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Delta opioid receptors, learning and motivation

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Abstract

Delta opioid receptor (DOR) displays a unique, highly conserved, structure and an original pattern of distribution in the central nervous system, pointing to a distinct and specific functional roleamong opioid peptide receptors. Over the last 15 years, *in vivo* pharmacology and genetic models have allowed significant advances in the understanding of this role. In this review, we will focus on the involvement of delta opioid receptor in modulating different types of hippocampal- and striatal-dependent learning processes, as well as motor function, motivation and reward.Remarkably, DOR seems to play a key role in balancing hippocampal and striatal functions, with major implications for the control of cognitive performance and motor function under healthy and pathological conditions.

Keywords: associative learning, procedural learning, drug-context associations, hippocampus, striatum, GPR88

1. Introduction

The opioid receptorsbelong to the large family of G-protein coupled receptors (GPCRs) and include four members: mu (MOR), delta (DOR) and kappa (KOR) opioid receptors, as well as the opioid-receptor-like nociceptin/orphanin FQ receptor (NOP/ORL1). Four genes encode these receptors: *Oprm1*, *Oprd1*, *Oprk1* and *Oprl1*. Endogenous opioid ligands, namely enkephalins, dynorphins and endorphins, derive

from large precursor proteins encoded by three genes, *Penk*, *Pdyn*, and *Pomc*, respectively. The*Pnoc*gene encodes nociceptin/orphanin FQ, the endogenous ligand of NOP/ORL1.

Among opioid receptors, DORs display a highly conserved sequence of amino acids across vertebrate species, especially within transmembrane and intracellular domains. This is particularly true among mammals, for which differences in the 372-amino acid sequence occur essentially at the C-terminus level. Resulting variability in the number of phosphorylation sites suggests quantitative differences in the recruitment of intracellular signaling pathways.Such remarkable conservation of DOR sequence in mammalian species points to a strong selection pressure for this receptor, and highly preserved functions between species. When comparing DOR sequences between non-mammals and mammals, a major divergence can be found in the extracellular loops and the N-terminus domain. These differences indicate that a shift in DOR function has probably occurred during the evolution from non-mammals to mammals. Furthermore, differences at extracellular domains suggest that DOR interacts with different extracellular partners(ligands) in these animals.

Regarding intracellular signaling, DOR activation activates the Gi/Go-associated pathway (Childers 1991), which inhibits cAMP production (Pei et al. 1995), recruits β-arrestins(Cen et al. 2001), stimulatessignaling kinases such as ERK and src(Shahabi et al. 1999; Zhang et al. 1999), inhibits voltage-gated calcium channels (Buzas et al. 1998) and opens of inward rectifying K+ channels(Kovoor et al. 1997). DORs are then internalized (Ko et al. 1999) and recycled or degraded in lysosomes (Tsao and von Zastrow 2000).The recently resolved crystal structure of the human DOR reveals the presence of a sodium ion pocket, with sodium ions acting as positive allosteric modulators of the receptor(Fenalti et al. 2014). Interestingly, this sodium binding pocket would play a role in β-arrestin signaling, which suggests that fine tune signaling of DORs could be more complex than initially stated.

2. Brain expression of the delta opioid receptors: hints for multiple roles in brain function

DORs are broadly expressed in the brain.Their distribution was assessed using either *in situ* hybridization (ISH) to localize neuronal cell bodies expressing *Oprd1* transcripts, or ligand autoradiography and fluorescent DORs (DOR-eGFP) to detect the receptors themselves. In this review, we will focus on ISH data to provide a summarized view of cerebral DOR distribution, based on literature (Mansour et al. 1995; Mansour et al. 1994; Mansour et al. 1993) and open resources (Allen Brain Atlas: http://www.brain-map.org/), having in mind that experimental data show only few mismatches between DOR mRNA and protein distribution(Erbs et al. 2015; Kitchen et al. 1997; Pradhan and Clarke 2005;

Scherrer et al. 2006; Slowe et al. 1999).Interestingly, the general pattern of DOR distribution appears highly informativeregarding the multiple roles proposed for these receptors in brain function (Figure 1).

