Review Article

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2022.41.006567

In Vivo Simultaneous Neurochemical, Electrophysiological and Behavioural Analysis of the Putative Antidepressant and Motor Stimulating Properties of Nociceptin/Orphanin FQ (N/OFQ) Receptor Antagonists: A Research Proposal

Francesco Crespi*

Voltammetry – NIRS Laboratories, Medicine Center, Italy

***Corresponding author:** Francesco Crespi, Voltammetry – NIRS Laboratories, Medicine Center, Verona, Italy

ARTICLE INFO

Received: January 12, 2022

Published: January 20, 2022

Citation: Francesco Crespi. *In Vivo* Simultaneous Neurochemical, Electrophysiological and Behavioural Analysis of the Putative Antidepressant and Motor Stimulating Properties of Nociceptin/Orphanin FQ (N/OFQ) Receptor Antagonists: A Research Proposal. Biomed J Sci & Tech Res 41(2)-2022. BJSTR. MS.ID.006567.

Abbreviations: FQ (N/OFQ): Nociceptin/Orphanin; DA: Dopamine; DPV: Differential Pulse Voltammetry; SN: Substance Nigra; SNr: Substantia Nigra Reticulata; CMS: Chronic Mild Stress; I.C.V: Intra-Cerebroventricularly; TH: Tyrosine Hydroxylase; DPV: Differential Pulse Voltammetry; DLS: Dorsolateral Striatum; FST: Forced Swimming Test; SSRI: Selective Serotonin Reuptake Inhibitor

ABSTRACT

Nociceptin/Orphanin FQ (N/OFQ) is a 17 amino acid endogenous opioid-like neuropeptide and the N/OFQ-NOP receptor system is widely represented throughout the rodent, primate and human. Administration of N/OFQ has been consistently shown to inhibit spontaneous locomotion as well as motor activity stimulated by pharmacological agents. Endogenous N/OFQ also inhibits motor behaviour since pharmacological or genetic blockade of N/OFQ transmission increases locomotor performance. The motor depressant action of endogenous N/OFQ has been related to N/OFQ ability to inhibit dopaminergic transmission along the nigrostriatal pathway. However, in a recent work we have observed either increase or decrease of Dopamine (DA) levels monitored with Differential Pulse Voltammetry (DPV) in the Substance Nigra (SN) of anaesthetized rats, depending on the amount of N/OFQ injected.

On the other hand, what appears more consistent as an effect of N/OFQ is the [negative] influence upon serotoninergic activities. Indeed, in earlier studies performed with DPV we have shown that microinjection of N/OFQ in the Substantia Nigra Reticulata (SNr) inhibits local serotonin (5-HT) release in anaesthetized rats. Thus, our hypothesis is that continuous motor activity may cause release of endogenous N/OFQ which therefore may act upon DA and subsequently upon 5-HT release in the basal ganglia, as previously observed in the SN, resulting in impaired locomotion. To prove this hypothesis, a specific study will be undertaken in awake rats prepared for voltammetry-electrophysiology recordings. These rodents will be freely moving and subjected to behavioral tests (i.e. the rotarod or the forced swimming test). Concomitant voltammetric and electrophysiological measurements of the dopaminergic and serotonergic activities will be performed at two different levels: cell bodies (i.e. SNr, RDN) and relevant nerve terminals i.e. amygdale, hippocampus, cortex.

Introduction

Nociceptin/Orphanin FQ (N/OFQ) is a 17 amino acid endogenous opioid-like neuropeptide [1] that activates a G-protein coupled nociceptin opioid peptide receptor [2,3], named NOP [4].The N/OFQ-NOP receptor system is widely represented throughout the rodent [5,6], primate [7] and human [8] CNS. Established neurobehavioral techniques as well as radio-imaging technologies have been applied to investigate this system in animals and

humans, in particular on the role of N/OFQ in the control of feeding, body weight homeostasis, stress, depression, anxiety, and in drug and alcohol dependence [9] and for reviews [10,11]. In rodents the N/OFQ receptor system is widely expressed in cortical and subcortical motor areas [5] and is involved in the modulation of a number of biological actions [12] for a review [13]. Previous works demonstrated that Intra-Cerebroventricular (I.C.V.) administration of N/OFQ has been consistently shown to inhibit spontaneous locomotion [14,15] as well as motor activity stimulated by pharmacological agents [16,17].

