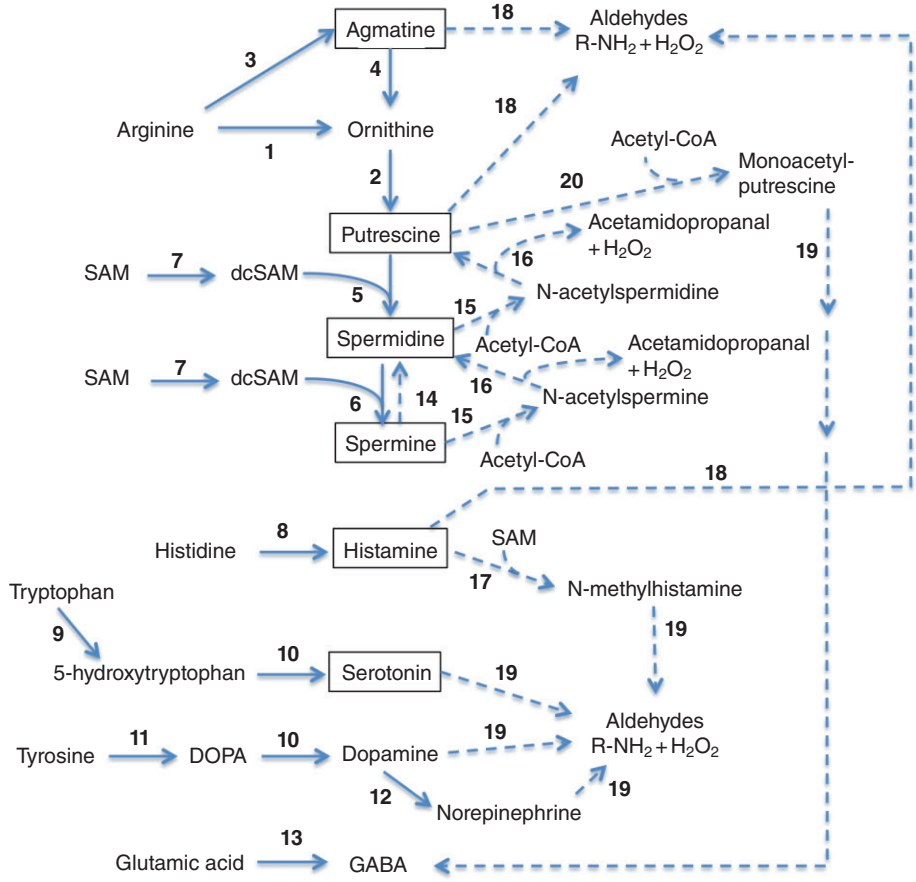

Figure 2

Overview of biogenic amine and polyamine metabolism in humans. Synthetic reactions are shown as solid lines, degradative reactions are shown as dashed lines. 1: arginase; 2: ornithine decarboxylase; 3: arginine decarboxylase (still controversial, Morris, 2007); 4: agmatinase; 5: spermidine synthase; 6: spermine synthase; 7: S-adenosylmethionine decarboxylase; 8: histidine decarboxylase; 9: tryptophan 5-monooxygenase; 10: aromatic L-amino acid decarboxylase (DDC); 11: tyrosine hydrolase; 12: dopamine monooxygenase; 13: glutamate decarboxylase; 14: spermine oxidases; 15: spermidine/spermine N^1-acetyltransferase; 16: polyamine oxidases; 17: histamine N-methtyltransferase 18: amine oxidases; 19: aldehyde dehydrogenases.

systems (Medina *et al.*, 1991) and spermine transporter systems (Fajardo *et al.*, 2001; Paz *et al.*, 2001).

