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QUANTUM ANALYSIS OF THE CYCLIC ADENOSINE MONOPHOSPHATE (AMPc) AND GUANOSINE MONOPHOSPHATE CYCLIC (GMPc) IN NEUROTRANSMITTERS

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ABSTRACT

Escherichia coli is a gram-negative bacteria in the form of bacilli that is part of the intestinal flora of birds and mammals. This bacterium has several mechanisms to adapt to its environment, among which is the generation of thermolabile enterotoxin that can cause high levels of GMPc y AMPc. Recent studies have found that the presence of this bacterium can be related to various neurological pathologies, since it is known that there is a bidirectional neurohumoral communication system, known as the gut-brain axis. The objective of the study is to determine, by means of the parametric semi-empirical parametric method (SE-PM3 / 1), which neurotransmitters have a greater affinity with the GMPc y AMPc, in order to understand the neuronal oxidative effect. The Hyperchem Professional software performed the Molecular Modeling and Analysis of the molecules of GMPc/AMPc and 9 of the main neurotransmitters. (Hyperchem, Hypercube, Multi On for Windows, Series 12-800-1501800080. Multi On, South 1236-301 Tlacoquemecatl Insurgentes Col. Del Valle, Benito Juarez, Mexico, CP 03200). The result of the simulations

of quantum wells reveals that these nucleotides have the ability to oxidize Adrenaline, which suggests that it may be linked to the neurological disorders of various diseases.

KEYWORDS: Neurotransmisores, Neurodegeneración, Escherichia-coli, AMPc, GMPc, Quantum Method, Hyperchem, SE-PM3.

INTRODUCCIÓN

Neurological diseases are pathologies that affect the integrity of our central and peripheral nervous system. That is, they will cause different damages and injuries to the brain, the spinal cord, the set of cranial and peripheral nerves, the nerve roots of the autonomic nervous system and the neuromuscular junctions.[1]

In recent years the investigation of these diseases has taken a different direction, because a bi-directional neurohumoral communication system has been found, known as the intestine-brain axis, which integrates the host's intestine and brain activities.[2, 3] This idea is supported because some bacteria have the ability to cross the blood-brain barrier when there is a high degree of bacteremia and invasion of cerebral microvascular endothelial cells.[4]

Several studies have shown that the intestinal microbiota regulates neuroinflammation and the toxic accumulation of proteins in patients with neurological pathologies.[5,6] On the other hand, research affirms that there is an increase in the Enterobacteriaceae family, including pathogens such as Echerichia-coli in people with neurological disorders.[7,8]

A recent investigation found the presence of Lipopolysaccharide (LPS) and Escherichia coli in brain samples of gray and white matter of Alzheimer's patients, demonstrating that this bacteria are associated with the etiopathogenesis of this disease.[9] The relative abundance of this bacterium was positively associated with the severity of the postural instability and the difficulty of walking correlating with Parkinson's disease.[10] Finally, it has been reported that there is a direct relationship between schizophrenia and intestinal microbiota.[11]

The objective of this study is to determine, using the semi-empirical quantum parametric method (SE-PM3/1), that the neurotransmitter has a high affinity with the molecules of Adenosín Monofosfato Cíclico (AMPc) and Guanosín Monofosfato Cíclico (). The GMPc and AMPc are nucleotides that function as second messengers in several biological processes. It is known that the presence of the bacterium Escherichia-coli increases the levels of GMPc and AMPc due to the pathogenic nature and the activity of the thermolabile enterotoxin.[12,13]

Some research suggests that a massive activation of GMPc and AMPc is related to the growth of some types of cancer.[14,15,16], but in our study we want to find out which neurotransmitter is affected by the presence of GMPc and AMPc at the neuronal level. In this study we will analyze 9 neurotransmitters which are: Adrenaline, Serotonin, Dopamine, GABA, Glutamic Acid, Histamine, Glycine, Noradrenaline and Acetylcholine. In Figure 1 the diagram of the molecules to be simulated is shown.