Alternatively other experiments showed that Nociceptin administered Intra-Cerebroventricularly (I.C.V.) at doses of 2, 5 and 10 nmol/rat changed neither DA nor metabolites release in the shell of the nucleus accumbens or in the nucleus caudate but was able to reduce morphine-induced DA and metabolites release in the shell of the nucleus accumbens, therefore possibly acting mainly as modulator of neurochemical and behavioral influence of drugs of abuse [18,19]. Endogenous N/OFQ also inhibits motor behaviour since pharmacological or genetic blockade of N/OFQ transmission increases locomotor performance on the rotarod [20]. Early pharmacological evidence also supports a role for the N/OFQ-NOP receptor system in the modulation of mood related behaviours in rodents, i.e. two chemically unrelated NOP receptor antagonists, the peptide [Nphe']N/OFQ(l-13)NH2 and the non-peptide J-l 13397, reduced the immobility time of mice in the forced swimming test (FST); [21] test that has been proved to be of utility to predict the clinical efficacy of antidepressants in rodents [22].

Later, these results were obtained also with the NOP receptor peptide antagonist UFP-101, i.e. in rodents administered i.c.v. it was followed by reduction of the immobility time and by increase of the climbing behaviour in rats submitted to the forced swimming test. These data were further supported with genetic observations, i.e. by challenging knockout mice [23] in the forced swimming and tail suspension tests [24]. Additionally, chronic treatment with UFP-101 produced antidepressant-like effects in rats subjected to a validated animal model of depression: the Chronic Mild Stress (CMS) [25]. The neurochemical substrate involved in the motor depressant action of endogenous N/OFQ and ii) the antidepressant-like action of NOP receptor antagonists is still matter of investigation. The motor depressant action of endogenous N/OFQ has been related to N/OFQ ability to inhibit dopaminergic transmission along the nigrostriatal pathway, since NOP receptor antagonists evoked striatal Dopamine (DA) release in the rat [20]. However, the influence of N/OFQ upon DA system is controversial as other works have shown that:

a. Nociceptin administered Intra-Cerebroventricularly (I.C.V.) at doses of 2, 5 and 10 nmol/rat changed neither DA nor metabolites release in the shell of the nucleus accumbens or in the nucleus caudate [18].

b. Orphanin FQ when applied to the ventral tegmental area of anesthetized rats by reverse dialysis at a probe concentration of 1 mM (but not at 0.1 mM) significantly reduced dopamine levels sampled with a second dialysis probe in the nucleusaccumbens. In contrast, the receptor-inactive analogue, des-Phe[1] Orphanin FQ (1 mM), produced a small but significant increase in nucleus accumbens dialysate dopamine levels [26].

c. *In vivo* microdialysis studies have shown a large increase ofdopamine release (in the order of 350-390% of control values)in striatum when treating conscious rats with nociceptin at themicro molar concentration [27].

Finally, in his review [28] reported about both facilitatory and inhibitory motor actions of N/OFQ and that both these effects were abolished in animals in which tyrosine hydroxylase (TH) activity was inhibited, indicating that endogenous DA is critical for both events [14]. In particular, [29] previously noted that the facilitatory effects of low doses of N/OFQ were abolished by haloperidol treatment, proposing a role for D_2 receptors. Again, in more recent work, we have observed either increase or decrease of DA levels monitored with differential pulse voltammetry (DPV) in the Substancia Nigra (SN) of anaesthetized rats, depending on the amount of N/OFQ injected locally into the SN [30]. On the other hand, what appears more consistent as an effect of N/OFQ is the [negative] influence upon serotoninergic activities. Indeed, in earlier studies performed with DPV we have shown that microinjection of N/OFQ in the Substantia Nigra Reticulata (SNr) inhibits local serotonin (5-HT) release in anaesthetized rats [31,30].

