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MINI-REVIEW

Cation-π Interaction as a Key Player in Healthcare: A Mini-Review

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Abstract

The cation-π interaction is a non-covalent interaction with significant role in healthcare such as biochemical systems or molecular neurobiology. The cation-π interaction is regarded as a strong non-covalent interaction in aqueous solutions essential for ligand–protein interfaces and delivery of chemical drugs. Limited knowledge is available regarding the manufacturing of synthetic functional materials (i.e. self-healing hydrogels) by availing the cation-π interaction. This mini-review aims to provide a brief summary on the importance of the cation-π interaction for protein stability and describes the impact on the secondary structure of proteins. Furthermore, it examines the cation-π interaction in medical applications and its impact in a receptor ligand that applies to neurobiology.

Keywords: cation-π interaction, alpha helices, beta hairpins, protein complexes, neurobiology, biomedicine

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1. Introduction

Carbonaceous compounds, such as biomolecules, frequently generate a soft liquid–solid interface in salt solution and dynamically influence the adjacent existing cations via hydrated cation-π interactions [1]. Researchers have developed techniques to use the non-covalent interactions i.e. hydrogen bonding, π–π stacking and hydrophobic interaction, to fabricate self-healing hydrogels [2–4].

The cation-π interaction is a non-covalent interaction with significant role in healthcare such as biochemical systems or molecular neurobiology [5–7]. Delicate folding of proteins is of vital importance for the survival of an organism. In the folding process, non-covalent intermolecular forces create the structure of biological macromolecules. Many non-covalent interactions have been extensively studied.

These include the salt bridges, hydrogen bonds and the hydrophobic effect [8]. A less considered non-covalent interaction is the cation-π binding. The cation-π binding is increasingly recognized as being of great importance for the structure and stability of the protein [9]. The cation-π binding interaction is an attractive interaction between an electron rich benzene ring and a cation. A benzene ring does not have a dipole moment because it is a symmetric molecule.

Nowadays, cation-π interactions have attracted the interest of researchers due to their wide existence in ligand–protein interfaces and delivery of chemical drugs [10]. In neurons, chemosignals satiety cues are denoted at the plasma membrane level and transmutation of neuronic activities are incurred within cystolic compartments[11]. A particular example is the presence of intracellular Ca^{2+} which aggrandizes and regulates neurotransmitter release [12].

There is, however, a higher electron density on top and below the benzene ring due to the electron rich π system. The partially negative top and bottom of the benzene ring is counteracted by a partially positive plane of the benzene ring. The non-covalent binding interaction of a positive cation to the electron dense aromatic ring, suggests that electrostatics play an important role in cation-π binding interactions [13]. An indication of this fact is the binding strength that alkali metals have with the benzene ring. A study showed that as the ion gets larger, the charge is dispersed over a larger sphere, leading to a weaker interaction [14]. These results confirm the importance of electrostatic interaction in the cation-π interactions [15, 16]. There are three amino acids that contain an aromatic ring. These are tryptophan, tyrosine and phenylalanine.

These three amino acids can interact via a cation-π interaction with cationic amino acid side chains (arginine and lysine) [9]. There seems to be a large bias towards tryptophan and arginine involved in cation-π binding. The protein database bank even shows that one in four tryptophan experiences an energetically significant cation-π interaction [9, 17].

In a previous study, researchers investigated the tendency of N-H groups in amino acids side chains to stick close to aromatic rings in other amino acids [18]. Their statistical analysis of the distance between nitrogen atoms in the side chains of asparagine, arginine, glutamine, histidine and lysine and the aromatic residue of phenylalanine, tryptophan and tyrosine showed that approximately 50% of aromatic residues were in close contact, less than 6 Å away. The researchers also found that more than 25% of the asparagine, glutamine, histidine and lysine were in van der Waals contact with the aromatic residues and that even 50% of the arginine were in van der Waals contact with the aromatic residues [19].

