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QUANTIC ANALYSIS OF THE EFFECT OF NICOTINE ON NEUROTRANSMITTERS

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ABSTRACT

Nicotine (NIC) is known for its adverse effects on health. It affects directly to Central Nervous System (CNS). NIC modifies the concentration of neurotransmitter (NT) and their specific function. The main goal of this work is to determine by Semi-empirical Parametrical Method 3 (SE-PM3) quantic analysis, the interaction between NIC and the main NT and their possible effects on the human's CNS. Hyperchem is a molecular modeling computational program. Researchers use Hyperchem to analyze the Electron Transfer Coefficient (ETC) of the compounds and to identify the possible interaction between compounds. We found that NIC directly affects to NT. The effects of NIC on NT depend on of the functions of the human body. As a result, we found that the NIC interacts with all NTs, both as an oxidizing or reducing agent. The work team concluded that NIC has a direct effect on the interaction with the most common NT highlighting adrenalin, dopamine, aspartic acid, glycine, Gamma-aminobutyric acid (GABA) and serotonin. The information we got as part of this study is congruent with data reported in the literature.

KEYWORDS: Nicotine, Neurotransmitters, Quantic analysis, Hyperchem, SE-PM3.

INTRODUCTION

Smoking is a disease that increases every day. Several researchers consider smoking as a 21st-century disease. Smoking is one of the deadliest diseases and affects 1 in 6 people.

Deaths from smoking increase more, more and overcome deaths caused by wars, catastrophes, terrorism, Acquired Immune Deficiency Syndrome (AIDS) and other drugs.[1-3]

Cigar consumption is an addition that affects the CNS. One cigar contains about 4000 substances harmful to the body. NIC is one of the substances that are in the cigar in greater proportion. The need or compulsion of periodic use of the substance is one effect of the NIC. NIC consumption develops tolerance and withdrawal syndrome in the absence of NIC.[4-7]

NIC is an alkaloid found in the tobacco plant *Nicotiana tabacum*. Leaves have NIC at high concentrations and people consume it in tobacco. NIC is a highly addictive alkaloid, which acts as a stimulant and sedative of the CNS.[4, 9-12]

Researchers have shown that NIC is one of the most addictive substances. The immediate effects of NIC include the increment of blood pressure, heart rate, rapid breathing and stimulation of the CNS. Short-term withdrawal symptoms are anxiety, depression, headaches and fatigue. Prolonged tobacco use leads to dependence and addiction to NIC. NIC dependence affects the CNS-acting as a stimulant and as a sedative. NIC modifies the release of NT and their functions.[10, 13-14]

NT is a chemical released from a nerve ending. The transmission of a neuron depends on the action of specific NT on specific receptors.[15]

The process of neurotransmission can increase or decrease and generate physiological changes. Neurological and psychiatric disorders are a cause of the increment or decrement in NT activity.[15-16]

GABA is the major brain inhibitory neurotransmitter. The role of the GABA is to inhibit or reduce neuronal activity. GABA has an important role in behavior, cognition and body's response to stress. On the other hand, GABA is a neurotransmitter that triggers anxiety disorders, sleeps problems, depression and schizophrenia.[16]

Different medications increase GABA levels in the brain and are used to treat epilepsy, Huntington's disease or to relieve anxiety. Researchers have found that GABA can reduce the enjoyable effects of smoking regarding duration and intensity.[17-18]

Serotonin (5-HT) is an important regulatory chemical. It plays a major role in sexuality, depression and bipolar disorder. Some medications increase serotonin levels and cause chills, diarrhea, fever, muscle stiffness and seizures. Chronic exposure to NIC can increase serotonin levels, causing chemical dependence.[19, 14]

Acetylcholine is the primary neurotransmitter of the bulbospinal motor neurons, the preganglionic nerve fibers and other CNS neuronal groups. NIC can bind to the same receptors in the brain as the acetylcholine. NIC adheres to the receptors of brain's cells and affects muscle movement, change in heart rate, breathing and concentration. NIC also has a bursting energy effect.[18, 20]

Dopamine is the neurotransmitter most associated with brain pleasure ant the reward center. Some researchers have identified the NIC as a drug that acts on the brain in addictive ways. The literature shows that addictive substances impair the flow of dopamine. NIC is part of addictive drugs that bind to chemical bonds of molecular receptors and increase brain concentration of dopamine.[21]