Facilitation of serotonergic transmission in the SNr enhances locomotion in rodents [32,33] and both dopaminergic and serotonergic transmission is increased in the SNr and striatum during continuous motor execution [34,35]. Moreover, some authors have suggested that the antidepressant action of NOP receptor antagonists is due to blockade of N/OFQ inhibition of central serotonergic transmission at two different levels: at the dorsal raphe nucleus (RDN) neurons, where N/OFQ causes hyperpolarization by increasing a K^+ conductance [36,28], and at cortical serotonergic nerve terminals, where N/OFQ inhibits 5-HT release [37,38]. It has been observed that local injection of N/OFQ into the hippocampus markedly decreased exploratory locomotor activity including vertical movements (rearing) in rats [39]. Furthermore it has been shown that it elicits hypo locomotion in rats submitted to elevated plus maze and in the conditioned defensive burying test [40].

Thus, our hypothesis is that continuous motor activity may cause release of endogenous N/OFQ which therefore may act upon DA and subsequently upon 5-HT release in the basal ganglia, as

previously observed in the SN, resulting in impaired locomotion. To prove this hypothesis, a specific study will be undertaken in awake rats prepared for voltammetry – electrophysiology recordings as already described [41,42]. In addition , these rodents will be freely moving and therefore subjected to behavioral tests (i.e. the rotarod or the forced swimming test) by employing a telemetric system that allows to correlate on line and with high-time resolution both neurochemical and behavioural parameters [43,44]. Furthermore, concomitant voltammetric and electrophysiological changes of the dopaminergic and serotonergic systems will be performed at two different levels: cell bodies (i.e. SNr, RDN) and relevant nerve terminals i.e. amygdale, hippocampus, cortex, as previously described [40,45,46].

Project Strategy

Animals: The difference between strains of rats has to be taken into consideration as it appears that combined behavioural-voltammetric investigations suggest that "behavioural despair" is the process interesting Wistar rats when submitted to FST while "learning to be immobile" is the process involving Sprague-Dawley CD rats [47].

Voltammetric Analysis and Behavior: Voltammetric analysis of 5-HT and DA release [48,44,31] will be performed in the SNr and dorsolateral striatum (DLS) of awake rats at rest and during performance on the rotarod. Then, the effect of selective NOP receptor agonists and antagonists (either injected into the SNr or given systemically) on nigral and striatal 5-HT and DA release will be investigated. Among agonists, N/OFQ will be tested while among antagonists, the peptide compound UFP-101 [49] and the non-peptide compound J-l 13397 [48] will be used. This will allow correlation between changes of 5-HT and DA release and motor effects of NOP receptor ligands. A telemetric system will be implemented to transmit data from the electrodes to the recording system [40,43].

Concomitant Electrophysiological Analysis performed in the cell bodiesand relevant terminal brain areas of anaesthetised rats [7] will give information on the effect of N/OFQ or NOP receptor blockade on cell firing. The feasibility of telemetric electrophysiological monitoring in conscious rats would be also assessed in order to correlate these outcomes with the biochemical data gathered in rotarod-behaving animals. In the attempt to verify the putative antidepressant action of NOP receptor antagonists the correlation between cortical 5-HT levels and the behavioural effects induced by the NOP antagonist UFP-101 will be analysed in rats subjected to the forced swimming test (FST) as previously described [50]. Briefly, in conscious rats previously prepared for voltammetric analysis in the cerebral cortex, an i.c.v. administration of UFP-101 at 1 and 10 nmol/rat will be performed 5 min before the FST. Three behavioral parameters, previously shown to be reliable and validated for the detection of antidepressant drug effects in the rat FST, will be scored:

a. Immobility time

b. Swimming time

c. Climbing time

Real time *in vivo* voltammetric measurement of 5-HT levels in the cerebral cortex will be assessed in rats before, during and after the FST, in order to correlate the behavioural effects induced by central administration of UFP-101 with 5-HT levels in the cerebral cortex.