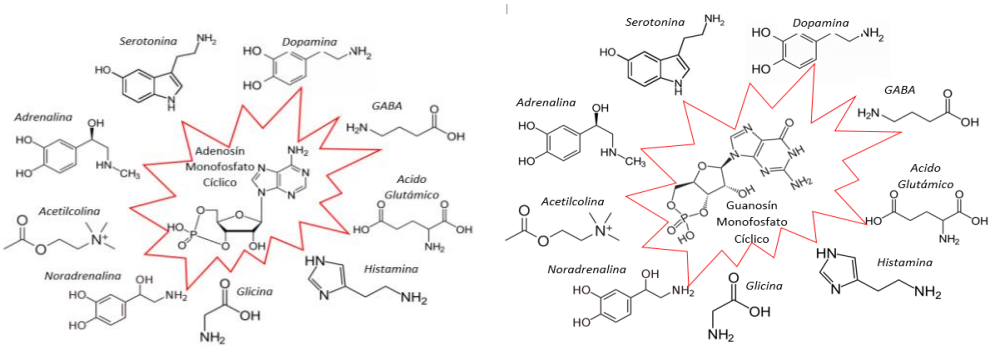


Figure 1: Interaction diagram of GMPc / AMPc and neurotransmitter molecules.

Hyperchem is a molecular modeling program with graphical interface, which allows researchers to carry out chemical simulations that facilitate multiple data entry. Through the program, it is possible to analyze the Electron Transfer Coefficient (ETC) of each interaction.

The theory of ETC is based on defining the bandgap or bandgap (BG), which is the difference in energy between the valence band and the driving band. In quantum theory, it is known as HOMO and LUMO, and in the old theory they are known as E- and E +. On the other hand, the quantum well is defined as the area in which the value of the ETC may fall. These zones are divided into 3 (Figure 2): 1. The high probability area (ZONE I), 2. The average probability area (ZONE II). 3. The area of low probability (ZONE III).[17,18]

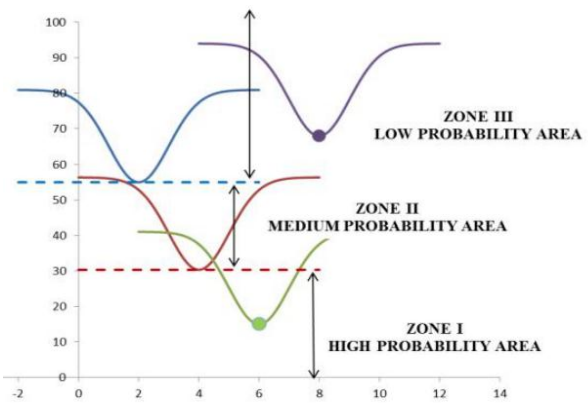


Figure 2: Probability zones in the quantum well, according to the theory of ETC's.

MATERIAL AND METHOD

The simulation of cAMP and cGMP molecules was carried out using the Hyperchem Software (Hypercube, Multi On for Windows, series 12-800-1501800080. Multi On, south 1236-301 Col. Insurgentes Tlacoquemecatl del Valle, Benito Juarez, City from Mexico, Mexico CP 03200). The simulation was carried out by means of the Semi-empirical method to perform the BG calculation, the Electrostatic Potential (EP) and the ETC. When the complete molecule is drawn, the values of HOMO (-), LUMO (+), E- and E + are obtained, in value at zero and with a density of 0.015. The values that are recorded will be captured on an Excel sheet, and he will perform operations to obtain BG, EP, ETC. To obtain the cross band of the compounds, it is done taking the HOMO and E- value of the first compound and the value of LUMO and E + the second compound. The lower ETC of the transverse band will be the value that will determine which compound will be most reactive and will serve as data that will be placed in the quantum well charts. To set the limits of the graphs, the highest ETC will be placed in the upper limit and the lower ETC as the lower limit of the compounds to be compared.[18,19]

