Minireview

Tissue distribution of the opioid receptor-like (ORL1) receptor

Catherine Mollereau*, Lionel Mouledous
Institut de Pharmacologie et Biologie Structurale, 205 route de Narbonne, 31077 Toulouse, France
Received 25 October 1999; accepted 20 March 2000

Abstract

The ORL1 receptor is a G protein-coupled receptor structurally related to the opioid receptors, whose endogenous ligand is the heptadecapeptide nociceptin/orphanin FQ. In this review, data which have contributed to the mapping of the anatomic distribution of the ORL1 receptor have been collated with an emphasis on their relation to physiological functions. The ORL1 receptor is widely expressed in the central nervous system, in particular in the forebrain (cortical areas, olfactory regions, limbic structures, thalamus), throughout the brainstem (central periaqueductal gray, substantia nigra, several sensory and motor nuclei), and in both the dorsal and ventral horns of the spinal cord. Regions almost devoid of ORL1 receptors are the caudate-putamen and the cerebellum. ORL1 mRNA and binding sites exhibit approximately the same distribution pattern, indicating that the ORL1 receptor is located on local neuronal circuits. The ORL1 receptor is also expressed at the periphery in smooth muscles, peripheral ganglia, and the immune system. The anatomic distribution of ORL1 receptor suggests a broad spectrum of action for the nociceptin/orphanin FQ system (sensory perception, memory process, emotional behavior, etc.). © 2000 Elsevier Science Inc. All rights reserved.

Keywords: Neuropeptide; Nociceptin or Orphanin FQ; ORL1 receptor; G protein-coupled receptor; Anatomic distribution

1. Introduction

Using molecular screening methods based on opioid receptor gene sequences, an orphan G protein-coupled receptor was identified by several groups in human [50], murine [3,9,23,41,60,83,85], and porcine [64] species. It has been referred to as ORL1 (for Opioid Receptor-Like) receptor because, although it shares a high sequence similarity with the μ-, δ-, and κ-opioid receptors, it does not bind opioid ligands.

At the cellular level, the ORL1 receptor is coupled, as are the opioid receptors, to Gi/Go-protein mediated transduction systems: inhibition of adenylate cyclase, activation of an inwardly rectifying K⁺ conductance, and inhibition of voltage-sensitive Ca²⁺ channels. These intracellular effects contribute to inhibit the release of several neurotransmitters and, therefore, confer a neuromodulatory function on the ORL1 receptor (for review, see refs. 34 and 47 and this issue).

The endogenous ligand of the ORL1 receptor has been purified from rat [48], porcine [68], and bovine [62] brain by monitoring adenylate cyclase inhibition in ORL1-transfected cells. It was named both nociceptin, because of its apparent pronociceptive properties [48], and orphanin FQ [68]. As a classic neuropeptide, nociceptin/orphanin FQ is present as a single copy flanked by basic proteolytic cleavage sites, in a larger, highly conserved, precursor [48,51,61,70]. Nociceptin/orphanin FQ is a heptadecapeptide (Phe-Gly-Phe-Thr-Gly Ala-Arg-Lys-Ser-Ala-Arg-Lys-Leu-Ala-Asn-Gln) with N-terminal tetrapeptide reminiscent to that of the opioid peptides. Moreover, its basic core is similar to that of the κ-opioid receptor endogenous ligand, dynorphin. However, nociceptin/orphanin FQ binds to the ORL1 receptor with high affinity (Kd ≈ 0.1 nM) and interacts poorly with the opioid receptors, in part because of the presence of a phenylalanine residue at position 1 of the peptide in place of the tyrosine of opioid peptides [4,34,47,68]. Furthermore, in vitro and in vivo effects induced by nociceptin/orphanin FQ are not reversed by the opioid antagonist naloxone. To date, the only peptide reported to behave as an antagonist at the ORL1 receptor, the analog [Phe¹ψ(CH2-NH)Gly²]nociceptin-(1–13)-NH₂ [29], has however also been shown to have agonist properties both in vitro [5] and in vivo [27,87].
The identification of the endogenous ligand of the ORL1 receptor has been an important step assisting in the characterization of the physiological properties of the ORL1 receptor. Most of the behavioral studies in the central nervous system have focused on pain perception because of the analogy between the ORL1 and opioid receptors (for review, see refs. 13, 34, and 47 and this issue). While many findings are sometimes contradictory, it is clear that the supraspinal action of nociceptin/orphanin FQ on nociception is not opioid-like [13]. Hyperalgesia has been observed in various pain tests following central injection of the peptide [7, 48, 59, 68, 92]. However, this effect was expected to be due to a reversal of the analgesia induced by the stress of the intracerebroventricular (i.c.v.) injection itself [49]. Moreover, nociceptin/orphanin FQ has been shown to behave as a supraspinal functional anti-opioid peptide [28, 49, 79, 92]. In contrast, spinal administration of nociceptin/orphanin FQ in the rat can induce, as opiates do, a strong analgesia [18, 79, 88, 89] and, even potentiates morphine antinociception [79]. In addition, both stimulatory [21] and inhibitory [15, 59, 68] effects of nociceptin/orphanin FQ on motricity have been observed in mouse and rat. Furthermore, nociceptin/orphanin FQ has been implicated in memory processes [44, 45, 71], feeding, and hormonal regulation [47]. The peptide possesses also anxiolytic properties [36].