Cation-π interactions have been studied in biological systems such as acetylcholine receptors and K^+ channels (figure 1). Sequence and mutagenesis

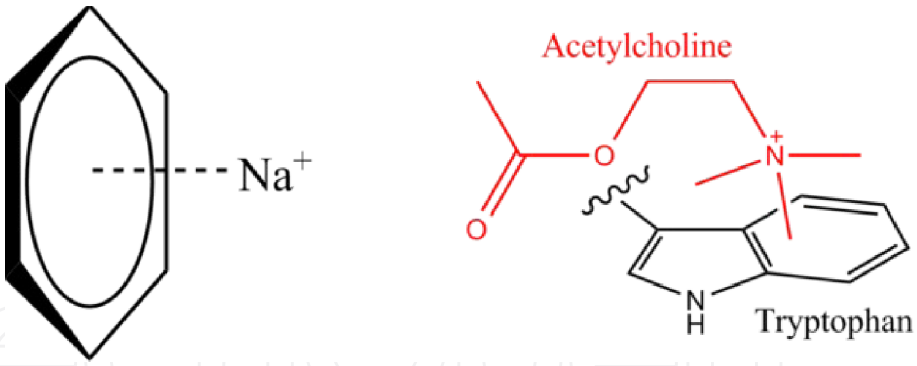

Figure 1. Cation-π interaction between benzene and a sodium cation (left) and cationic acetylcholine binding to a tryptophan residue of the nicotinamide acetylcholine receptor via a cation-π effect (right) [17].

analyses of muscarinic and nicotinic acetylcholine receptors have shown that conserved clusters of aromatic amino acids are involved in ligand binding [20]. X-ray crystallography has provided more direct evidence of cation-π interactions [21–23]. The cation-π interaction can be of great interest in neurosciences, as neurotransmitters contain cationic moieties [24]. The main goal of this mini-review will be to provide an overview of the importance of the cation-π interaction for protein stability. It also describes the impact on the secondary structure of proteins. Furthermore, it examines the cation-π interaction in protein complexes and its impact in a receptor ligand that applies to medical applications.

2. Secondary structure of proteins

The primary structure of proteins is simply the sequence of amino acids. The secondary structure refers to coiling processes in proteins like alpha helices and beta sheets. The coiling of a protein is determined by non-covalent interactions. One of these non-covalent interactions is the cation-π interaction. This interaction is recognized by chemists as one of the forces behind secondary protein structure and drug recognition [14].

Proteins in cells are in an aqueous environment. Few non-covalent interactions are resistant to an aqueous medium. A previous study showed that hydrogen bond formation is opposed in an aqueous environment by competing interactions with water [25]. The hydrophobic effect is an non-specific interaction and salt bridges are very strong in a non-polar medium, but they are far weaker in an aqueous medium.

It is estimated that a protein contains at least 1 cation-π interaction per 77 amino acids [9]. This means they are prevalent in proteins. Dougherty and Gallivan [9] compared the strength of the non-covalent binding of salt bridges and the cation-π

interaction in different solvents. For the cation-π interaction, they used benzene with methylammonium as a model.

The researchers used these molecules because they mimic the reaction between phenylalanine and lysine. For the salt bridge, they used acetate and methylammonium. The authors noticed that the interaction of acetate with methylammonium is stronger in solvent with a low dielectric constant.

But in water, which has a high dielectric constant, the cation-π interaction is stronger. Additionally, the researchers found that the strength of salt bridge interaction drops by a factor of 50, while the strength of the cation-π interaction only weakened by a factor of 3. These results show that the cation-π interaction may have a greater stabilizing effect on the secondary structure of proteins than the salt bridge.

Another interesting point requiring examination is on the position of the cation-π interaction within the protein. Due to their hydrophobic nature, the aromatic amino acids, namely phenylalanine, tyrosine and tryptophan, tend to be tarried inside the protein. Therefore, these amino acids are rarely exposed to water [9]. The cationic amino acids tend to be exposed to water due to their hydrophilic nature. However, studies have shown that amino acids that interact with each other via cation-π interactions do not resemble the average of the cationic and the aromatic amino acids in exposure to water.

Theoretically, the cation-π interaction should have a significant impact on the structure of a protein. Compared to the salt bridge, it is a stronger interaction in an aqueous environment. The diligent obstinacy of the neurotransmitter dopamine's modulation in aqueous solution is imperative to apprehend the neurobiological functions [26].

There is, however, limited experimental data that confirms the previous statement. The effect of the cation-π interaction in proteins can be studied by mutating an amino acid which forms cation-π interactions to an amino acid that is not able to form cation-π interactions. A former study examined the mutation of lysine to glutamine [25]. The stability of a protein can be determined by chemical and thermal denaturation. The study concludes that the influence of cation-π interactions is smaller than the calculated theorized impact [27].

The average difference in free energy between the calculated and the experimentally confirmed data is 2.9 kcal/mol per cation-π interaction [25]. At 298 K, the average stability that was provided by the cation-π interaction equalled to 0.4 kcal/mol. At the temperature (Tm), which is the point where half of the proteins are in denatured state, the average stability that was provided by the cation-π interaction was 1.1 kcal/mol. In some cases, the cation-π interaction even seems to

have a destabilizing effect. However, at higher temperatures, the stabilizing effect of the cation-π interaction is greater.