Other common macromolecular binding targets have been described for biogenic amines and polyamines that are clearly very important for human physiopathology, as well as for prevention of unwanted pharmacological side effects. For instance, biogenic amines and polyamines are able to bind to members of the cytochrome P450 (CYP) family, which constitute a major pathway for detoxification of chemical environmental hazards (Maréchal *et al.*, 2008). The NMDA receptor also binds both histamine and polyamines (including agmatine and amine analogues), although the preferential binding modes are still under discussion (Watanabe *et al.*, 2008; Mony *et al.*, 2009; Burban *et al.*, 2010). Both polyamines (spermidine and spermine) and diamines (putrescine and histamine) can also bind to nucleic acids (Ruiz-Chica *et al.*, 1999; 2001). The preferential binding modes have been studied for all of them and the presence of histamine in mammalian cell nuclei has also been observed (Medina *et al.*, 2006). In spite of the importance of amine and amine analogue-induced structural changes on nucleic acids (Medina *et al.*, 1998 and; 2003; Ruiz-Chica *et al.*, 1999), the characterization of specific amine effects on gene expression is very difficult because of the chemical nature of the interactions. These are weak but specific electrostatic interactions with ill-defined three-dimensional (3D) structures of nucleic acids, along with many other possibilities for non-specific interactions as organic cations (Igarashi and Kashiwagi, 2000). In any case, such interactions should not be overlooked during pre-clinical evaluation of amine analogues.

A very interesting discovery made more than 25 years ago (Fesus *et al.*, 1985) has required technological development in order to be studied further. In mammalian cells, transglutaminases (EC 2.3.2.13; protein-glutamine γ-glutamyltransferase) are able to covalently bind biogenic amines and polyamines to proteins, including small GTPases (Tabolacci *et al.*, 2012). In a recent review, Walther *et al.* (2011) summarized the potential regulatory roles of protein 'histaminylation', 'serotonylation', 'dopaminylation' and 'norepinephrinylation' on the function of small GTPases, heterotrimeric G-protein and lipid signalling, as well as for modulation of metabolic enzymes, with implications for many different pathophysi-

ological processes, including mast cell activation, bleeding disorders, primary pulmonary hypertension and diabetes. The application of proteomic technologies advance the progress in this interesting topic with clear translational value (Grosso and Mouradian, 2012; Vowinckel *et al.*, 2012).

Inputs and outputs of amines: a dynamic balance with many gaps of information

In its most simple abstraction, the dynamics of every living process can be defined as the balance between inputs and outputs of the participating components (Figure 1). Amine inputs come from uptake and endogenous synthesis (Figure 1). Amine outputs depend on endogenous degradation and excretion of amines or their derivatives.

Endogenous concomitant synthesis of histamine, serotonin and polyamines occurs in the stomach. The essential role of histamine for gastric secretion is well known. At least in rat, both ornithine decarboxylase (ODC) and HDC activities are affected by food intake, ranitidine, omeprazole and $NaHCO_3$ (Ding *et al.*, 1996). Histamine has a relevant role on *Helicobacter pylori*-induced inflammatory response, as studied in $HDC^{-/-}$ mice (Klausz *et al.*, 2004). Spermine oxidase has also been recently related to carcinogenesis induced by *H. pylori* infection. Thus, dietary histamine and polyamine content should be restricted to patients with *H. pylori* infections (Chaturvedi *et al.*, 2012).

Amino acid decarboxylases, and consequently amine biosynthetic pathways, can be found in almost all living organisms (Recsei and Snell, 1985; Medina *et al.*, 2003; Moya-García *et al.*, 2006, 2009), including gut microbiota. As concluded by previous COST Actions (European Science Foundation, http://www.cost.eu/) devoted to dietary amines (Eerola and Maijala, 2004), this could be a major problem for the control of amine availability, as gut microbiota could contribute a very important percentage to the pool, even when a low-amine diet is provided. Nevertheless, it is a highly complex and controversial issue that needs further research efforts. On one hand, anti-ageing and anti-inflammatory effects of microbiota-produced polyamines have been reported (Li *et al.*, 2001; Matsumoto *et al.*, 2011). On the other hand, pharmacological or dietary polyamine deprivation has been demonstrated to be effective in clinical trials for preventing the occurrence of multiple adenomas closely associated with the development of colon cancers (Gerner and Meyskens, 2009) and dietary polyamine input has been proposed as one of the major reasons for reducing effectiveness of anti-tumour strategies based on polyamine deprivation (Cipolla *et al.*, 2007). In addition, polyamines are described as both growth and death promoters depending on their concentrations, the cell type and its environment (e.g. the presence of amino oxidases) (Coffino and Poznanski, 1991; Averill-Bates *et al.*, 2008). The relationships between polyamine concentrations and the corresponding benefits and hazards caused by them in the gut must depend on a delicate balance influenced by both genetics and environment.