One means to obtain an insight into the complexity of the pharmacological actions of nociceptin/orphanin FQ, and to identify new physiological activities, is to analyze the tissue distribution of the peptide and its receptor. This review is a compilation of the various studies that have shown the ORL1 receptor to be widely expressed in the brain and spinal cord, a number of peripheral organs (intestine, vas deferens, arteries), and the immune system.

2. Anatomical distribution of the ORL1 receptor

Before the endogenous ligand of the ORL1 receptor was identified, the distribution of ORL1 transcripts in murine tissues was investigated by in situ hybridization studies [3, 23, 41, 50, 85] and Northern [9] and RT-PCR [83] analyses. Immunolocalization of the receptor protein, using a monoclonal antibody raised against the N-terminal extracellular domain of the rat ORL1 receptor, provided a detailed mapping of the rat brain [2] and spinal cord [52]. Following the identification of nociceptin/orphanin FQ, the ORL1 receptor distribution was confirmed by autoradiographic studies based, either on agonist-stimulated [35S]guanylyl-5’-O-(γ-thio)-triphosphate ([35S]GTPγS) G protein-binding [72–74], or routine binding procedures using [125I][Tyr14]nociceptin/orphanin FQ [22, 26] or [3H]nociceptin/orphanin FQ [20, 37]. Recently, a more complete analysis of the ORL1 receptor distribution in the rat brain has been reported, in which the ORL1 receptor binding and mRNA hybridization were exhaustively compared [56]. Analysis of nociceptin/orphanin FQ-stimulated and μ, δ, and κ opioid-stimulated [35S]GTPγS binding in the guinea pig brain, clearly shows the distribution of the ORL1 receptor to be unique. This may explain the different, and sometimes opposite, pharmacological effects of nociceptin/orphanin FQ and opioids [73]. Moreover, the ORL1 receptor distribution in the brain, in contrast to that of opioid receptors, appears to be the same in different species.

2.1. The periphery

2.1.1. Immune system

Aside from the nervous system, the immune system is one of the principal locations of the ORL1 receptor. mRNA transcripts have been detected in mouse splenic lymphocytes (CD4+; CD8+; CD4−; and CD8−) [31]. Many human immune tissues also express ORL1 mRNA: lymphocytic B and T cell lines, monocytes, and granulocytes, as well as circulating lymphocytes and monocytes [67, 86]. In both mouse [31] and human [86], lymphocyte activation led to the induction of ORL1 mRNA expression, suggesting an autocrine role in immunocompetence (antibody production, proliferation). Conversely, ORL1 receptor-specific antisense oligonucleotides block antibody production in stimulated lymphocytes [31]. However, ORL1 receptor-deficient mice fail to show abnormalities in their immune system [59].