Noradrenaline is the NT of most postganglionic sympathetic fibers and central neurons. Noradrenaline interacts with adrenergic receptors. NIC act on Noradrenaline in a withdrawal syndrome. Noradrenaline together with NIC influences cognitive functions and generate stress symptoms due to NIC pullout.[20-22]

Glycine has some operates as a neurotransmitter in the CNS. Glycine activates receptors with inhibitory effect. Activation of N-Methyl-D-aspartate (NMDA) glutamate is of excitatory effect. Researchers describe that it has cytoprotective, anti-inflammatory and immunomodulatory effects that are affected by the interaction of NIC.[19-22]

Hyperchem is a molecular modeling program. Hyper chem's graphical interface allows researchers to make chemical simulations that facilitate the entry of multiple data. Through the program, researchers analyze the ETC of each interaction. The ETC is the parameter that identifies the probability of a union between compounds.[23-27]

The main goal of this work is to determine by SE-M3 quantic analysis the interaction between NIC and the main NT and their possible effects on the human's CNS.

MATERIALS AND METHODS

Software and Simulation

It used Hyper Chem molecular simulator for Windows Serial # 12-800-1501800080 SE-PM3 to extracting the molecules.

General Setting

SE-PM3 a total load of around 0. Multiplicity1. Pairing turns the RHF. State under the Convergent limit of 0.01. 50. Limit iteration accelerates convergence Yes. Polarizability. Geometry Optimization: Algorithms Polak-Ribiere (conjugate gradient). RMS termination condition gradient 0.1 kcal / Amol. Algorithm Polak-Ribiere (conjugate gradient), the termination condition or 1000 cycles Maximum. Algorithm Polak-Ribiere (conjugate gradient).

Particular Setting

Table 1. Parameters used for quantum computing molecular orbitals - HOMO and LUMO

Parameter	Value	Parameter	Value
Total Charge	0	Polarizability	Not
Spin Multiplicity	1	Geometry Optimization algorithm	Polak-Ribiere (Conjugated Gradient)
Spin Pairing	RHF	Termination condition RMS gradient of	0.1kcal/Amol
State Lowest Convergent Limit	0.01	Termination condition or	195 maximum cycles
Interation Limit	50	Termination condition or	In vacuo
Accelerate Convergence	Yes	Screen refresh period	1 cycles

Table 2. Parameters used to visualize the map of the electrostatic potential of the molecules.

Parameter	Value	Parameter	Value
Molecular Property	Property Electrostatic Potential	Contour Grid Increment	0.05
Representation	3D Mapped isosurface	Mapped Function Options	Default
Isosurface Grid: Grid Mesh Size	Coarse	Transparency level	A criteria
Isosurface Grid: Grid Layout	Default	Isosurface Rendering: Total charge density contour value	0.015
Contour Grid: Starting Value	Default	Rendering Wire Mesh	

Hardware

Hardware ATA ST500DM002 IDB14SCSI. 6.1.7600.16385.

ETC Theory.

When comparing the interaction of two substances by this theory, there is a range between the ETC of a substance A and an ETC of substance B. Therefore; there are 3 zones in which the ETC value of its cross bands can fall. One in range and two out of range (Figure 1). The area of greatest electronic interaction is I. In this zone I a chemical reaction has a very high probability of being carried out. Zone II is of medium probability; While Zone III is the very low likelihood of interaction between these two substances.

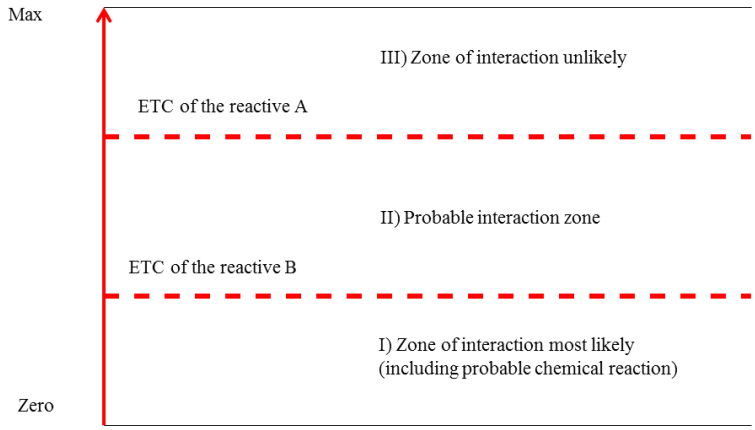

Figure 1. The zones of the interaction of two substance according to of ETC Theory. The first zone (I), is the most likely interaction and possible chemical reaction. The second area (II) is the standard probability interaction zone. This zone II is within the range of ETCs of the two substances. The third area (III) is the least interaction area; it is improbable one chemical reaction.