In the gastrointestinal tract, polyamine transport is mediated by both caveolar endocytosis and the solute carrier transporter SLC3A2 (Uemura *et al.*, 2010). In rat intestine, histamine uptake is modified by other biogenic diamines such as cadaverine (Lyons *et al.*, 1983).

Histamine deficiency can promote carcinogenesis through aberrant myeloid cell differentiation (Yang *et al.*, 2011), but an excess of histamine uptake also becomes a problem for patients with inflammatory bowel diseases, in spite of the presence of amine catabolic enzymes *in situ* (Fogel *et al.*, 2007). Taking into account the current information on the relationship between chronic inflammation and cancer (Demaria *et al.*, 2010), the question mentioned above arises again; are amine-containing diets and amine-producing probiotics 'good or bad' for inflammatory bowel disease patients in the long term? The answer probably depends on the genetic and epigenetic background of each person, and consequently it will require a more comprehensive view of the molecular networks established into and among the different involved cell types. Structural and functional genomics combined with systems biology could contribute greatly to the characterization of this complex system, which would help to develop more efficient personalized treatments (including preventive prebiotics or pharmacological treatments).

With respect to amine degradation, diamines such as putrescine and histamine are substrates of DAO (or histaminidase, EC1.4.3.22). The enzyme is the product of the human *abp1* (amiloride binding protein 1) gene, mainly expressed in placenta, kidney, colon, prostate and lymphoblasts (see BioGPS database, Wu *et al.*, 2012).

N-methylation and/or *N*-acetylation of amines facilitate their transport through biological membranes, as these derivatives have a reduced polarity. Histamine can be *N*-methylated by histamine *N*-methyl transferase before its degradation by MAOs (La Regina *et al.*, 2007), and spermidine and spermine are acetylated by spermidine/spermine acetyl-transferase before their degradation by polyamine oxidases or spermine oxidase (Figure 2; Cervelli *et al.*, 2012; Polticelli *et al.*, 2012). These processes consume two energy-consuming compounds with wide metabolic importance: S-adenosylmethionine (SAM) and acetyl-CoA respectively (Figure 2). Therefore, active amine degradation could alter the levels of these key metabolic components, thus spreading the metabolic consequences of amine pool alteration (Correa-Fiz *et al.*, 2012). As amine alkyl derivatives can behave as substrates of MAOs (Figure 2) and these enzymes play a relevant role in detoxification mechanisms for xenobiotics (Strolin Benedetti, 2011), we suggest that the potential interferences of those compounds on drug metabolism should be carefully studied.

Agmatine [1-(4-aminobutyl) guanidine] is a precursor of polyamine metabolism and a cell growth modulator that has been claimed to be involved in several neurological responses and disorders (Agostinelli *et al.*, 2010; Winter *et al.*, 2011). Agmatine, histamine and putrescine uptake is carried out by the organic cation transport systems OCT2/SLC22A2 in renal cells (Ogasawara *et al.*, 2006; Winter *et al.*, 2011). Agmatine is also a substrate of the multidrug and toxin extrusion transporter-1 (MATE1/SLC47A1) in kidney and liver, among other cell types and tissues (Winter *et al.*, 2011; see BioGPS database, Wu *et al.*, 2012). This system also participates in the clearance of many different drugs and toxins; for example, the histamine H_2 receptor antagonist, cimetidine (Kurata

et al., 2010). Therefore, competition for the transport systems could have consequences in renal clearance of biogenic amines or analogues, and consequently in the physiological processes in which the amines are involved (including neurological functions). In a recent work, Meyer zu Schwabedissen *et al*. (2010) concluded that the coordinated function of MATE1 with OCT2 probably contributes to the renal elimination of organic cationic drugs. Thus, altered MATE1 activity, whether by drugs or polymorphisms, could be considered an important determinant of renal cationic drug elimination.