2.1.2. Peripheral organs

The ORL1 receptor has clearly been identified in the peripheral nervous system and several isolated organs. RT-PCR techniques indicate that the ORL1 receptor is expressed in rat intestine and vas deferens [83] as well as porcine gastrointestinal tract and kidney [64]. ORL1 transcripts were also detected by RT-PCR in several guinea-pig ganglia [19, 39]; prevertebral sympathetic ganglia (coeliacosuperior mesenteric, inferior mesenteric), paravertebreal sympathetic ganglia (superior cervical, stellate, lumbar chain), and jugular ganglia. Finally, high affinity binding sites for nociceptin/orphanin FQ have been detected in the retina [42] and the heart [17] of the rat.

Even when the presence of ORL1 mRNA or receptors has not been directly demonstrated, it has been inferred by the non-opioid activity of nociceptin/orphanin FQ on isolated organs, or after local administration. The peptide induces vasorelaxation of isolated rat arteries [30] and inhibits contractions in isolated guinea-pig bronchus [69] and ileum [91], mouse vas deferens [69, 91], and rat bladder [24]. Furthermore, it potently contracts isolated rat [78] and mouse [63] colon. In all these tissues, the ORL1 receptor seems to be present in the peripheral endings of sensory, parasympathetic, and/or sympathetic nerves, where it exerts prejunctional modulation of mediator release (for review, see refs. 34 and 47 and this issue).
2.2. The brain

2.2.1. Rodent brain

The ORL1 receptor is densely expressed in layers II to VI of all cortical areas, the anterior olfactory nuclei, the CA1-CA4 fields of Ammon’s horn and the dentate gyrus of the hippocampus, and the amygdaloid nuclear complex [2,20,22,56,72–74]. The presence of functional ORL1 receptors has been demonstrated in rat cerebrocortical slices where nociceptin/orphanin FQ inhibits the potassium-evoked release of glutamate [58]. High expression of ORL1 mRNA and receptors was also detected in the septum nuclei, the bed nucleus of the stria terminalis, the nuclei of the diagonal band of Broca; NTS, nucleus of the solitary tract; POA, preoptic area; PTN, pedunculopontine tegmental nucleus; RM, raphe magnus; RME, median raphe; SN, substantia nigra; VTA, ventral tegmental area; ZI, zona incerta. Note that in the basal nucleus of Meynert, ORL1 mRNA and ORL1-like immunoreactivity are detected whereas there is no nociceptin/orphanin FQ binding. Adapted from ref. 13.

High expression of the ORL1 receptor and mRNA have been observed in many brainstem areas, including the substantia nigra, the ventral tegmental area, the interpeduncular nucleus, the locus coeruleus, the raphe complex (Fig. 1), the superior and inferior colliculi (Fig. 3), the central gray, and several sensory and motor nuclei located along the pons and medulla (sensory and motor trigeminal nuclei, facial nucleus, nucleus of the solitary tract, nucleus ambiguus, vestibular complex, nuclei of the reticular formation) [2,25,56] (Fig. 4).

The ORL1 receptor and mRNA are moderately expressed in the olfactory bulb and in the nucleus accumbens [56]. The weak immuno- and radio-detection in the nucleus accumbens correlates with sparse mRNA hybridization [50, 56] and low [35S]GTPγS binding stimulation [73] in this region. However abundant nociceptin/orphanin FQ binding sites have been detected in the nucleus accumbens of the mouse [20] and the rat [22], and injection of the peptide in this area stimulates food intake in the satiated rat [76].

The caudate-putamen, where μ and δ receptors are expressed, appears to be almost devoid of ORL1 mRNA [3,23,35,41,50,56,85] and receptors [2,56,74]. However, in rat striatum, nociceptin/orphanin FQ binding sites have been observed [42] and ORL1 mRNA have been detected using PCR techniques that are more sensitive than Northern blot and in situ hybridization methods [83]. Finally, the cerebellum contains only few deep nuclei with a high density of ORL1 mRNA [35,56] but poor ORL1 receptor expression [2,56].