Additional Assessment

Additionally, a parallel approach to verify the effect of UFP-101 upon the serotonergic system could be by applying the *ex vivo* voltammetric method analyzing 5-HT levels in rat platelet-rich plasma versus 5-HT levels in isolated platelets. Definitely, neurons and platelets display structural and functional similarities, so that the latter have been proposed as a peripheral model of central functions [51,52]. In particular, in blood more than 99% of 5-HT is contained in platelets, so that one could consider changes in 5-HT levels in platelets as a mirror of changes in central 5-HT. Indeed, it has been shown that peripheral 5-HT in rat platelet-rich plasma mirrors cerebral extracellular 5-HT levels, whilst 5-HT in isolated platelets mirrors neuronal 5-HT changes and that following FST as well as treatment with selective serotonin reuptake inhibitor (SSRI) fluoxetine peripheral 5-HT platelet levels can reflect the state of the central 5-HT system in conditions of depression [50,53,54].

Conclusion

It is known that the generation of specific agonists, antagonists and receptor deficient mice and rats has enabled progress in elucidating the biological functions of N/OFQ receptor system. Furthermore it has been shown that UFP-101 exhibits pronounced antidepressant-like effects in different species and animal models, possibly by preventing the inhibitory effects of endogenous N/OFQ on brain monoaminergic (in particular serotonergic) neurotransmission. The present experiments will possibly further support the involvement of the N/OFQ-NOP receptor system in mood modulation so that it can be proposed as another potential targets for antidepressant drug development.