Much is currently known regarding the input and output of biogenic amine–polyamines but much more remains to be discovered in order to provide hints with real effects on clinical conditions. On one hand, biogenic amine–polyamine uptake seems to be dependent on gut microbiota activity and is probably modulated by not fully characterized metabolic interferences among different amines. In order to get a deeper knowledge of the biological bases of these processes, it would be extremely useful to design and carry out new and more systematic strategies and approaches. The results would help analysis of pathologies such as cancer and inflammatory diseases, especially those located in the gastrointestinal tract. On the other hand, biogenic amine–polyamine catabolism and elimination involves – among others – changes in global redox state and methylation pattern with potential effects on the general health of the organism. This is an additional area of research with many current uncertainties and requires further experimental efforts. In summary, as in other areas of biomedicine, much more additional basic knowledge is required in this area for future effective translational initiatives. However, more accumulated knowledge is not enough and there is also an urgent need of additional efforts for integrative analysis of all the available data. We believe that the present and future 'omics' analyses of both gut microbiota and patients could provide highly valuable data. New information derived from systematic analyses of these data could be applied to a wide spectrum of emergent and rare human pathologies.

Biogenic amines and analogues in the liver: the major controller of homeostasis

The liver is the major organ for the control of human homeostasis and detoxification. It buffers most of the dietary and pharmacological input via the gut (Figure 1). Consequently, its biochemical characteristics in terms of biogenic amine–polyamine metabolism are important in order to explain the final levels of circulating amines and amine analogues. Under healthy conditions, the adult liver synthesizes only low levels of biogenic amines and growth-related polyamines. An increase in hepatic polyamine biosynthesis can be indicative of, and could take part in, a neoplastic process (Smirnova *et al*., 2012). Histamine and serotonin synthesis can be observed in the liver as a consequence of macrophage infiltration (Correa-Fiz *et al*., 2012).

It is well known that CYP comprises a large superfamily of proteins (from more than 50 genes in the human genome) (Nelson, 2009). Members of CYP 1–3 families play important roles in liver drug detoxification. A recent review on hepatocytes summarised the role of the phase I enzymes, including CYP isoforms in this task (Sevior *et al*., 2012). Both histamine and polyamines and analogues of both amine families, including anti-histaminic drugs and other histamine receptor agonists and antagonists, and polyamine analogues, have been described as CYP ligands (Sharma and Hamelin, 2003; Ghosal *et al*., 2009; Gaertner *et al*., 2012) and this property may explain the growth regulatory effects of these amines (LaBella and Brandes, 2000). Serotonin and dopamine are also described as CYP isoform regulators with clinical relevance for neuropathology (Wójcikowski and Daniel, 2009). For instance, altered levels of brain or plasma serotonin (caused by a tryptophan-free diet) modulated the hepatic CYP isozymic pattern in rats, and consequently the global hepatic CYP activity, suggesting that such modulations may also be exhibited by drugs acting via the serotonergic system (Kot *et al*., 2012). MAO inhibitors inactivate human drug-metabolizing CYP enzymes, suggesting that impaired metabolic clearance of biogenic amines or their analogues may contribute to undesired amine and drug–drug interactions (Polasek *et al*., 2006). The histamine receptor antagonist, cimetidine, inhibits cytochrome isoforms CYP2D6, CYP2C19 and CYP3A4, and such inhibition could enhance serotonin toxicity (serotonin syndrome) (Talarico *et al*., 2011). All this information emphasizes that these CYP isoforms could be important factors in amine system pharmacology.

Biocomputational techniques may promise efficient progress in the knowledge of 3D structures of mammalian CYP enzymes and their interactions with biomolecules and drugs. There are some recent studies applying quantitative structure–activity relationship methods (Sridhar *et al*., 2012), molecular dynamics and virtual screening methods (Mo *et al*., 2011; Vass *et al*., 2012) to the structural characterization of CYP-ligand interactions. These approaches have also been successfully applied for another amine-related receptor, the NMDA receptor (Krueger *et al*., 2009), among others. Such approaches could help to predict *in silico* and to prevent unwanted amine and drug–drug interactions involving biogenic amines and/or their analogues. In addition, there are also animal models (transgenic mice expressing hepatic human CYP isoforms) that could provide interesting experimental platforms for pre-clinical validation of the predicted results (Sevior *et al*., 2012).

This strategy would also benefit the characterization of the binding details of biogenic amines and polyamines within these enzymes and their putative interferences with drug detoxification processes. In addition, *in silico* metabolic modelling approaches could help evaluate the metabolic flux changes induced by drugs under different hepatic circumstances. A lot of information on human hepatic elements and their affinity and kinetic constants has been collected in public databases (Kanehisa *et al*., 2010; Takarabe *et al*., 2011), and predictive mathematical models exist for hepatic cationic amino acid metabolism (Reyes-Palomares *et al*., 2012).