A good correlation exists between nociceptin/orphanin FQ binding and ORL1 mRNA hybridization in most regions of the rodent brain [56], indicating that ORL1 receptors are predominantly located on local neuronal circuits, where...
they may exert a modulatory function. However, in some areas, including the hilus of the dentate gyrus, the basal nucleus of Meynert, the red nucleus, the basomedial amygdala, the pontine reticular nucleus, both ORL1 mRNA hybridization and ORL1-like immunoreactivity are present, whereas nociceptin/orphanin FQ binding is not detected, suggesting that the active ORL1 receptor is transported more distally [2,56]. In addition, mismatches thought to be due to limitations in the sensitivity of the detection techniques or to poor antibody specificity, are sometimes observed [56]. In the thalamus, most nuclei display high nociceptin/orphanin FQ binding, but very low ORL1 immunostaining and mRNA content [2,56]. In the central amygdaloid nucleus, ORL1-like immunoreactivity alone has been observed [2].

2.2. Human brain

Only one report has described the distribution of human ORL1 receptor transcripts in different brain regions using RT-PCR technique [67]. The highest amplification was observed in cortical areas (the frontal and temporal cortex, and to a lesser extent the parietal and occipital cortex). High amounts of ORL1 mRNA were also detected in the hypothalamus, mammillary bodies, the substantia nigra, and thalamus nuclei. The presence of $[^{125}I]_{Tyr^{14}}$ nociceptin/orphanin FQ high affinity ($K_d = 0.2$ nM) binding sites in human fetal hypothalamus membranes has been elsewhere described [43]. Transcripts have also been detected in limbic structures (the hippocampus and amygdala), brainstem (colliculi, the ventral tegmental area, the locus coeruleus), and the pituitary gland [67]. This distribution, which is similar to that of the rodents, suggests the participation of the ORL1 receptor in numerous human physiological functions, such as emotive and cognitive processes, neuroendocrine and sensory regulation, and autonomic functions. However, the main difference in human compared to rodents, is the high expression (similar to that observed in thalamus and hypothalamus) detected in the striatal structures (caudate, putamen) and the nucleus accumbens, regions known to be involved in the regulation of extrapyramidal motor pathways and in motivational behavior, notably drug abuse.

2.3. The spinal cord

ORL1 mRNA and receptors have been detected by hybridization (3,12,35,41,56,85) and immuno- (2,52) histochemistry and autoradiography [26,37,56] in the gray matter of both the dorsal and ventral horns throughout all of the rat spinal cord (Fig. 4).

In the superficial layers of the dorsal horn, immunostaining was observed in fiber processes, with the highest labeling levels in the lamina II [2]. Similarly, high affinity binding sites for $[^{3}H]$nociceptin [37] or $[^{125}I]_{Tyr^{14}}$nociceptin [26,56] were found in laminae II-IV, and, to a lesser extent, in laminae V-VII. Detection of ORL1 mRNA, although weak, in almost all neurons of these regions indicates that the bulk of the ORL1 receptors are located on interneurons of the dorsal horn where they may participate in the local regulation of pain transmission [35]. However, it cannot be excluded that ORL1 receptors are expressed on
the endings of central descending pathways and/or peripheral sensory afferences. In this respect, presence of strong ORL1 mRNA hybridization in the cell bodies of rat dorsal root ganglia [35,56,85] without ORL1 immuno- or radio-detection [52,56], suggests that the receptor is transported to either the sensory projections endings in laminae II and III, or to the nerve terminals in peripheral tissues (as discussed above).

In the ventral horn (laminae VIII-IX) of the rat spinal cord (Fig. 4), high level of ORL1 mRNA [35,50,56] and ORL1 immunolabeling [2] were observed, particularly in the cell bodies of large motoneurones. However, only moderate nociceptin/orphanin FQ binding was detected in these areas, suggesting that ORL1 receptors are transported distally [26,56].

3. Functional distribution of the ORL1 receptor

3.1. Distribution in relation to aminergic system

As illustrated in Fig. 1, it is of note that the ORL1 receptor is located in nearly all nuclear groups of the diffuse modulatory system, i.e. adrenergic/noradrenergic, cholinergic, dopaminergic, and serotonergic nuclei. It may therefore be involved in the modulation of amine release in the brain, and thus influence many important physiological functions.