References

1. Meunier JC, Mollereau C, Toll L, Suaudeau C, C Moisand, et al. (1995) Isolation and structure of the endogenous agonist of opioid receptor-like ORL_1 receptor. Nature 377(6549): 532-535.
2. Reinscheid RK, Nothacker HP, Bourson A, Ardati A, O Civelli, et al. (1995) Orphanin FQ: a neuropeptide that activates an opioidlike G protein-coupled receptor. Science (New York, N.Y.) 270(5237): 792-794.
3. Saez C, Mortrud M, Bouvier C, M Low, D K Grandy, et al. (1994) Molecular cloning and tissue distribution of a putative member of the rat opioid receptor gene family that is not a μ, δ or κ opioid receptor type, FEBS Letters 347(2-3): 284-288.
4. Cox BM (2013) Recent Developments in the Study of Opioid Receptors. Molecular Pharmacology 83(4): 723-728.
5. Darland T, Heinricher MM, Grandy DK (1998) Orphanin FQ/nociceptin: a role in pain and analgesia, but so much more. Trends Neurosci 21(5): 215-221.
6. Slowe SJ, Clarke S, Lena I, Goody RJ (2001) Autoradiographic mapping of the opioid receptor-like 1 (ORL1) receptor in the brains of μ-, δ- or κ-opioid receptor knockout mice Neuroscience 106(3): 469-480.
7. Bridge KE, Wainwright A, Reilly K, Oliver KR (2003) Autoradiographic localization of 125I [Tyr14] nociceptin/orphanin FQ binding sites in macaque primate CNS. Neuroscience 118(2): 513-23.
8. Witta J, Palkovits M, Rosenberger J, Cox BM (2004) Distribution of nociceptin/orphanin FQ in adult human brain. Brain Res 997(1): 24-29.
9. Kiguchi N, Ding H, Ko MC (2020) Therapeutic potentials of NOP and MOP receptor coactivation for the treatment of pain and opioid abuse. Journal of Neuroscience Research 100(2): 191-202.
10. Witkin JM, Statnick MA, Rorick Kehn LM, Pintar JE (2014) The biology of Nociceptin/Orphanin FQ (N/OFQ) related to obesity, stress, anxiety, mood, and drug dependence. Pharmacology & Therapeutics 141(3): 283-299.
11. Zaveri NT (2016) Nociceptin Opioid Receptor (NOP) as a Therapeutic Target: Progress in Translation from Preclinical Research to Clinical Utility: Miniperspective. J Med Chem 59(15): 7011-7028.
12. Lambert DG (2008) The nociceptin/orphanin FQ receptor: a target with broad therapeutic potential. Nat Rev Drug Discov 7(8): 694-710.
13. Mogil JS, Pasternak GW (2001) The molecular and behavioral pharmacology of the orphanin FQ/nociceptin peptide and receptor family. Pharmacol Rev 53(3): 381-415.
14. Kuzmin A, Sandin J, Terenius L, Ögren SO (2004) Evidence in locomotion test for the functional heterogeneity of ORL-1 receptors. Br. J Pharmacol 141(1): 132-140.
15. Bebawy D, Marquez P, Samboul S, Parikh D, Kabirullah Lutfy, et al. (2010) Orphanin FQ/Nociceptin Not Only Blocks but Also Reverses Behavioral Adaptive Changes Induced by Repeated Cocaine in Mice. Biological Psychiatry 68(3): 223-230.
16. Lutfy K, Do T, Maidment NT (2001) Orphanin FQ/nociceptin attenuates motor stimulation and changes in nucleus accumbens extracellular dopamine induced by cocaine in rats. Psychopharmacology (Berl) 154(1): 1-7.
17. Narayanan S, Lam H, Carroll FI, Lutfy K (2004) Orphanin FQ/nociceptin suppresses motor activity through an action along the mesoaccumbens axis in rats. J Psychiatry Neurosci 29(2): 116-123.
18. Di Giannuario A, Pieretti S (2000) Nociceptin differentially affects morphine-induced dopamine release from the nucleus accumbens and nucleus caudate in rats. Peptides 21(7):1125-1130.
19. Koizumi M, Midorikawa N, Takeshima H, Murphy NP (2004) Exogenous, but not endogenous nociceptin modulates mesolimbic dopamine release in mice. J Neurochemistry 89(1): 257-263.
20. Marti M, Mela F, Veronesi C, Guerrini R, Severo Salvadori, et al. (2004) Blockade of Nociceptin/Orphanin FQ Receptor Signaling in Rat Substantia Nigra Pars Reticulata Stimulates Nigrostriatal Dopaminergic Transmission and Motor Behavior. Journal of Neuroscience 24(30): 6659-6666.
21. Redrobe JP, Calo G, Regoli D, Quirion R (2002) Nociceptin receptor antagonists display antidepressant-like properties in the mouse forced swimming test. Naunyn-Schmied Arch Pharmacol 365(2): 164-167.
22. Porsolt RD, Le Pichon M, Jalfre M (1977) Depression: A New Animal Model Sensitive to Anti-Depressant Treat-ments. Nature 266(5604): 730-732.
23. Chia R, Achilli F, Festing M (2005) The origins and uses of mouse outbred stocks. Nat Genet 37(11): 1181-1186.
24. Gavioli EC, Vaughan CW, Marzola, G, Guerrini R (2004) Antidepressant-like effects of the nociceptin/orphanin FQ receptor antagonist UFP-101: new evidence from rats and mice. Naunyn-Schmiedeberg's Arch Pharmacol 369(6): 547-553.
25. Vitale G, Ruggieri V, Filaferro M, Claudio Frigeri, Silvia Alboni, et al. (2009) Chronic treatment with the selective NOP receptor antagonist [$Nphe^1$, Arg^{14}, Lys^{15}] N/OFQ-NH_2 (UFP-101) reverses the behavioural and biochemical effects of unpredictable chronic mild stress in rats. Psychopharmacology 207(2): 173-189.
26. Murphy NP, Maidment NT (1999) Orphanin FQ/Nociceptin Modulation of Mesolimbic Dopamine Transmission Determined by Microdialysis. JNC 73(1): 179-186.
27. Konya H, Masuda H, Itoh K, Nagai K, Kakishita E, et al. (1998) Modification of dopamine release by nociceptin in conscious rat striatum. Brain Research 788(1-2): 341-344.
28. Toll L, Bruchas MR, Calo' G, Cox M, Zaveri NT (2016) Nociceptin/Orphanin FQ Receptor Structure, Signaling, Ligands, Functions, and Interactions with Opioid Systems Pharmacological Reviews 68(2): 419-457.
29. Florin S, Suaudeau C, Meunier JC, Costentin J (1996) Nociceptin stimulates locomotion and exploratory behaviour in mice. Eur J Pharmacol 317(1): 9-13.
30. Crespi F (2019) Concomitant *in Vivo* Voltammetric and Electrophysiological Analysis Indicate that Nociceptin/Orphanin FQ Affects Dopamine and then Serotonin Activities in Brain Substancia Nigra. International Physiology Journal 2(3): 1-9.
31. Marti M, Manzalini M, Bianchi C, Heidbreder C, Morari M, et al. (2005) Nociceptin/Orphanin FQ Modulates Neurotransmitter Release in the Substantia Nigra: Biochemical and Behavioural Outcome. In: Bolam JP, Ingham CA, Magill PJ (Eds.)., Springer, Boston, New England, pp. 187-192.
32. Jacobs BL, Fornal CA (1997) Serotonin and motor activity. Curr Opin Neurobiol 7(6): 820-825.
33. Bata Garcia JL, Heredia Lopez FJ, Alvarez Cervera FJ, Arankowsky Sandoval G, Gongora Alfaro JL (2002) Circling behaviour induced by injection of serotonin reuptake inhibitors in the substantia nigra. Pharmacol Biochem Behavior 71(1-2): 353-363.
34. Bergquist F, Shahabi HN, Nissbrand H (2003) Somatodendritic dopamine release in rat substantia nigra influences motor performance on the accelerating rod. Brain Res 973(1): 81-91.