In addition, amine metabolic pathways are SAM-consuming processes as mentioned before (Figure 2); consequently, changes in amine metabolic fluxes can be transmitted to sulphur-containing amino acid metabolic pathways (such as the folate cycle, homocysteine and glutathione syn-

thesis), with important consequences for gene methylation and/or redox status (Reyes-Palomares *et al.*, 2012) and *vice versa* (Karouzakis *et al.*, 2012). In mice a long-term diet supplemented with methionine altered SAM, polyamine and histamine levels in liver with important consequences on other hepatic stress markers (Correa-Fiz *et al.*, 2012).

In summary, interactions between amino acid and amine metabolism and primary hepatic functions should be considered during pharmacokinetic studies and evaluation of pharmacological treatments in general (Funayama *et al.*, 2010).

Amines and mast cells: an interesting model of amine metabolism organization

The role of histamine and serotonin in the immune system has recently been thoroughly analysed by several excellent reviews (Ringvall *et al.*, 2008; O'Mahony *et al.*, 2011; Simon *et al.*, 2011; Ferstl *et al.*, 2012; Gibbs and Levi-Schaffer, 2012). Among the different cell types involved in immune responses, the mast cell can be a particularly interesting model to study amine metabolism crosstalk as mast cells are able to synthesize polyamines, histamine and serotonin. Results from different research groups (including ours) suggest that regulatory mechanisms have evolved to avoid the simultaneous synthesis of these amines. For instance, during differentiation of cultured mouse bone marrow-derived mast cells (BMMC), the maximum of polyamine content preceded the maximum of histamine synthesis, while the peak of serotonin was attained after the maximum of histamine production (García-Faroldi *et al.*, 2009, 2010). *In vivo*, mature mast cells are specialized in storing mainly histamine or serotonin depending on their differentiation program and environment. As will be explained below, an interaction between polyamine synthesis and serotonin secretion has also been observed in serotonin-producing mast cells (Kanerva *et al.*, 2009).

The active enzyme responsible for histamine synthesis, HDC, (EC 4.1.1.22), is a 110 kDa homodimer. The monomers are translated as 74 kDa polypeptide precursors that need to be processed by proteolytic removal of their carboxy-terminal fragments to give rise to the fully active enzyme (Fleming *et al.*, 2004). This C-terminal portion of the full-length polypeptide contains the signal to drive the HDC monomers to the endoplasmic reticulum before their maturation (Suzuki *et al.*, 1998; Fleming *et al.*, 2004; Furuta *et al.*, 2006). These facts indicate that preventing cytosolic HDC activity is important for mammalian histamine-producing cell homeostasis or function. On the contrary, the other two decarboxylases producing amines in mast cells, ODC and dopamine decarboxylase (DDC), are located in the cytosol. The primary sequence of human DDC is highly homologous to the human HDC active monomer sequence. However, human ODC seems to have another evolutionary origin (Sandmeier *et al.*, 1994). Their separate syntheses do not preclude the final spatial convergence of the products during mast cell differentiation. In fact, as mentioned earlier, BMMCs are able to produce histamine, serotonin and polyamines during *in vitro* differentiation, the latter also being important for granule homeostasis (García-Faroldi *et al.*, 2010).

ODC activity is a major determinant for polyamine biosynthesis. Its activity, as well as the uptake of exogenous polyamines, is regulated by inhibitory ODC-binding proteins named antizymes. Two polypeptides homologous to ODC (antizyme inhibitors I and II) have been detected in different human cell types. They bind antizymes with higher affinity than the ODC monomer, so acting as indirect ODC activators (Kahana, 2009). Expression of the antizyme inhibitor II has been detected in mast cells and is related to exocytosis of serotonin-containing mast cell granules (Kanerva *et al.*, 2009; López-Contreras *et al.*, 2010). These findings indicate a key role for polyamines in the structure and dynamics of mast cell granules, a key process for many immune responses.

It is also tempting to think that spatial and temporal compartmentalization of amine synthesis is a mechanism evolved to avoid an excess of SAM consumption and/or aldehydes and ROS derived from concomitant amine metabolism. Polyamine deficit has been described as deleterious for both mast cell homeostasis and correct development of the immune system in general (Jolois *et al.*, 2002; García-Faroldi *et al.*, 2010). However, both polyamine uptake and synthesis are inhibited by histamine or their analogues (Fajardo *et al.*, 2001; Paz *et al.*, 2001). These crosstalk mechanisms lead us to suggest that amine metabolic pathways have important roles as part of a coordinated programme between immune cell proliferation and immune cell differentiation. Thus, pharmacological intervention in one of these pathways or processes could affect the others.