3.1.1. Adrenergic nuclear groups

The locus coeruleus contains high levels of ORL1 mRNA and receptors [2,23,56] that have been shown to be coupled to inwardly rectifying K⁺ conductance [11]. Because this nucleus projects to multiple regions in the brain, the ORL1 receptor may modulate numerous autonomic and behavioral functions in response to exterior and stressful stimuli. The ORL1 receptor is also present in the nucleus of the solitary tract and the lateral reticular nuclei in the bulb [2,35,52,56]. These nuclei are involved in the control of vegetative functions such as arterial pressure, cardiac frequency, respiration, and endocrine regulation.

3.1.2. Cholinergic nuclear groups

ORL1 receptors have been detected in the basal anterior cholinergic complex of the brain in the core of the telencephalon (medial septum, vertical and horizontal limbs of the diagonal band of Broca, the basal nucleus of Meynert, the preoptic nucleus, the substantia innominata, the medial
habenula) and in the pedunculopontine tegmental nuclei. Cholinergic nuclei are connected to all cortical areas, hippocampus, thalamus and brainstem and are involved in attentional processes, learning, motricity control, and sensorial relay regulation in the thalamus. The amacrine cells of the retina also contain cholinergic neurons. As mentioned above, the presence of nociceptin/orphanin FQ binding sites has been demonstrated in the rat retina [42]. Moreover, the peptide is able to reduce the light-evoked release of acetylcholine from amacrine cells in the rabbit retina [57].

### 3.1.3. Dopaminergic nuclear groups

The expression of ORL1 receptors and mRNA in the substantia nigra suggests that nociceptin/orphanin FQ may modulate the nigro-striatal projections implicated in voluntary movement coordination. Detection in the ventral teg-
mental area indicates that the ORL1 receptor could influence the mesocorticollimbic system involved in motivational motricity, reward, mood, and cognition. Indeed, it has been recently demonstrated that injection of nociceptin/orphanin FQ in this area decreases dopamine release in the nucleus accumbens [55]. However, at this time, although the peptide has been recently reported to impair morphine-conditioned place preference in the rat [54], it has no intrinsic aversive or rewarding properties in the same test [14], and has no effect over heroin self administration [82]. Finally, in the dopamine neurons of the arcuate nucleus of the hypothalamus, nociceptin/orphanin FQ increases potassium conductance, suggesting that the ORL1 receptor may also regulate the dopaminergic hypothalamo-pituitary axis [81].

3.1.4. Serotonergic nuclear groups

The raphe complex, the sole locus of serotonin synthesis in the brain, expresses ORL1 receptors and mRNA, the dorsal raphe nucleus being the most enriched [2,41,56]. In this nucleus, it has been shown that nociceptin/orphanin FQ inhibits neuronal activity by opening inwardly rectifying K⁺ channels [80]. Together with the presence of ORL1 receptors in the locus coeruleus (as mentioned above), this suggests a role for the peptide in brain vigilance, sleep-wake cycle, and aggression control. Moreover, the presence of ORL1 receptors in the raphe magnus nucleus [2,52,56], the principal nucleus involved in the modulation of pain transmission by its spinal projection, provides a possible explanation of the supraspinal inhibitory action of nociceptin/orphanin FQ on opioid analgesia (see below).

3.2. Distribution in relation to limbic system

As shown in Fig. 2, all of the structures constituting the limbic system (the hippocampal formation, the septum, the bed nucleus of the stria terminalis, the diagonal band of Broca, the anterodorsal thalamus, the habenula, the amygdaloid complex) and associated hypothalamic areas, express ORL1 mRNA [3,41,50,85], ORL1 receptors [2,20,56], and exhibit strong nociceptin/orphanin FQ-induced GTPγS binding stimulation [72,74]. This distribution suggests that the ORL1 receptor may participate in the modulation of autonomic functions, instinctive and emotional behavior, and is consistent with the following pharmacological data.

The presence of functional ORL1 receptors in the hippocampal formation has been confirmed through the demonstration that nociceptin/orphanin FQ inhibits synaptic transmission and long-term potentiation in the rat dentate gyrus [90]. These results can be related both to the severe impairment of spatial learning in the Morris water task and the decrease in exploratory locomotor activity observed following injection of the peptide in the CA3 region [71]. Conversely, the facilitation of long-term potentiation in the CA1 region, and the enhancement of learning ability and spatial memory have been described in animals with a disrupted ORL1 receptor gene [45]. Together, these results emphasize the role of the ORL1 receptor in memory processes.