35. Pruett BS, Salvatore MF (2013) Nigral GFRα1 Infusion in Aged Rats Increases Locomotor Activity, Nigral Tyrosine Hydroxylase, and Dopamine Content in Synchronicity. Mol Neurobiol 47(3): 988-999.

36. Vaughan CW, Christie MJ (1996) Increase by the ORL1 receptor (opioid receptor-like1) ligand, nociceptin, of inwardly rectifying K conductance in dorsal raphe nucleus neurones. Br J Pharmacol 117(8): 1609-1611.

37. Mela F, Marti M, Ulazzi L, Vaccari E (2004) Pharmacological profile of nociceptin/orphanin FQ receptors regulating 5-hydroxytryptamine release in the mouse neocortex. European Journal of Neuroscience 19(5): 1317-1324.

38. Tao T, Ma Z, Thakkar MM, McCarley RW, Auerbach SB (2007) Nociceptin/orphanin FQ decreases serotonin efflux in the rat brain but in contrast to a κ-opioid has no antagonistic effect on μ-opioid-induced increases in serotonin efflux. Neuroscience 147(1): 106-116.

39. Sandin J, Georgieva J, Schött PA, Ögren SO, Terenius L (1997) Nociceptin/Orphanin FQ Microinjected into Hippocampus Impairs Spatial Learning in Rats. EJN 9(1): 194-197.

40. Vitale G, Arletti R, Ruggieri V, Cifani C, Massi M (2006) Anxiolytic-like effects of nociceptin/orphanin FQ in the elevated plus maze and in the conditioned defensive burying test in rats. Peptides 27(9): 2193-2200.