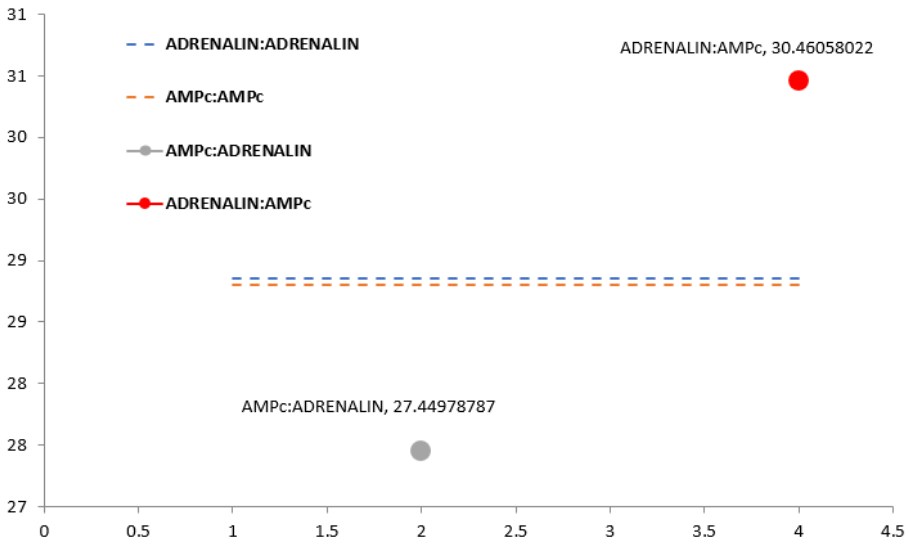
RESULTS AND DISCUSSION

Table 1 shows the interaction of AMPc against the main neurotransmitters with their respective ETC's, emphasizing that Adrenaline presents a lower energy for the jump of electrons.

Table 1: AMPc vs Neurotransmitters

Antioxidant	Oxidant	HOMO	LUMO	BG	E-	E+	EP	ETC
AMPc	ACETYLCHOLINE	-8.911768	1.034277	9.946045	-0.13	0.105	0.235	42.3235957
AMPc	NORADRENALINE	-8.911768	-0.00427538	8.90749262	-0.13	-0.222	0.092	96.820572
AMPc	GLUTAMIC ACID	-8.911768	0.5059321	9.4177001	-0.13	0.161	0.291	32.3632306
AMPc	GLYCINE	-8.911768	0.8744405	9.7862085	-0.13	0.188	0.318	30.7742406
AMPc	HISTAMINE	-8.911768	0.675378	9.587146	-0.13	0.163	0.293	32.7206348
AMPc	GABA	-8.911768	0.9385893	9.8503573	-0.13	0.18	0.31	31.7753461
AMPc	DOPAMINE	-8.911768	0.1988791	9.1106471	-0.13	0.189	0.319	28.5600223
AMPc	SEROTONIN	-8.911768	-0.1294475	8.7823205	-0.13	0.141	0.271	32.4070867
AMPc	**ADRENALIN**	-8.911768	0.09176242	9.00353042	-0.13	0.198	0.328	**27.4497879**

The interaction of Adrenaline and AMPc in quantum wells is shown below (Graph 1), where it is shown that there is a high probability of oxidation of this neurotransmitter.



Graph 1: Quantum well of AMPc vs Adrenalina.

Another interaction that can be carried out is the cross bands of neurotransmitters with AMPc. That is, the crossed bands simulate the interaction between the same neurotransmitters against the simulated substance, which allows to analyze the molecular combination with greater probability of oxidation or reduction. In Table 2 you can see the results of the crossed bands.

Table 2: AMPc vs Neurotransmitter Cross Bands.