The dense labeling in the amygdaloid nuclei is particularly noteworthy since this complex is known to be involved in aggressive behavior, fear, and anxiety. Indeed, nociceptin/orphanin FQ impairs neuronal excitability in 98% and 55% of the cells in the rat lateral and central amygdala, respectively, suggesting that ORL1 receptors may contribute to the diminution of the fear response and stress [46]. This is consistent with the anxiolytic properties of nociceptin/orphanin FQ observed in different tests in mice and rats [36].

The ventromedial hypothalamus exhibits one of the densest levels of ORL1 mRNA and receptors in the brain [2,3,41,50,56,85]. Injection of nociceptin/orphanin FQ in this area stimulates food intake in the satiated rat [76]. It also induces lordosis behavior in the female [75]. Furthermore, oestrogen treatment increases the density of ORL1 receptors in this region [75], indicating a role for nociceptin/orphanin FQ in sexual and reproductive behavior. Intense ORL1 mRNA hybridization and moderate ORL1 receptor expression is also observed in the paraventricular nucleus of the hypothalamus, where nociceptin/orphanin FQ could modulate corticotropin-releasing factor secretion, thereby influencing the hypothalamic-pituitary-adrenocortical axis known to contribute to stress [13]. Injection of nociceptin/orphanin FQ in the supraoptic nucleus of the hypothalamus inhibits oxytocin and vasopressin neurons activity [16], which could be related to the diuretic and antinatriuretic effects of the peptide [38].

Finally, the presence of ORL1 receptors and mRNA in septum nuclei may also indicate that the ORL1 receptor is involved in reinforcement processes, since this area is one of the major autostimulation sites in the rat brain.

3.3. Distribution in relation to sensory perception

3.3.1. Auditory, visual and olfactory pathways

As illustrated in Fig. 3, ORL1 receptors and mRNA are found in nuclear relays implicated in auditory function: the dorsal and ventral cochlear nuclei, the superior olivary complex and the nucleus of the trapezoid bodies, the dorsal cortex of the inferior colliculus, and the temporal auditory cortex [2,3,20,35,56,73]. This distribution pattern suggests the participation of the nociceptin/orphanin FQ system in the acoustic reflex and the integrational processes that contribute to the spatial localization of sounds. It is further consistent with the observation that ORL1 receptor-knockout mice show an impaired hearing ability recovery following intense sound exposure, as compared to wild-type animals [59].

The contribution of the nociceptin/orphanin FQ system to visual function has not as yet been investigated. However, the ORL1 receptor is present in many vision-related areas, such as the retina, the nucleus of the optic tract, the lateral geniculate nucleus, the superior colliculus, the
Edinger-Westphal, oculomotor, trochlear and abducens motor nuclei, the visual striate cortex, and the suprabachismatic nucleus [2,3,20,35,42,56,73]. Expression in the motor nuclei innervating the pupil (Edinger-Westphal nucleus), and the eye and eyelid musculature (occulomotor, trochlear, and abducens nuclei, in which ORL1 mRNA hybridization levels are higher than protein expression), suggests that the ORL1 receptor is predominantly involved in the visual reflex rather than visual perception per se. In addition, the presence of high ORL1 expression levels in the superior colliculus, the nucleus that integrates not only visual, but also acoustic and sensorial perception, and from which the tectospinal tract originates, may indicate that the ORL1 receptor is involved in integrational processes that contribute to the spatial orientation of the head in relation to visual adjustment. Nociceptin/orphanin FQ binding sites are also detected in the rat suprabachismatic nucleus, the main brain center implicated in the regulation of the circadian rhythm [20,56]. The peptide inhibits 88% of the cells in this area, consistent with a reduction in the light-induced phase shift of the circadian activity rhythm in the hamster [1]. When considered alongside with the distribution of ORL1 receptors in the serotoninergic neurons (see above), it may be postulated that the ORL1 receptor regulates the vigilance/sleep state.

