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Francesco Crespi*

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Review Article

In vivo Simultaneous Neurochemical, Electrophysiological and Behavioral 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, Verona, Italy.

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

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Abstract

Nociceptin/Orphanin FQ (N/OFQ) is a 17 amino acid endogenous opioid-like neuropeptide (Meunier et al. 1995; Reinscheid et al. 1995) that activates a G-protein coupled nociceptin opioid peptide receptor

Key words: simultaneous neurochemical; electrophysiological; behavioral

Introduction

Nociceptin/Orphanin FQ (N/OFQ) is a 17 amino acid endogenous opioid-like neuropeptide (Meunier et al. 1995; Reinscheid et al. 1995) that activates a G-protein coupled nociceptin opioid peptide receptor (Bunzow et al. 1994), named NOP (Cox 2013).
The N/OFQ-NOP receptor system is widely represented throughout the rodent (Darland et al. 1998; Slowe et al. 2001), primate (Bridge et al. 2003) and human (Witta et al. 2004) 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 (Kiguchi et al. 2020 and for reviews Witkin et al. 2014; Zaveri 2016).

In rodents the N/OFQ receptor system is widely expressed in cortical and subcortical motor areas (Darland et al., 1998) and is involved in the modulation of a number of biological actions (Lambert 2008; for a review Mogil and Pasternak 2001).

Previous works demonstrated that intra-cerebroventricular (i.c.v.) administration of N/OFQ has been consistently shown to inhibit spontaneous locomotion (Kuzmin et al. 2004; Bebawy et al. 2010**)** as well as motor activity stimulated by pharmacological agents (Lutfy et al., 2001, Narayanan et al., 2004). 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 (Di Giannuario and Pieretti.2000; Koizumi et al., 2004).
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Endogenous N/OFQ also inhibits motor behaviour since pharmacological or genetic blockade of N/OFQ transmission increases locomotor performance on the rotarod (Marti et al., 2004). 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; Redrobe et al., 2002), test that has been proved to be of utility to predict the clinical efficacy of antidepressants in rodents (Porsolt et al. 1977).

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 behavior in rats submitted to the forced swimming test. These data were further supported with genetic observations, i.e. by challenging knockout mice
(Chia et al. 2005) in the forced swimming and tail suspension tests (Gavioli et al. 2004).
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) (Vitale et al. 2009).

The neurochemical substrate involved in i) 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 (Marti et al. 2004).
However, the influence of N/OFQ upon DA system is controversial as other works have shown 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 (Di Giannuario and Pieretti 2000);

-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 nucleus accumbens. 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. (Murphy and Maidment 1999).

-In vivo microdialysis studies have shown a large increase of dopamine release (in the order of 350-390% of control values) in striatum when treating conscious rats with nociceptin at the micromolar concentration (Konia et al. 1998).

Finally, in his review Toll et al. (2016) 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 (Kuzmin et al. 2004). In particular, Florin et al. (1996) 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 (Crespi 2019).

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 (Marti et al. 2005; Crespi 2019). Facilitation of serotonergic transmission in the SNr enhances locomotion in rodents (Jacobs and Fornal 1997; Bata-Garcia et al. 2002) and both dopaminergic and serotonergic transmission is increased in the SNr and striatum during continuous motor execution (Bergquist et al. 2003, Pruett et al. 2013).

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 (Vaughan and Christie, 1996; Toll et al. 2016), and at cortical serotonergic nerve terminals, where N/OFQ inhibits 5-HT release (Mela et al. 2004; Tao et al. 2007).
It has been observed that local injection of N/OFQ into the hippocampus markedly decreased exploratory locomotor activity including vertical movements (rearing) in rats (Sandin et al., 1997). Furthermore, it has been shown that it elicits hypolocomotion in rats submitted to elevated plus maze and in the conditioned defensive burying test (Vitale et al. 2006).

Thus, our hypothesis is that continuous motor activity causes release of endogenous N/OFQ which therefore may act upon DA an then 5-HT release in the basal ganglia, as previously observed in the SN (Crespi 2019)**, 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 (Crespi 2002, 2017).515-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 (Crespi 2010a, 2013).

Furthermore, concomitant voltammetric and electrophysiological changes of the serotonergic system will be performed at two different levels: cell bodies (i.e. SNr, RDN) and relevant serotonergic nerve terminals i.e. amygdale, hippocampus, cortex, as previously described (Crespi 2002, 2010b, 2018).

Project Strategy

Animals

The difference between strains of rats has to be taken into consideration as it appears that
combined behavioral-voltammetric investigations suggest that "behavioral despair" is the process interesting Wistar rats when submitted to FST while "learning to be immobile" is the process involving Sprague-Dawley CD rats (Crespi 2010c).

Voltammetric Analysis and Behavior

Voltammetric analysis of 5-HT and DA release (Crespi et al. 1988, Crespi 2013, 2019) 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 (Calo et al. 2002) and the non-peptide compound J-l 13397 (Kawamoto et al., 1999) 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 (Crespi 2010a, 2013).

Concomitant electrophysiological analysis in cell bodies and relevant terminal areas in anaesthetised rats (Crespi, 2002) 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 behavioral effects induced by the NOP antagonist UFP-101 will be analyzed in rats subjected to the forced swimming test (FST) as previously described (Crespi 2002). 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:

I. Immobility time,
II. Swimming time,
III. 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 behavioral 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 (Sneddon 1973; Sthal 1977). 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 (Bianchi et al. 2002; Maurer-Spurej et al. 2004).

In 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.

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