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Research article

WOULD D(+)ADRENALINE HAVE A THERAPEUTIC EFFECT IN DEPRESSION

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Abstract

In this article, we will analyze a possible therapeutic effect that the enantiomer D (+) of the epinephrine molecule (C9H13NO3) produces in a person who is in a state of depressive anxiety. After presenting a brief historical overview of the depression problem, the discovery of neurotransmitters, the role of enantiomers and the treatment by antidepressants. Just like Citalopram (C20H21N2FO) (Escitalopram), whose antidepressant effect is restricted only to its positive enantiomer [S (+)], we conjecture the existence of an antidepressant effect due to adrenaline also restricted to its positive enantiomer [D (+)].However, up to the moment the production of theD(+)– adrenaline in human body has not been detected yet. We conjecture that the presence of this enantiomer in human body is likely to be detected in blood tests done immediately after parachute jumps. We propose that the D(+) Adrenalineproduction during parachute jumps be caused by the violent emotional shock due to the confrontation with death and that this production happens through the following processes: (a) Almost all L (-) adrenaline becomes D (+) adrenaline through anultra-fast racemization (b) the body itself begins to produce a D(+) adrenaline at large amount. Thus, the **sense of well-being felt by** parachutists during and after the jump, result from the presence of adrenaline D (+) which would work, therefore, as an antidepressant.

Keywords: D(+) Adrenaline; Antidepressants.

1. INTRODUCTION

As is widely documented in the scientific literature, emotions can both cause, cure or prevent anxiety – depressive[1-3] outbreaks. However, this relationship of cause and effect remains to be explained. In an article written in 2012[4], we wondered what "mechanism" enables an emotion to prevent or produce a depression.

In a recent paper[5] we proposed for that "mechanism", the following conjecture;
When a person receives an emotional shock, there is a discharge of L (-) - adrenaline into the blood stream. And in its flow, the molecules begin to collide with some of them turning into D (+) - adrenaline. Depending on your emotional conditions, theD (+) adrenaline may quickly dissipate for being, probably less potent as it happens when obtained in the laboratory. However, depending on the emotional control of this person , there may be an increase of its power and, therefore, occur the desired racemization and thereby,the prevention of a psychosomatic illness.

Thus, we analyzed one aspect of this conjecture related to the emotional shock that a person in a state of depressive anxiety, suffers when performing a parachute jump. According to one of the authors (JPOF) (who went through health changes as a result of skydiving[6]) when a person jumps from an airplane at a speed of 220 km /h and a height of 4,000 m, during the 55 seconds of free fall (before opening the parachute), he experiences the Buddhist passage rite of “death and rebirth of the Ego”,because his unconscious is not aware of the flight safety.So, at that moment of time, the person performs unconsciously the Ícarus myth[7]which reflects the ancestral human being desire of flying, and experiencing, as well, the feeling of finally reborning from the ashes, as in the myth of Phoenix[7]. In the jump course, we conjecture in that article that, during the jump, the initial burst of L (-) - adrenaline undergoes a racemization[8] process becoming D (+) - adrenaline and therefore, at the end of the jump, due to this racemization , the parachutist feels that there was a "rebirth in his life", which allows him to reflect, afterwards, on the problems that were afflicting him. Yet in that article, we published ten (10) testimonials from people who have experienced that "rebirth" and at the end of that article, we presented a conjecture on how this D (+) – adrenaline enantiomer could be obtained in a laboratory.

2. WOULD THE D(+)-ADRENALINEHAVE A THERAPEUTIC ACTION IN DEPRESSION?

Before answering this question, we will present a brief history on how were discovered the Selective Serotonin Reuptake Inhibitors (SSRI)[9], commonly used in depression. Depression (or states recognized as such and subtly different) and their disorders have been described by ordinary people, philosophers and physicians over thousands of years. For example, in the 2nd Century BC, the Greek physicianHippocrates (460-370) treated patients suffering from insomnia, lack of appetite, excessive fear and discouragement; symptoms that he considered due to an illness: melancholia. In the Middle Ages, the strong influence of the Catholic Religion characterized these symptoms as a result of certain sins of the people carrying these symptoms.The neurologist-psychiatrist Austro-Hungarian Sigmund (Schlomo) Freud (1856-1939)[10],also used the term melancholy to describe a psychological illness that seemed likethe mourningacquired by a person after losing animportant relationship or possession. However, as it seemed to come out of "nothing", such losses should be unconscious.