3. Cation-π interaction in alpha helices

A very important and well-known motif in proteins is the alpha helix. In the alpha helix, the N-H group of 1 amino acid makes a bond via a hydrogen with the C=O of another amino acid. The most important non-covalent interaction in the alpha helix is the hydrogen bond, as this interaction forms the backbone of the structure. The cation-π interaction, however, is also regarded as a key element in this secondary structure motif. It has been discovered that the Phe–Lys, Lys–Phe, Phe–Arg, Arg–Phe and Tyr–Lys are all stabilizing by −0.10 to −0.18 kcal/mol [28].

The crystal structure analysis revealed that the primary contributor to this increased stability is the establishment of hydrophobic interactions between the CH_2 groups of Arg and Lys and the aromatic rings. No evidence of further stabilization by the cation-π interaction has been found (figure 2).

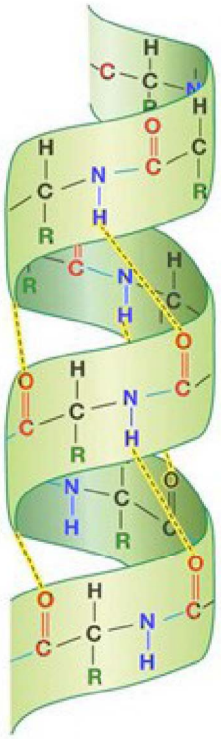

Figure 2. An alpha helix [29].

4. Cation-π interaction in beta hairpins

A beta hairpin is a protein structural motif consisting of two beta strands in the shape of a hairpin. The two strands of the motif are oriented in an anti-parallel

direction and are linked by a short loop of five amino acids. The structure of the beta hairpins is stabilized by hydrogen bonds between the two beta strands. The hydrogen bond is not the only interaction that plays a role in the stability of the beta hairpin [30]. The stability of the structure is also determined by cross-strand interactions and beta-sheet propensity interactions. The cation-π interaction is also hypothesized to have an impact on the stability of these structures which is experimentally determined to be 0.20–0.48 kcal/mol. This is similar compared to the strength that is provided by the beta-sheet propensity interactions and the cross-strand interactions [31]. But this is a lot less than the value that was calculated [32].

The calculated effect of the cation-π interaction on the stability of a protein seems to be far greater than the experimentally found effect. An important point to make is that at a higher temperature the effect of the cation-π interaction increases. In thermophiles living at high temperatures, the cation-π interaction can play a bigger role. In thermophiles, the percentage of Arg side chains close to aromatic side chains that are involved in cation-π interactions on the surface of proteins is greater than in non-thermophiles [33]. This increased frequency suggests that, in thermophiles, the cation-π interaction has a significant stabilizing effect in proteins at higher temperatures [34].

5. *Cation-π interaction in protein complexes*

Protein-DNA binding is important for post-translational modifications like the methylation and acetylation of DNA. To allow these processes to happen, proteins must approach the DNA strands. The cation-π interaction allows molecules to come close to the DNA strands, by making proteins able to form the non-covalent interaction with DNA. This vital process in the cell is supported by the cation-π interaction.

An important RNA and DNA binding protein that is essential for DNA and RNA binding is the fused in sarcoma (FUS) protein[35]. This protein regulates different steps in gene expression including transcription, mRNA splicing, and transport [36]. The ability of the FUS protein to rapidly change its state is needed for the creation of ribonucleoprotein granules [37]. Ribonucleoprotein granules take up, sequester, transport and then release key RNA and protein cargos that regulate local RNA and protein metabolism in subcellular niches, such as axon terminals and dendrites [38, 39]. When these processes are inhibited, due to pathogenically induced mutations, i.e. mutations leading to diseases, cation-π interactions are needed to rapidly induce the FUS phase separation. FUS proteins contain many arginine residues and tyrosine residues where these amino acids can form cation-π interaction. This allows the protein to rapidly undergo the phase separation. Researchers stated that phase separation occurs with the help of intermolecular beta-sheet-rich fibrils [36]. They performed experiments that supported and extended this view. They also found that

FUS separation is regulated by an additional factor: the cation-π interaction. These interactions occur between the tyrosine residues in the low-complexity (LC) domain and the arginine residues in the C-terminal domain (CTD).