RESULTS AND DISCUSSION

Table 3 shows the calculation of the ETCs of each substance involved in this investigation. The NIC is highlighted in red. NTs are highlighted in green. All these ETCs are ordered from highest to lowest. NIC has an intermediate value; this means that it can attack both as an oxidizing agent and as a reducing agent. For this reason, the NIC is dangerous to the nervous systems of any living being.

Table 3. ETC of the interaction of all substances. NIC-NIC (red), NT-NT (green).

NIC	NORADRENALINE	-9.1973	-0.0043	9.1931	-0.155	-0.222	0.067	137.21
ACETYLCHOLINE	**ACETYLCHOLINE**	**-9.242**	**1.0343**	**10.276**	**-0.028**	**0.105**	**0.133**	**77.265**
NORADRENALINE	**NORADRENALINE**	**-9.1518**	**-0.0043**	**9.1475**	**-0.083**	**-0.222**	**0.139**	**65.81**
ACETYLCHOLINE	NIC	-9.242	0.1011	9.3431	-0.028	0.125	0.153	61.066
GLUTAMIC ACID	NIC	-10.044	0.1011	10.146	-0.084	0.125	0.209	48.543
NORADRENALINE	NIC	-9.1518	0.1011	9.2529	-0.083	0.125	0.208	44.485

ASPARTIC ACID	NIC	-10.242	0.1011	10.343	-0.109	0.125	0.234	44.201
DOPAMINE	NIC	-8.8678	0.1011	8.9689	-0.098	0.125	0.223	40.219
GLYCINE	NIC	-9.853	0.1011	9.9541	-0.126	0.125	0.251	39.658
NIC	ACETYLCHOLINE	-9.1973	1.0343	10.232	-0.155	0.105	0.26	39.352
GLUTAMIC ACID	**GLUTAMIC ACID**	**-10.044**	**0.5371**	**10.582**	**-0.084**	**0.197**	**0.281**	**37.657**
ADRENALIN	NIC	-8.9984	0.1011	9.0995	-0.117	0.125	0.242	37.601
GABA	NIC	-9.5615	0.1011	9.6626	-0.14	0.125	0.265	36.463
ASPARTIC ACID	**ASPARTIC ACID**	**-10.242**	**0.5162**	**10.758**	**-0.109**	**0.198**	**0.307**	**35.042**
GLYCINE	**GLYCINE**	**-9.853**	**0.8744**	**10.727**	**-0.126**	**0.188**	**0.314**	**34.164**
SEROTONIN	NIC	-8.9484	0.1011	9.0495	-0.145	0.125	0.27	33.517
NIC	**NIC**	**-9.1973**	**0.1011**	**9.2984**	**-0.155**	**0.125**	**0.28**	**33.209**
GABA	**GABA**	**-9.5615**	**0.9386**	**10.5**	**-0.14**	**0.18**	**0.32**	**32.813**
DOPAMINE	DOPAMINE	-8.8678	0.1989	9.0667	-0.098	0.189	0.287	31.591
SEROTONIN	**SEROTONIN**	**-8.9484**	**-0.1294**	**8.819**	**-0.145**	**0.141**	**0.286**	**30.836**
NIC	SEROTONIN	-9.1973	-0.1294	9.0679	-0.155	0.141	0.296	30.635
NIC	GABA	-9.1973	0.9386	10.136	-0.155	0.18	0.335	30.257
NIC	GLYCINE	-9.1973	0.8744	10.072	-0.155	0.188	0.343	29.364
ADRENALIN	**ADRENALIN**	**-8.9984**	**0.0918**	**9.0901**	**-0.117**	**0.198**	**0.315**	**28.858**
NIC	GLUTAMIC ACID	-9.1973	0.5371	9.7345	-0.155	0.197	0.352	27.655
NIC	ASPARTIC ACID	-9.1973	0.5162	9.7135	-0.155	0.198	0.353	27.517
NIC	DOPAMINE	-9.1973	0.1989	9.3962	-0.155	0.189	0.344	27.315
NIC	ADRENALIN	-9.1973	0.0918	9.2891	-0.155	0.198	0.353	26.315