Amines as double agents during anti-parasitic wars

The relationships among host and parasites are also an interesting scenario when studying the pathophysiological effects of amines (Figure 1). Typical immune histamine-producing cells, mast cells and basophils, evolved as part of the adaptive immune system with the physiological mission, among others, to protect animals against parasitic infections. Histamine is one of the key mediators secreted by these cells that participate in the defence response against parasites (Karasuyama *et al.*, 2011; Specht *et al.*, 2011; Ferstl *et al.*, 2012). Nevertheless, it could depend on a delicate equilibrium, as a dysregulated balance of the inflammatory response (including histamine release) has recently been proposed as a major factor for malaria pathogenesis and parasite (*Plasmodium falciparum*) transmission (Mecheri, 2012).

Parasite proliferation, as almost any other living cell/organism, needs higher polyamines (spermidine/spermine). Some parasitic protozoa, such as *Trypanosoma cruzi*, are unable to synthesize putrescine by themselves, so they are strictly dependent on the polyamine supply from the host. Even when they can produce polyamines to some extent, as in *T. brucei* and *Leishmania*, their requirements are higher than the endogenous synthetic capacity as they expend important quantities of spermidine in the production of trypanothione [bis(glutathionyl)spermidine], a natural redox buffer that confers an advantage to the parasite (Krauth-Siegel and Comini, 2008). The absolute dependence of the parasite progression on polyamines, together with the structural and

regulatory differences found among the key enzymes and transporters of host and parasite polyamine metabolism, encourage the development of anti-parasite strategies based on these features (Birkholtz *et al.*, 2011). In fact, the first ODC inhibitor, difluoromethyl ornithine (DFMO), is effective as a anti-parasitic treatment, together with other polyamine analogues and this strategy has shown promise against several parasite infections, especially in combined therapies (Müller *et al.*, 2008). Another potential lead is that *P. falciparum* growth *in vitro* was inhibited by the putrescine analogue, 1-amino-oxy-3-aminopropane (Das Gupta *et al.*, 2005), and with inhibitors of spermidine synthesis (Blavid *et al.*, 2010). However, *P. berghei* seems to be more resistant than *P. falciparum* to intervention with polyamine synthesis analogues or inhibitors (Wright *et al.*, 1991). It is also worth mentioning that some diamines (1,4- and 1–5-diamines) are able to reverse the cytostatic effects of DFMO on *P. falciparum* (Assaraf *et al.*, 1987).

Nature provides evidence to support the hypothesis that interference with biogenic amines during parasite infection could be beneficial. Polypeptides able to scavenge biogenic amines are used as generalized anti-inflammatory mechanisms by haematophagous arachnids (soft ticks), assassin bugs and mosquitoes. In the case of soft ticks, these polypeptides belong to the class of polypeptide named lipocalins, as monomine and monotonin, acting as scavengers of histamine and serotonin respectively. They confer advantage to the parasite by preventing the immune and haemostatic response of the host (Mans *et al.*, 2008). Structural and docking data of these polypeptides (and maybe other amine binding proteins) could provide the basis for the design of new biogenic amine scavengers with potential pharmacological applications.

Amines and combined therapies: the risk of 'pleiotropy'

Histamine can be considered the most 'pleiotropic' amine, affecting most of the important biological functions of humans: defence, nutrition, neurological activity, growth, development and fertility. In this sense, it can be considered an important link between different modules of human (mammalian) physiology. A recent review shows genetic and biochemical evidence supporting the involvement of histamine in more than 20 rare diseases (Pino-Ángeles *et al.*, 2012). For neurological and neuroinflammatory diseases in particular, clear evidence of interaction between histamine-related and dopamine and serotonin-related components was found.