As shown in Fig. 3, components of the olfactory system, in particular the olfactory bulb, the anterior olfactory nuclei, the vomeronasal nerve, the nucleus of the lateral olfactory tract, the olfactory tubercule area, and the habenula, contain ORL1 receptors and mRNA [2,20,35,50,56,72].

3.3.2. Somatosensory perception

As illustrated in Fig. 4, ORL1 receptors [2,26,37,52,56] and mRNA [3,12,35,41,50,85] have been detected in many central regions (the dorsal horn of the spinal cord, intralaminar nuclei of the thalamus, the periaqueductal gray, brainstem nuclei, and the somatosensory parietal cortex) that are involved in extero- and proprioceptive sensitivity. In particular, ORL1 receptors are localized on both the main ascending (the spinothalamic and spinoreticular projections, the trigeminal system contributing to facial sensitivity) and descending (the periaqueductal gray, the raphe magnus nucleus, the reticular formation) pathways of pain processing.

The presence of ORL1 receptors in the superficial layers of the dorsal horn, known to participate in transmission and control of the sensory perception, is consistent with pharmacological findings that ORL1 receptor activation inhibits pain transmission in the spinal cord [18,79,88,89]. Interestingly, up-regulation of nociceptin/orphanin FQ binding sites has been observed in laminae I and II during persistent peripheral inflammation [37], or following tolerance induced by intrathecal morphine perfusion [26]. Moreover, there is much evidence to suppose that the mechanisms underlying ORL1-mediated spinal analgesia are supported by neuronal circuits different from those of opioid receptors. There is no co-localization of ORL1 and µ-receptor immunostaining in the superficial layers I-III of the dorsal horn [52], no cross tolerance between nociceptin/orphanin FQ and morphine spinal analgesia [32], and naloxone is unable to reverse nociceptin analgesia [18,88,89].

The parafascicular nucleus of the thalamus that receives the ascendental thermal and pain sensitive spinal projections from the lateral lemniscus, the principal sensory trigeminal nucleus where facial nociceptive information arrives, and the nucleus of the solitary tract that receives the visceral-sensitive projections of the vagus and glossopharyngeal nerves, all exhibit dense ORL1 immunolabeling [2] and contain high numbers of nociceptin/orphanin FQ binding sites [56].

In the brainstem (Fig. 4), ORL1 receptors are highly expressed in the periaqueductal gray, the nucleus raphe magnus, and the gigantocellular reticular nucleus, areas that have been implicated in the descending control of pain processing [52,56]. It may be postulated that ORL1 receptors present in these regions are responsible for the anti-opioid effect of supraspinal nociceptin/orphanin FQ administration. In agreement with this hypothesis, ORL1 receptor immunostaining has been detected in the periaqueductal gray, in a dense network of fibers distinct from those expressing µ-receptor labeling [52]. In addition, injection of nociceptin/orphanin FQ in this area inhibits morphine-induced antinociception by blocking the periaqueductal gray output neurons that receive information from opioid-sensitive neurons [53]. Finally, the anti-opioid effect of nociceptin/orphanin FQ has also been demonstrated in the rostral ventromedial medulla surrounding the nucleus raphe magnus. Infusion of the peptide here suppresses the indirect opioid-activated firing of «off»-cells, and thus blocks locally induced opioid analgesia without modifying the pain threshold itself [33]. Moreover, injection of nociceptin/orphanin FQ in the guinea pig periaqueductal gray, blocks glutamatergic projections of the anterior cingulate cortex relaying electrically elicited vocalizations that mimic the separation call emitted upon social isolation of the animal [40].

However, since the nuclei of the reticular formation, the nucleus of the solitary tract, the trigeminal nucleus and the dorsal horn of the spinal cord, are also implicated in the processing of sensorial information other than pain and thermal stimuli, involvement of the ORL1 receptor in the regulation of non-painful somatosensory perception cannot be excluded. In this regard, nociceptin/orphanin FQ has been shown to inhibit both noxious and non-noxious stimuli, and to depress excitatory amino acids-evoked firing, in sensitive neurons of the trigeminal nucleus caudalis, an area that relays wide somatosensory information from the orofacial region [84].