41. Crespi F (2002) *In vivo* voltammetry and concomitant electrophysiology at a single biosensor to analyse ischaemia, depression and drug dependence. J Neurosci Methods 119(2): 173-184.

42. Crespi F (2017) Monitoring *in vivo* and in real time the influence of selective antisense on GABAA receptors in rat brain Brain and Nerves 1(1): 1-3.

43. Crespi F (2010a) Wireless *in vivo* voltammetric measurements of neurotransmitters in freely behaving rats. Biosensors and Bioelectronics 25(11): 2425-2430.

44. Crespi F (2013) Invasive or Non-Invasive Techniques and Sensors for Real Time. *In Vivo* Sensing in the Brain. In: Kin Fong Lei (Edt.)., Microelectrodes: Techniques, Structures for Biosensing and Potential Applications. Laboratory and Clinical Research, Nova Science Publishers, USA, pp. 233-254.

45. Crespi F (2010b) SK channel blocker apamin attenuates the effect of SSRI fluoxetine upon cell firing in dorsal raphe nucleus: A concomitant electrophysiological and electrochemical *in vivo* study reveals implications for modulating extracellular 5-HT. Brain Research 1334: 1-11.

46. Crespi F (2018) Concomitant Behavioral, Electrochemical and Electrophysiological Study in Real Time on the Role of CRF and CRF Antagonist(s) in Anxiety and Depression: Possible Association CRF + 5-HT Receptor Antagonists? Int J Brain Disord Treat 4: 022.

47. Crespi F (2010c) Is a Divergent Central Serotonergic Activity Responsible for Either Despair or Learning Behavior in Intact Wistar or Sprague-Dawley CD Rats, Respectively? A Concomitant Behavioral and Electrochemical Analysis. Psychology 1(3): 209-219.

48. Crespi F, Martin KF, Marsden CA (1998) Measurement of extracellular basal levels of serotonin *in vivo* using nafion-coated carbon fibre electrodes combined with differential pulse voltammetry, Neuroscience 27(3): 885-896.

49. Calo G, Rizzi A, Rizzi D, Severo Salvadori, Domenico Regoli, et al. (2002) [Nphe1, Arg14, Lys15]nociceptin-NH2, a novel potent and selective antagonist of the nociceptin/orphanin FQ receptor. British Journal of Pharmacology 136(2): 303-311.

50. Sneddon JM (1973) Blood platelets as a model for monoamine-containing neurones, Progress in Neurobiology 1(2): 151-198.

51. Stahl SM (1977) The Human Platelet: A Diagnostic and Research Tool for the Study of Biogenic Amines in Psychiatric and Neurologic Disorders. Arch Gen Psychiatry 34(5): 509-516.

52. Bianchi M, Moser C, Lazzarini C, Crespi F (2002) Forced swimming test and fluoxetine treatment: *in vivo* evidence that peripheral 5-HT in rat platelet-rich plasma mirrors cerebral extracellular 5-HT levels, whilst 5-HT in isolated platelets mirrors neuronal 5-HT changes. Exp Brain Res 143(2): 191-197.

53. Maurer Spurej E, Pittendreigh C, Solomons K (2004) The influence of selective serotonin reuptake inhibitors on human platelet serotonin. Thrombosis and Haemostasis 91(1): 119-128.

54. Kawamoto H, Ozaki S, Itoh Y, H Ohta, Y Iwasawa, et al. (1999) Discovery of the first potent and selective small molecule opioid receptor-like (ORL1) antagonist: 1-[(3R,4R)-1-cyclooctylmethyl-3- hydroxymethyl-4-piperidyl]-3-ethyl-1, 3-dihydro-2H-benzimidazol-2-one (J-113397). Journal of Medicinal Chemistry 42(25): 5061-5063.

ISSN: 2574-1241

DOI: 10.26717/BJSTR.2022.41.006567

Francesco Crespi. Biomed J Sci & Tech Res