The modern treatment for such “disease” begun with the discovery of the neurotransmitters (also known as neurohormones, as its production and actuation were interconnected with the endocrine system), which are molecules from different chemical origins.Its classification and denomination depend on their origin, type of action and actuation area, as a same neurotransmitter can act differently in different tissues and cells.
Nowadays, more than ninety natural (endogenous) neurotransmitters are known to be capable of exerting some action in the synapses (spaces between the neurons), which function as a kind of switch which remains constantly off.When it receives a nervous impulse, it “turns on” and allows the communication between the cells. In view of the scope of this paperwe will discuss only four of these neurotransmitters:***acetylcholine***, ***noradrenaline*** (***norepinephrine***), ***adrenaline*** (***epinephrine***) e ***serotonin*** (***enteramine***)[11].

Initially we will present how the four chosen moleculeswere discovered and, afterwards, its neurotransmission function.In our article[5] we showed that adrenaline ($C_9H_{13}NO_3$) was discovered, independently, by four researchers: the north American physician William Horatio Bates (1860-1931), in 1886; the Polish physiologist Napoleon Cybulski (1854-1919), in 1895; the biochemist and pharmacologist John Jacob Abel (1857-1938), in 1897; and the Japonese biochemistJokichiTakamine (1854-1922), in 1901, who coined the name: ***ad*** (latin prefix for proximity), ***renal*** (relative to kidneys,*renalis* in latim) and ***ine*** (sufic applied to some

chemical substances).Adrenaline was artificially synthesized in 1904 by the German Friedrich Stolz (1860-1936).

Acetylcholine (ACh)[$C_{10}H_{12}N_2$ ou 5-HT (*5-Hidroxitriptamina*)] was first identified in 1915, by the English pharmacologist and physiologist Sir Henry Hallett Dale (1875-1968; PNM/F, 1936)[12]due to its action in the heart tissue.Later, in 1921, the German pharmacologistOtto Loewi (1873-1961; PNM/F, 1936)[13]confirmed the existence of this molecule, named by him***vagusstoff***,because it was released by the ***vagus*** nerve. As ACh functions as a transmission agent for nerve impulses, it was considered the first neurotransmissor.

Serotonin [C10H12N2 OR 5 -HT (5-hydroxytryptamine)] was initially discovered by the Italian pharmacologist and chemist Italian Vittorio Erspamer (1909-1999) in 1935 in an extract prepared fromenterochromaffin cells taken from amphibians tissues. Some chemists thought that it was ***Adrenaline***. Only in 1937Erspamer showed what it was an amine, still unknown, and called ***enteramine***[14].In 1948[15], the American biochemists Maurice A. Rapport (1919-2011), Arda Alden Green (1899-1958) and Irvine Heinly Page (1901-1991) found a vasoconstrictor substance in blood serum, and since it affected the vascular tone, they named it serotonin . In 1949[16,17], Rapport identified serotonin as being 5-HT . Later, in 1953[18], the physiologist and German biologist Wilhelm Siegmund Feldberg (1900-1993) and C. C. Toh, when examining the wall of the intestinal tract of rats, showed that serotonin was the same substance as enteramine.

Finally, noradrenaline (NAd) (C8H11NO3) was discovered by the Swedish biologist Ulf von Euler (1905-1983; SLP/M, 1970) in 1946. After this discovery, von Euler and his research group studied the distribution of NAd in biological tissues and in the nervous system, in physiological and pathological conditions and found that it was produced and stored in synaptic nerve terminals in intracellular vesicles[19].