Noradrenaline and Acetylcholine have the highest ETCs of all substances. Then, this NT are the more unstable than the others. This instability may be because they have multiples in the body. In the other hand, researchers identify these two compounds as responsible for the functioning of the autonomic nervous system. NT regulates the CNT.[26] Acetylcholine is the neurotransmitter responsible for preganglionic fibers at the sympathetic and parasympathetic level. Noradrenaline is the NT of postganglionic sympathetic fibers. Both NT work together.[26]

We can see in this table 1 that almost all cross-linking interactions of NIC with NTs are very low except the interaction of Noradrenaline-NIC, which is the highest. It can say that the NIC attacks the NT by donating or accepting electrons.

Table 4 shows the interactions of each NT with the NIC. The zones of interaction shown in Figure 1 are clearly visible. Zone I is shown below the ETC (green, pink bottom); Zone II is shown in the middle; Zone III is shown above the larger ETC (red).

In this table 4 are also shown in the left column the reducing agents (antioxidants) and in the right column the oxidizing agents. Therefore, the NIC attacks the NT in both directions as an oxidizing agent or as a reducing agent. Two more observations are important: 1) No

interaction in zone II (probable); 2) All interactions occupy a zone III (most likely or almost certainly the attack). We conclude that all interactions are likely.

Table 4. A particular analysis of NT interactions with NIC taken in pairs. The highest level indicated in red; the lowest level indicated in green.

Reducing Agent (Antioxidant)	Oxidizing Agent	ETC
ADRENALIN	NIC	37.601
NIC	**NIC**	**33.209**
ADRENALIN	**ADRENALIN**	**28.858**
NIC	ADRENALIN	26.315

Reducing Agent (Antioxidant)	Oxidizing Agent	ETC
DOPAMINE	NIC	40.219
NIC	**NIC**	**33.209**
DOPAMINE	**DOPAMINE**	**31.591**
NIC	DOPAMINE	27.315

ASPARTIC ACID	NIC	44.201
ASPARTIC ACID	**ASPARTIC ACID**	**35.042**
NIC	**NIC**	**33.209**
NIC	ASPARTIC ACID	27.517

GLUTAMIC ACID	NIC	48.543
GLUTAMIC ACID	**GLUTAMIC ACID**	**37.657**
NIC	**NIC**	**33.209**
NIC	GLUTAMIC ACID	27.655

GLYCINE	NIC	39.658
GLYCINE	**GLYCINE**	**34.164**
NIC	**NIC**	**33.209**
NIC	GLYCINE	29.364

GABA	NIC	36.463
NIC	**NIC**	**33.209**
GABA	**GABA**	**32.813**
NIC	GABA	30.257

SEROTONIN	NIC	33.517
NIC	**NIC**	**33.209**
SEROTONIN	**SEROTONIN**	**30.836**
NIC	SEROTONIN	30.635

ACETYLCHOLINE	ACETYLCHOLINE	77.265
ACETYLCHOLINE	**NIC**	**61.066**
NIC	**ACETYLCHOLINE**	**39.352**
NIC	NIC	33.209

NIC	NORADRENALINE	137.210
NORADRENALINE	**NORADRENALINE**	**65.810**
NORADRENALINE	**NIC**	**44.485**
NIC	NIC	33.209

THE NIC INTERACTIONS WITH ALL THESE NEUROTRANSMISORS IN BOTH SENSES OXIDATION - REDUCTION

As we mentioned earlier, serotonin has as the main function in functions such as regulation of sleep cycles, stress management, appetite or body temperature.[26] The literature confirms that NIC affects appetite levels by avoiding immediate hunger. On the other hand, the smoking people say to lower their standard of stress when having contact with the cigar.

Based on the above GABA has as a function the communication between neurons. GABA helps reduce neuronal activity. GABA has an important role in behavior and response to stress. GABA contributes to control fear and anxiety when neurons are overexcited.[27]

This information helps researchers identify NIC as a compound that, when interacting with both serotonin and GABA, has a neuronal blockage that forms a cycle of decreasing anxiety or stress.

CONCLUSION

We identify NIC as a compound capable of interacting easily with most NT. As the main ones, we mention Adrenalin, Dopamine, Aspartic acid and Glutamic acid. The interaction with NIC has a direct reaction to stress. Through this study, we identified that NIC could lower stress levels and cause a decrease in the neuronal expiratory level which encourages the reduction of neuronal activity.

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