The molecular bases of the histamine 'pleiotropy' are mainly explained by the existence of four types of histamine GPCRs that can, in turn, be promiscuous in their protein–protein interactions (Ferrada *et al.*, 2009). In addition, histamine can also bind to NMDA receptors (Watanabe *et al.*, 2008), as can many other biogenic amines, polyamines and analogues. The existence of histamine-linked chloride-like channels in the mammalian brain has also been proposed (Fleck *et al.*, 2012). These findings would suggest that histamine could interfere with the metabolic and signalling pathways of other amines and related compounds. It could therefore affect pharmacological interventions of many pathological processes. In a recent study of drug interactions in palliative care (Gaertner *et al.*, 2012), the authors identify drugs (inter-) acting via histamine receptors as among the best candidates for drug–drug interactions, which is a logical consequence of histamine 'pleiotropy'. Taking into account that patients with palliative care treatments usually suffer pain, weakness and other phenotypic features related to histamine, these drug–drug interactions deserve further pharmacological interest.

In general, the 'pleiotropy' of biogenic amines could contribute to many unexpected interactions, thus making pharmacovigilance advisable and even necessary. The multiple advertisements concerning the use of MAO inhibitors in combined therapies against neurological, neuroinflammatory and immune treatments are good examples of this (Montastruc *et al.*, 2000; Sommet *et al.*, 2007).

Amines and human reproduction

We would like to mention some recent observations that should be taken into account not only during pregnancy but also during preparation for fertility treatments. Spermine was discovered in seminal fluids more than a century ago, as it is essential for correct spermatogenesis. Seminal fluid is rich in both polyamines spermidine and spermine and the indirect activator of ODC, the antizyme inhibitor II, is preferentially expressed in testes.(López-Contreras *et al.*, 2010). Polyamines play roles in embryo implantation, in decidualization and in placental formation and function (Lefèvre *et al.*, 2011). Serotonin and other monoamines also play important roles in decidualization and embryo implantation and different biogenic amine transport activities have been observed in the endometrium (Hansson *et al.*, 2009). Monoamine transporters may serve as a protective mechanism preventing vasoconstriction in the placental vascular bed and thereby securing a stable blood flow to the foetus (Bottalico *et al.*, 2004). High levels of HDC expression in placenta has also been reported, suggesting that histamine contributes to embryo-uterine interactions due to its vasoactive, differentiation and/or growth-promoting properties (Brew *et al.*, 2007). However, its benefits on successful pregnancy seem to be dependent on a delicate equilibrium between histamine synthesis and degradation because reduced DAO activity correlated with abortion risk and trophoblastic disorders (Maintz *et al.*, 2008). DAO can also degrade putrescine (Figure 2). Results obtained with $HDC^{-/-}$ mice indicated that peripheral histamine was an important regulatory factor of male gonadal development during embryogenesis and of sex steroid metabolism later in adulthood (Pap *et al.*, 2002). These data imply that human reproduction needs biogenic amines at different stages of the process. Perhaps, as in other developmental processes (i.e. mast cell differentiation), the requirement for the different amines during reproduction is a part of a coordinated programme. More efforts should be made to clarify their roles during different stages of reproduction and human embryogenesis in order to control the process as they appear to be important for correct human reproduction and differentiation.

Concluding remarks and future prospects

It is clear that crosstalk among biogenic amines, including polyamines, plays an important role in neurology and the neuroendocrine system (data not discussed here). Nevertheless, in other physiological subsystems, interactions between components related to biogenic amines such as histamine, serotonin and arginine/ornithine-derived polyamines can also be involved in and even control, other processes essential for human health, homeostatic control, defence and reproduction.

The four main steps followed by any drug provided to an organism (for instance, a patient) are summarized in the ADME concept, that is, absorption, distribution, metabolism and excretion. Based on the previously mentioned 'pleiotropy' of biogenic amine actions and their metabolic crosstalk, we would predict that the metabolism of exogenous and endogenous biogenic amines (Figure 1) could interfere with any of these four key steps of drug ADME, thus reinforcing our previous claim of appropriate pharmacovigilance. Furthermore, we would also expect that drugs targeted against specific steps of the metabolism of one of the biogenic amines could also affect the metabolism and signalling of the others. This review provides several examples of such possibilities which have been recently revealed. The gaps in our knowledge are still considerable and further efforts to fill them are necessary, as this information may contribute to the development of new and more efficient strategies of prevention and therapy for many biomedical problems over the medium or long term, after the appropriate pre-clinical validation and clinical trial phases (Table 1).