Reductor	Oxidante	HOMO	LUMO	BG	E-	E+	EP	ETC
AMPc	ADRENALIN--ADRENALIN	-8.911768	0.09176242	9.00353042	-0.13	0.198	0.328	27.4497879
AMPc	SEROTONIN--ADRENALIN	-8.911768	0.09176242	9.00353042	-0.13	0.198	0.328	27.4497879
AMPc	DOPAMINE--ADRENALIN	-8.911768	0.09176242	9.00353042	-0.13	0.198	0.328	27.4497879
AMPc	GABA--ADRENALIN	-8.911768	0.09176242	9.00353042	-0.13	0.198	0.328	27.4497879
AMPc	GLUTAMIC ACID--ADRENALIN	-8.911768	0.09176242	9.00353042	-0.13	0.198	0.328	27.4497879
AMPc	GLYCINE--ADRENALIN	-8.911768	0.09176242	9.00353042	-0.13	0.198	0.328	27.4497879
AMPc	HISTAMINE--ADRENALIN	-8.911768	0.09176242	9.00353042	-0.13	0.198	0.328	27.4497879
AMPc	NORADRENALINE--ADRENALIN	-8.911768	0.09176242	9.00353042	-0.13	0.198	0.328	27.4497879
AMPc	ACETYLCHOLINE--ADRENALIN	-8.911768	0.09176242	9.00353042	-0.13	0.198	0.328	27.4497879

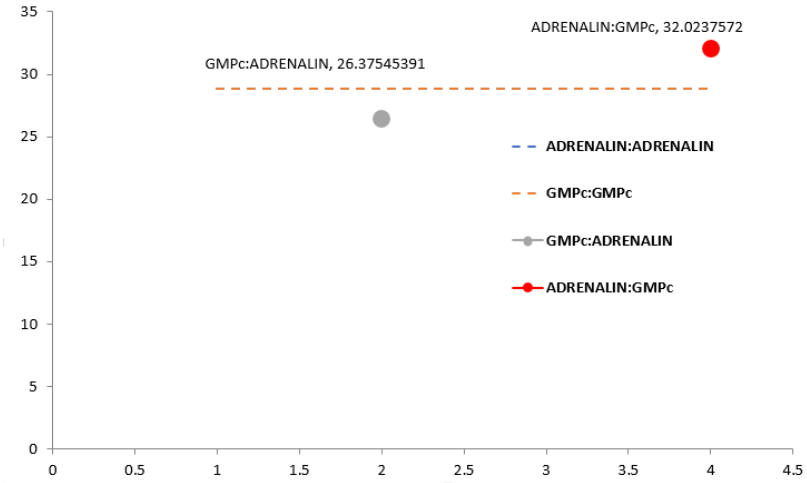
In the crossed bands (Table 2), it is observed that all the combinations with Adrenaline give an ETC of 27.4497879 which indicates that any combination that occurs with this neurotransmitter, will have the same possibility of being oxidized by AMPc.

In the same way, the interaction of GMPc against the main neurotransmitters was performed, finding that the lowest ETC is also Adrenaline, which indicates that this neurotransmitter has a high probability of being oxidized by GMPc. In Table 3, said interaction is appreciated.

Table 3: GMPc vs Neurotransmitters.

Antioxidant	Oxidant	HOMO	LUMO	BG	E-	E+	EP	ETC
GMPc	ACETYLCHOLINE	-8.823141	1.034277	9.857418	-0.14	0.105	0.245	40.2343592
GMPc	NORADRENALINE	-8.823141	-0.00427538	8.81886562	-0.14	-0.222	0.082	107.547142
GMPc	GLUTAMIC ACID	-8.823141	0.5059321	9.3290731	-0.14	0.161	0.301	30.9935983
GMPc	GLYCINE	-8.823141	0.8744405	9.6975815	-0.14	0.188	0.328	29.5657973
GMPc	HISTAMINE	-8.823141	0.675378	9.498519	-0.14	0.163	0.303	31.3482475
GMPc	GABA	-8.823141	0.9385893	9.7617303	-0.14	0.18	0.32	30.5054072
GMPc	DOPAMINE	-8.823141	0.1988791	9.0220201	-0.14	0.189	0.329	27.4225535
GMPc	SEROTONIN	-8.823141	-0.1294475	8.6936935	-0.14	0.141	0.281	30.938411
GMPc	**ADRENALIN**	-8.823141	0.09176242	8.91490342	-0.14	0.198	0.338	**26.3754539**

Graph 2 shows the interaction of Adrenaline and GMPc in quantum wells, where it is shown that there is a high probability of oxidation of said neurotransmitter.



Graph 2: Quantum well of AMPc vs Adrenaline.