Let's see, now, the use of antidepressants and the role of the enantiomers of certain molecules in medicine. The use of the nowadays calledantidepressants was discovered accidentally. According to Katherine Sharpe[9], on July 5, 1952, the New York Times called attention to a mystery that was happening to the use of the iproniazid molecule ($C_9H_{13}N_3O$), with the trade name Marsilid, used to treat tuberculosis in two New York hospitals and that, although not helping the healing of these patients, however, produced a "state of euphoria"in them.As a result, research in search for antidepressants was continued and, in 1954, the Swiss psychiatrist Roland Kuhn (1912-2005) discovered the imipramine molecule ($C_{19}H_{24}N_2$), marketed as Trofanil[20], beginning the era of antidepressants.

In turn, in England and Germany between 1956 and 1963, it was discovered the role of enantiomers in medicine, starting with the famous case of thalidomide (C13H10N2O4), in which it was observed that women who used a certain syrup (containing thalidomide), indicated for coughs and also prescribed to reduce nausea, its use was causing the birth of thousands of deformed children. Withdrawn from the market, this syrup begun to be studied.Then it was found that the D (+) - enantiomer of thalidomide cured nausea, whereas the L (-) - enantiomer caused defects in fetus [4,5]. It is worth noting that since the 1950s, began to be studied in rats the effects of two enantiomers of adrenaline: L (-) - adrenaline and D (+) - adrenaline , the first ten times more potent than the second[21].However, the advance in medical research has revealed new uses for L (-) - adrenaline, such as local anesthesia in medical emergencies[22] and in patients with rheumatic arthritis[23]. Note that the (+) enantiomers are also referred to as S (+) ("S" from the English word "Slow") enantiomers and (-) R (-) ("R" from the english word "rapid").

In 1989, the pharmaceutical company Lundbeck, in Copenhagen, Denmark, created the chiral molecule ***citalopram*** (C20H21N2FO) which has two enantiomers: 1) S (+) - ***citalopram*** ; 2) R (-) - ***citalopram***. Initially presented under the tradename ***Citalopram***, it was formed by the racemic mixture (50 % vs 50 %) of these two enantiomers[24].However, in 2004[25], U. Lepola , A. Wade and Andersen HF showed that the S (+) - citalopram had a better antidepressant effect than the R (-) , and then he has come to be marketed and manufactured by Lundbeck with the name Escitalopram . It was obtained as a result of a racemic purification of the two enantiomers of citalopram, resulting in a highly selective molecule, as it only acts in Serotonin uptake without affecting other receptors[26]

In view of theexplanations presented so far and considering the results and conjectures presented in our two other articles[4,5], we believe that the answer to the question in the title of this article is translated by the following conjecture: Is it possible to produce the***"Ed (s) Adrenaline"***, using the racemic purification[27] of the two *enantiomers* of ***adrenaline*** and could it be used as an *antidepressant* ?[28]

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5**.** Oliveira Filho, J. P. de, Cattani, M.**,** Bassalo, J. M. F., and Souza, N. P. C. de, 2013. **The (+)-adrenaline and skydiving as a solution to psychogenic symptoms and a possible prevention of psychosomatic diseases.** *International Research Journal of Biochemistry and Bioinformatics* **3**(5), pp. 97-103.

6. JOPF suffered from a gastric hyperacidity that tormented him a lot. One day, after a few parachute jumps, he realized he had been cured of hyperacidity. As a therapist physician with over twenty years of practice, he asked the obvious question: what happened? He then began to reflect on what happened and intuitively realized that this result was a consequence of this your experience with skydiving, as he reported in the article by Bruno Carachesti, Leap for life, published in the newspaper Diary of Para 1 (33), pp . 34-36, in January 13, 2013.

7**.**Guirand, F. 1971. **Mitología General**, Editorial Labor, S. A.