Table 1

Physiological subsystems for amine interplay beyond neurotransmission, their major current basic knowledge gaps and their potential interest for pharmacology

Subsystem	Further basic research efforts are required on:	Potential interest for Pharmacology[a]
Amine uptake	• Integrative efforts for characterization of microbiota amine metabolism. • Integrative efforts for characterization of amine transport systems in the different gastrointestinal epithelia and their modulation by amines and drugs. • Integrative analysis of patient functional genomic data and microbiota properties.	• Gastrointestinal epithelia protection; probiotics and chemoprevention. • New possibilities for treatment of gastrointestinal inflammatory diseases. New combined therapy protocols.
Amine efflux	• Systematic characterization of amine–amine and amine–drug interferences during renal filtration on animal models (e.g. humanized mice).	• Improvement of pharmacovigilance actions.
Amines in liver	• Molecular dynamic studies of CYP-amine and CYP-drug preferential binding modes. • Metabolic interferences of amines with redox metabolism and gene methylation. Metabolomic and proteomic approaches, and systemic analyses. • Systemic evaluation of CYP 1-3 ligand co-occurrence (amines and drugs) in cell and/or humanized animal models.	• Prevention/Intervention of hepatic degeneration and homeostatic imbalance. • Improvement of drug pharmacokinetic and pharmacodynamic properties. • Improvement of pharmacovigilance actions.
Multiamine[b] producing cells and tissues	• Systemic studies using transgenic models. • Identification of the major amine crosstalk responsible elements in the different cell types/tissues assisted by *in silico* simulations. Experimental validation.	• Multiple potential applications in diagnosis, prevention and treatment of neurological, inflammatory and neuroinflammatory emergent and rare diseases, including neoplasms.
Amines in host-parasite interactions	• Detailed structural characterization of docking events among amine-related elements important for host–parasite interactions and compounds with anti-parasitic potential. Combination of *in silico* (i.e. molecular dynamics) and experimental approaches.	• Selective inhibition of parasite infection and/or proliferation. • Modulation of the immune response. • Chemoprevention.
Amines in reproduction	• Generation of genetically manipulated cell lines and animal models. • Integrative characterization on the expression pattern evolution of amine-related genes during the different fertilization and gestation phases.	• Improvement of pharmacovigilance actions during pregnancy. • Abortion prevention. • Increased success in assisted fertilization therapies

[a]This column mentions several possibilities for application of the knowledge obtained from basic results at medium and long term. Of course, as any other translational process in pharmacology, they would need to be submitted to the appropriate phases of pre-clinical validations and clinical trials before they could be approved for clinical use.
[b]Multiamine producing cell and tissue. This describes those cells and tissues able to synthesize biogenic amines and polyamines as part of their physiological mission, such as mast cells and other immune cells, enterochromaffin-like cells and salivary gland cells.

In cases where targets have been located and well characterized, *in silico* approaches (for instance, molecular modelling and virtual screening) could efficiently provide new pharmacological solutions, as has already occurred in some cases.

The wide spectrum of physiological scenarios for biogenic amine interactions and their pathological consequences is a reflection of the highly complex biochemical interaction networks among the components involved. In fact, biogenic amines participate in all types of biochemical networks: metabolic pathways, internal signal transduction mechanisms and intercellular communication. A current challenge for analysis of biological and biomedical networks is how to manage highly connected components of a given network. In the case of theoretical metabolic models, a risky but frequently useful option to simplify the analysis is to remove the most frequent components (Ma and Zeng, 2003). In the field of amine physiology and pharmacology, this solution makes no sense, as the pharmacological targets could be included in the group of the most interconnected components in some of the involved networks. Thus, further efforts are necessary to analyse these complex metabolic networks, as well as to develop better ADME-TOX evaluators.

In summary, amine pharmacology is a perfect candidate to benefit from the advances in network theory and systems biology technologies, in general, as the most efficient way to progress towards more personalized solutions for a wide range of pathological circumstances. Multidisciplinary groups or R&D networks working in a coordinated way are needed to fill gaps in basic, clinical and pharmacological information, as well as providing new bioinformatic solutions, making the analysis of the integrated amine information possible. Some ongoing initiatives should be potentiated as the field is clearly included in the current world-wide R&D priorities (in terms of both concept and technology).

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Conflict of interest

No conflict of interests has been stated.

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