3.4. Distribution in relation to motor function

The ORL1 receptor has been found in central areas involved in motor control [2,56] (Fig. 4), notably regions of the extrapyramidal tract that have been implicated in motor...
coordination and posture control (the substantia nigra, the globus pallidus, and the subthalamic nuclei, although not the caudate putamen where expression is very low). Conflicting findings have been reported concerning locomotor behavior induced by central injection of nociceptin/orphanin FQ. Based on the anatomic distribution, it may be proposed that stimulatory action [21] is the expression of enhanced attention and exploratory behavior arising from the stimulation of the activatory ascendant reticular system (serotonergic raphe complex and adrenergic locus coeruleus). On the other hand, locomotor activity impairment causing ataxia and unsteady locomotion [15,68] is consistent with an action on the extrapyramidal system and on the brainstem reticular and motor nuclei, in particular those involved in balance control and muscular tone. In the medial vestibular nucleus of the brainstem, which contains ORL1 receptors and mRNA [2,56], nociceptin/orphanin FQ decreases neuronal activity in 86% of neurons in vitro. This effect correlates with a reduction of the vestibulo-ocular reflex in the vigilant rat upon i.c.v. administration of the peptide [77]. Finally, the presence of ORL1 receptors [2] and mRNA [35] in cell bodies of large motoneurones in the ventral horn, which receives the vestibulo- and reticulo-spinal tracts efferences, suggests also spinal ORL1 receptor control of movement.

Interestingly, the ORL1 receptor is highly expressed in many sensorymotor nuclei of the brainstem [2,56]. These include the motor trigeminal nucleus, the facial nucleus, and the nucleus of the hypoglossal nerve involved in the facial muscular control (Fig. 4) and the nuclei implicated in ocular movement as discussed above (Fig. 3). Also, in agreement with a number of pharmacological results, the circulatory and respiratory centers of the reticular formation, the nucleus of the solitary tract, and visceromotor nuclei such as the nucleus ambiguus and the dorsal nucleus of the vagus nerve (Fig. 4), all contain a high density of ORL1 receptors [2,56]. Indeed, inhibition of the cardio-motor neurons in the rat rostral ventromedulla by nociceptin/orphanin FQ has been reported to contribute to the central depression of arterial blood pressure and heart rate [10].

4. Conclusion

Anatomic data reveal that the ORL1 receptor is widely expressed in the brain, spinal cord, and peripheral nervous system. It is not present in brain structures associated with a single physiological function or neurotransmitter system, but is found in areas involved in various processes, among them, pain and sensory perception, memory, stress, motricity, hormonal regulation. This widespread distribution could reflect the association of the ORL1 receptor with a large number of physiological responses, or, more probably, that the ORL1 receptor contributes generally to homeostasis by modulating neuronal circuitry. This may explain why the disruption of the ORL1 receptor gene in mice has little obvious impact [59], and also why pharmacological effects of nociceptin/orphanin FQ are sometimes contradictory (e.g. in pain and locomotory tests), depending on the locus of injection and the dose, i.e. on the local neuronal circuitry recruited.

The anatomic distribution of the ORL1 receptor also reveals that pharmacological effects, other than those on which many studies have already focused, are worthwhile to explore. In particular, because the ORL1 receptor is present in many nuclei of the hypothalamus, the role of nociceptin/orphanin FQ in hormonal regulation should be further investigated. Studies of the effect of the peptide on aggression and mood may also be of value since the ORL1 receptor is expressed in the serotonergic raphe nuclei and in the amygdala. Implication in sleep is indirectly suggested by the presence of the ORL1 receptor in the suprachiasmatic nucleus and the raphe nuclei. Finally, since the ORL1 receptor is expressed in aminergic nuclei (Fig. 1), its involvement in human neuronal diseases such as breakdown, schizophrenia, Alzheimer’s and Parkinson’s diseases, and/or psychotropic processes merits further investigation.

Acknowledgments

We thank Drs J. M. Zajac, M. Roumy, S. Schiffmann, and J. C. Meunier for critical review of the manuscript and Dr C. Topham for language correction. C.M. is supported by the Centre National de la Recherche Scientifique and L.M. is supported by the Ministère de l’Éducation Nationale, de l’Enseignement Supérieur et de la Recherche.

References