The researchers have also shown that the phase separation is maintained when the amino acids are replaced with an amino acid that preserves the cation-π interaction [36]. This experiment is done by converting arginine to lysine and tyrosine to phenylalanine. The outcome of the experiment showed the role the cation-π interaction plays in the phase separation of the FUS protein. Methylation status of the arginine also influences the FUS phase separation. The methylation of arginine weakens the cation-π interaction. The weakened cation-π interaction leads to a slower gel separation transition phase. When the gel separation is slower, it takes longer for the protein to reach the fibrillary state. In the fibrillary state, the tyrosine residues in the LC domain all form hydrogen bonds between each other. This is a very stable state and once this state is reached, the proteins cannot revert to the previous states. Researchers showed that the fibrillary state causes the ribonucleoprotein (RNP) to have an impaired function, and thus this state shouldn't be reached. With the hypomethylation and hypermethylation of the arginine residues, the FUS separation state can be regulated.

When adding more methylated arginine residues, thus weakening the cation-π interaction, the droplet state of the FUS protein will be made more unstable. The authors found that addition of a small amount of unmethylated arginine (less than 5%) to demethylated arginine FUS resulted in rapid phase separation and gelation. The results of this example show that the cation-π interaction plays an essential role in the gelation of the FUS proteins. The strength of cation-π interaction is regulated by arginine methylation, with more methylation resulting in a weaker cation-π interaction and less methylation causing a stronger cation-π interaction. On the one hand the cation-π interaction is necessary for the FUS phase separation to occur. While on the other hand a cation-π interaction that is too strong leads to the impairment of the RNP complex. The cation-π interaction is thus very important for the regulation of the FUS phase separation state.

6. Medical uses for the cation-π interaction

Neural activity involves coordination of many processes, and cation-π interaction is vital to inaugurate drug-target interaction which can influence the diverse functions of neuronal pathways [40]. Ligands such as drugs and neurotransmitters that are affixed to the receptor may induce its activation and influence specific biochemical cellular functions, including ion conductance, protein phosphorylation, and enzymatic activity [41].

G-protein coupled receptors (GPCRs) are the largest group of transmembrane receptor proteins. The GPCRs detect molecules outside the cell and activate internal

signal transduction which leads to a cellular response. GPCRs represent the largest class of transmembrane receptor proteins and are a prominent class of targets for the pharmaceutical industry at about a third of all modern medical drugs [42].

An example of a GPCR is the D2 dopamine receptor. The D2 dopamine receptor is the site of action for most antipsychotic drugs [43]. In mice, it has an impact in the retrieval of fear memories in the prelimbic cortex [44]. The binding region in the D2 dopamine receptor is rich in aromatic amino acids and dopamine has an ammonium group. It was observed that D2 receptor forms a cation-π interaction between the agonist dopamine and the tryptophan in helix 6 on position 48 (W6.48) [45]. To examine the magnitude of the effect of the cation-π interaction, the interaction should be progressively weakened. This can be achieved by using fluorine to replace hydrogen in the benzene ring of the tryptophan and phenylalanine residues in the reactive site of the receptor. The affinity of the drug for the receptor should then steadily decrease as more hydrogen is substituted for fluorine in the benzene ring. The difficult part in an experiment like this is that the reactive site contains several aromatic amino acids that could undergo a cation-π interaction with a drug. In the case of the D2 dopamine receptor, there are 5 amino acids that can take part in a cation-π interaction. These amino acids should be fluorinated to check the effect of the change on the binding affinity with the drug. EC50 quantification is used to determine the effect of a drug on a specific receptor. EC50 is the concentration of the drug that induces a response half as strong as the maximal response on the drug. When the aromatic amino acids are fluorinated, the cation-π interaction between the drug and the receptor is weakened. This should lead to a higher EC50. The difference in EC50 between receptor with natural amino acids and unnatural amino acids will be taken as an indication of the strength of the cation-π interaction.

The progressive fluorination of W6.48 provided a linear relation between the degree of fluorination and the EC50 of dopamine and showed that increased fluorination of W6.48 weakens the binding between the receptor and dopamine. This proves that the cation-π interaction is responsible for the change in binding affinity between the receptor and dopamine. These results indicate that the cation-π interaction plays a key role in receptor binding function. Research knowledge has stated that the cation-π interaction plays an intrinsic role in neurotransmitters for drug–receptor binding with a cardinal example of the binding of nicotine to ACh receptors in the brain [14].