8. Let's look at a short historical summary on enantiomers and racemization . The tartaric acid (TA) [$H_2C_4H_4O_6$ $(CHOH.COOH)_2$] , acid obtained from Tartars , which are deposits that form in the fermentation of the grape, was already known by the ancient Greeks and Romans under the form of potassium acid salt - Tatar : $KHC_4H_4O_6$. However, only in the 18th century, the TA was isolated as a free acid by the Swedish chemist and pharmacist Carl Wilhelm Scheele (1742-1786). A second form of this acid, paratartaric (TPA), was mistakenly taken as oxalic acid [$H_2C_2O_4$ (HOOC.COOH)], around 1819, by the wine manufacturer the French Paul Kestner.Later, in 1828, the french chemist Joseph Louis Gay-Lussac (1778-1850) showed that APT had the same chemical composition of the AT, and then gave him the name of racemic acid (RA), which derives from the Latin word racemus, which means grape. In 1831, the Swedish chemist Jöns Jacob Berzelius (1779-1848) showed that grape acids (TA and RA), as he denominated them in 1830, had the same chemical composition, but with different properties, a phenomenon denominated by him isomerism (which derives from the Greek word isomeric, which means two parts). In 1985, the French physicist Jean Baptiste Biot (1774-1862) noticed that the APT (AR), in solution, showed optical activity since it turned the plane of polarization of light to the right. In 1838, Biot realized that free AT and AR were optically inactive. The detailed study of these acids and their salts were performed by the chemists, Frenchman Hervé Ferdinand Frédéric de la Provostaye (1812-1863) in 1841, and the German Carl Remigius Fresenius (1818-1897) and EilhardtMitscherlich (1794- 1863) in 1842. In 1844, after sending a letter to Biot, Mitscherlich presented to the French Academy of Science the result of his experiments in which he observed that while the commercial AT salt crystals had optical activity, i.e., they rotated the plane of polarization of the light that passed through, the same did not happen with crystals AR. Such results were an enigma, sincethese acids besides having identical chemical compositions had the same structure, that is, they werestereoisomers.The above riddle was solved by the French chemist Louis Pasteur (1822-1895), in 1848 and 1850, while studying these acid crystals, mainly AR (*paratartaric*, as he denominated it) with the aid of a microscope. Indeed, by observing the crystals AR, Pasteur found that there are two kinds of them, one being the mirror image of the other. He obtained these crystals from a solution that did not rotate the plane of polarization of the incident light on them and, immediately he guessed that a 50% x 50% mixture (racemization) of two types of crystals wasthe explanation for the observed optical inactivity.Thus, with the aid of clamps, he carefully separated the crystals in two mounds and, by passing again polarized light through it, he realized that one of the mounds rotated theplane of polarization of the light clockwise and the other counterclockwise. Pasteur also observed that one of the two forms of AR was identical to AT.In view of this, he described the crystals studied in two types: ***levorotatory***[L (-)] (lefthand)and ***dextral***[D (+)] (right-hand). Today, these molecules known as chirals (from the Greek word keir, meaning hand) are called ***enantiomers*** and are of two

types: L (-) - ***enantiomer*** and D (+) - ***enantiomer***. These molecules have a property; there cannot be an overlap between its structural representation and its mirror image. For more details about ***racemization***see the references:

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27. Since racemization of the adrenaline injections stockpiled (in vitro) takes about four hours (Fyllingen , G. , Langvik , MT , Hasselgård and Roksvaag , PO 1990. racemization and Oxidation in Adrenaline Injections, Acta Pharm Nord 2, pp . 355- 3620), another possibility would be the following: the emotional shock from the confrontation with death during the parachute jump would induce the body to begin producing only theD (+) adrenaline in a great quantity. Thus, the well-being experienced by parachute during and after the jump, would be due to the production of d (+) and not to racemization L (-) → D (+). Thus, only by measuringand identifying the adrenalins, before and after the jump can one of these two conjectures (racemization/production) be proved.

28. We believe it is opportune to say that we are continuing our research seeking to understand the bio-physico-chemical action between antidepressants and neurotransmitters, from the point of view of Quantum Neuroscience. And, for that, we exchanged emails with some foreign researchers (whose ideas were helpful in writing this article and therefore we take this opportunity to thank their collaborations), highlighting: Dr. Niels Christensen of the University of Copenhagen , on May 5, 7, 10, 20, 23 and 27 and June 4, 2013, the neurobiologist Dr. Konstantinos Mandilarasfrom the University of London, on October 9 and 31, 2013 and Dr . Melanie Schnell the Max Planck Institute,on December 20, 2013.