Next, the crossed bands of the neurotransmitters with the GMPc will be shown in Table 4 to observe the molecular combinations that are more likely to be oxidized or reduced.

Table 4: GMPc vs Neurotransmitter Cross Bands.

Reductor	Oxidante	HOMO	LUMO	BG	E-	E+	EP	ETC
AMPc	ADRENALIN--ADRENALIN	-8.823141	0.09176242	8.91490342	-0.14	0.198	0.338	26.3754539
AMPc	SEROTONIN--ADRENALIN	-8.823141	0.09176242	8.91490342	-0.14	0.198	0.338	26.3754539
AMPc	DOPAMINE--ADRENALIN	-8.823141	0.09176242	8.91490342	-0.14	0.198	0.338	26.3754539
AMPc	GABA--ADRENALIN	-8.823141	0.09176242	8.91490342	-0.14	0.198	0.338	26.3754539
AMPc	GLUTAMIC ACID--ADRENALIN	-8.823141	0.09176242	8.91490342	-0.14	0.198	0.338	26.3754539
AMPc	GLYCINE--ADRENALIN	-8.823141	0.09176242	8.91490342	-0.14	0.198	0.338	26.3754539
AMPc	HISTAMINE--ADRENALIN	-8.823141	0.09176242	8.91490342	-0.14	0.198	0.338	26.3754539
AMPc	NORADRENALINE--ADRENALIN	-8.823141	0.09176242	8.91490342	-0.14	0.198	0.338	26.3754539
AMPc	ACETYLCHOLINE--ADRENALIN	-8.823141	0.09176242	8.91490342	-0.14	0.198	0.338	26.3754539

In the crossed bands (Table 4), it is observed that all the combinations with Adrenaline give an ETC of 26.3754539 which indicates that any combination that is present with this neurotransmitter, will have the same possibility of being oxidized by the GMPc.

CONCLUSIONS

In quantum well analysis and the interactions of the ETC's indicates that there is a high probability of oxidation of the neurotransmitter Adrenaline in the presence of cGMP and cAMP. This may suggest that the thermolabile enterotoxin secreted by the bacterium Escherichia-coli may be linked to the neurological disorders that plague our society. It should be noted that this type of quantum analysis is based on probabilistic systems.

There is strong experimental evidence that oxidative stress is a causal factor in the pathophysiology of several neurodegenerative disorders in adults, as well as cerebrovascular accidents, traumatisms and seizures.

The product of the oxidation of Adrenaline is also called Adenochrome.[20] Adenochrome is a substance that strongly stimulates the absorption of oxygen, causing a self-oxidation affecting other catecholamines. The oxygen consumed is converted into hydrogen peroxide, which can activate physiopathological mechanisms of diseases such as Parkinson's, schizophrenia and Alzheimer's.[21,22,23,24] On the other hand Adenochrome has been shown to be a neurotoxic with psychotomimetic properties.[25]

Studies of the mid-twentieth century have indicated that Adrenochrome is metabolized from one of two substances, dihydroxy-indole or adrenolutin. Dihydroxy-indole can balance anxiety and depressive effects of adrenaline, to reduce tension and irritability. However, the defective processing of Adrenochrome favors the generation of the toxic substance Adrenolutin, which is combined with Adrenochrome. The Adrenochrome-Adrenolutin combination, which was hypothesized by Dr. Abram Hoffer and Humphry Osmond, would result from the disruption of normal brain processes in the brain. This interruption, according to his hypothesis, would be responsible for the symptomatology of schizophrenia.[26]

In conclusion we can say that the oxidation of this neurotransmitter can be the origin of some pathology. The proper functioning of our neurotransmitters gives us a regular balance in all our Nervous System functions. Now, either by our genes or by the environment, the

production or erroneous synthesis of various neurotransmitters can lead to disorders or physical and psychological disorders.

The study of quantum wells between substances and chemical compounds created by the human body, gives us the possibility to study and analyze the interactions between them. In the particular case of the oxidation of Adrenaline by cGMP or cAMP (Figures 1-2), we can conclude that this alteration correlates with the side effects of said additive, giving rise to future investigations.

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