Researchers found that of the cation-π interacting residues, arginine and lysine were mostly found in the exposed regions, whereas the aromatic residues - phenylalanine, tyrosine and tryptophan appeared to be in the buried and partially buried regions in the protein structures [46]. These results can play a significant role for further investigation of the RNA binding proteins attributes such as specificity and selectivity. Researchers performed computational binding models of the

endogenous neurotransmitter ACh and the smoking cessation drug cytisine. They examined the impact of selective cytosine derivatives on the ligand structure, concluding that certain nicotinic acetylcholine receptor (nAChR) targeted ligands can be availed to improve the design of advanced therapies [47].

The effect of cation-π interaction on 54 N-methyl-d-aspartate (NMDA) receptor inhibitory potencies of inhaled drugs has been examined in a previous research study [48]. They concluded that the engagement of cation-π interaction enhances the binding of inhaled drugs to the NMDA receptor. A vibrational experimental research has been elaborated on dopamine [4-(2-aminoethyl) benzene-1,2-diol to investigate the hydrogen bonding [49]. The authors stated that the charge transfer within molecule provokes the pharmacological activity of the dopamine molecule.

Inward currents elicited by adenophostin analogues have been recorded on the accessory olfactory system which is regarded as a primary detector for odor information. Adenophostin analogues initiate currents in turtle olfactory sensory neurons and can be agonists [50]. A former study examined the cation-π interaction between adenophostin and Arg504 of 56Ins(1,4,5)P3R receptor, and the authors stated that the high potency of adenophostin A is due to H-bonding in combination with the cation-π interaction between the base moiety and Arg504 [51].

Limited knowledge exists on the impact of cation-π interaction in the sorption of fluoroquinolone antibiotics by pyrogenic carbonaceous materials. A former study examined the contribution of the cation-π interaction in the sorption of ciprofloxacin on graphite. The authors concluded that decreased amount of sorbed carbonaceous material by treatment with benzylamine represents the contribution of cation-π interactions [52]. A former study examined the harnessing of the cation-π interactions in manufacturing of self-healing hydrogels. The authors fabricated injectable synthetic hydrogel using a thermoresponsive ABA triblock copolymer. Due to the thermal gelation of cationic and aromatic components, robust cation-π interactions upon hydrogel damage were seen. Further research is required to provide infallible knowledge on cation-π interaction engagement on this type of biomedical application [53].

7. Future prospects

The cation-π interaction has proven to be a very interesting interaction that has an essential function in several molecular processes. The binding strength of the cation-π interaction proved to be smaller than the expected strength, thus its effect on protein structure is less. This doesn't mean, however, that the added stability provided by the cation-π interaction should be entirely forgotten. Proteins in cells have to be very flexible for efficient folding. The binding strength of non-covalent interactions is lower than that of the covalent interactions, allowing more flexibility.

Therefore, non-covalent interactions dominate the binding of proteins to each other, DNA and RNA.

The cation-π interaction is very important in a protein complex for the regulation of the FUS phase separation [36]. This is essential for the creation of ribonucleoprotein granules used for the transport of RNA and protein cargos. RNA is important for the production of proteins in the body. The translation of RNA is one of the most important jobs in all biology. All life on earth is based on the transcription of DNA to RNA and the translation of RNA to proteins. The fact that the cation-π interaction plays a significant role in this process makes it a noteworthy interaction.

In medicine, the cation-π interaction is connected to drug binding receptors in the body. The cation-π interaction can enhance the binding of drugs to the receptor [14]. The cation-π interaction is shown to have a big impact in the binding of dopamine to the D2 dopaminergic receptor.

To get a proper overview of all the molecular mechanisms in the body, it is very important to start at the smallest scale. The folding of proteins is still one of the mysteries of cellular biology. It is an unbelievable feature of the human body that its proteins are able to fold at a speed as high as N/100 μs for a generic N-residue single domain protein [53]. This process is a combination of all kinds of non-covalent molecular interactions. Compared to the salt bridges, hydrogen bonds and hydrophobic effect, the cation-π interaction is not as well known. However, to get a more complete picture of all the processes in the cells of organisms, it is essential to incorporate all interactions present. Further research will facilitate an improved molecular design of drugs with advanced pharmacological properties [54].

8. Conclusion

This mini-review aimed to provide aspects of the cation-π interaction and its potential in healthcare. Correct protein folding is important for the efficient ligand recognition of their functions. Researchers strive to investigate the cation-π interaction and expand its implementation in biological and medical applications. These interactions are of significant importance in neurobiology as they can activate neuronal signals and thus improve the drug-receptor binding. Limited knowledge of cation-π interaction is provided in biological systems. This interaction allows molecules to approach the DNA strands, by crafting proteins adept to establish non-covalent interaction with the DNA.

Conflict of interest

The authors declare no conflict of interest.

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