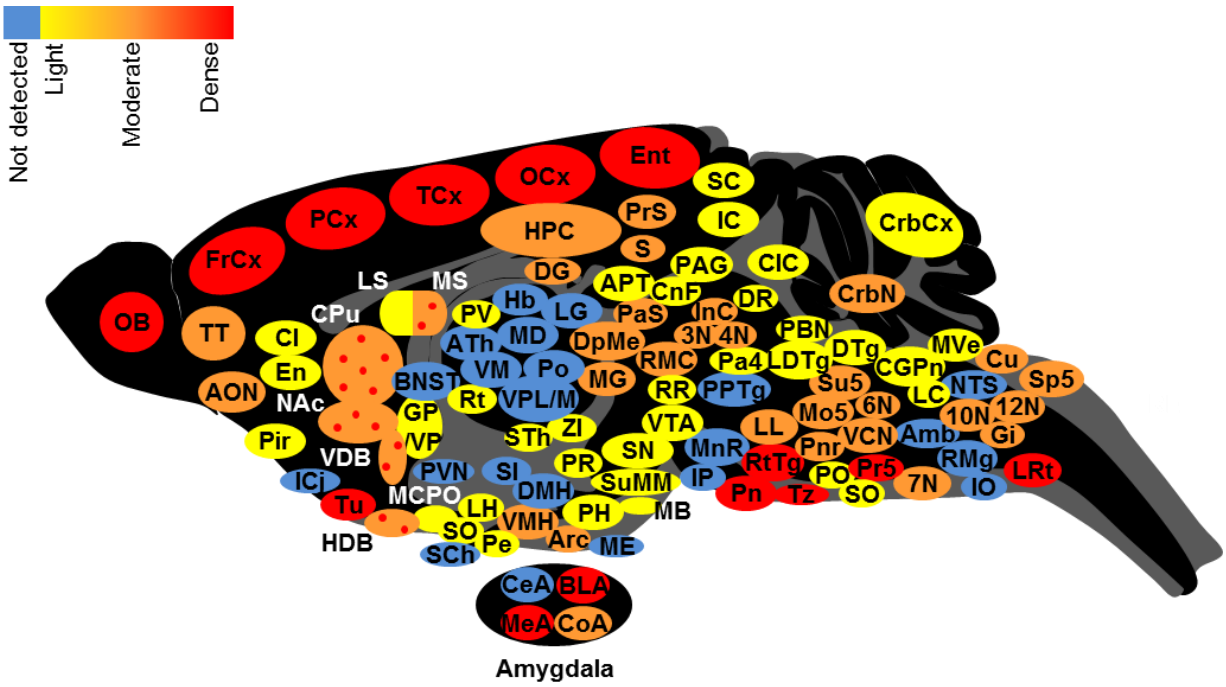

Figure 1.Distribution of *Oprd1* transcripts in the brain.Intensity of expression varies from low (blue) to high (red) (see scale for intermediate colors). In striatal regions, septum and diagonal band, red dots depict particularly high level of expression in cholinergic neurons. Abbreviations - 3N: oculomotor nucleus, 4N: trochlear nucleus, 6N: abducens nucleus, 7N: facial nucleus, 10N: dorsal motor nucleus of vague, 11N: accessory nucleus, 12N: hypoglossal nucleus, Amb: ambiguus nucleus, AON: anterior olfactory nucleus, APT: anterior pretectal nucleus, Arc: arcuate hypothalamic nucleus, Ath: Anterior thalamus, BLA: basolateral nucleus of the amygdala, BNST: bed nucleus of the stria terminalis, CeA: central nucleus of the amygdala, CGPN: central gray of the pons, CI: claustrum, CIC: central nucleus of the inferior colliculus, CnF: cuneiform nucleus, CoA: cortical nucleus of the amygdala, CPu: caudate putamen, CrbCx: cerebellar cortex, CrbN: cerebellar deep nuclei, Cu: cuneate nucleus, DG: dentate gyrus, DMH: dorsomedial nucleus of the hypothalamus, DpMe: deep mesencephalic nucleus, DR: dorsal raphe nucleus, DTg: dorsal tegmental nucleus, En: endopyriform cortex, Ent: entorhinal cortex, FrCx: frontal cortex, Gi: gigantocellular reticular nucleus, GP/VP: globus pallidus/ventral pallidum, Hb: habebula, HDB: nucleus of the horizontal limb of the diagonal band, HPC: hippocampus, IC: inferior colliculus, Icj: Islands of Calleja, InC: interstitial nucleus of Cajal, IO: inferior olive, IP: interpeduncular nucleus, LC: locus coeruleus, LDTg: laterodorsal tegmental nucleus, LG: lateral geniculate nucleus, LH: lateral hypothalamus, LL: lateral lemniscus, LRt: lateral reticular nucleus, LS: lateral septal nucleus, MB: mammillary bodies, MCPO: magnocellular preoptic nucleus, MD: mediodorsal nucleus of the thalamus, ME: medial eminence, MeA: medial nucleus of the amygdala, MG: medial geniculate nucleus, MnR: median raphe nucleus, Mo5: motor trigeminal nucleus, MS: medial septal nucleus, Mve: medial vestibular nucleus, NAc: nucleus accumbens, NTS: nucleus tractussolitarius, OB: olfactory bulbs, Ocx: occipital cortex, Pa4: paratrochlear nucleus, PAG: periaqueductal gray, PaS: parasubiculum, PBN: parabrachial nucleus, PCx: parietal cortex, Pe: periventricular nucleus of the hypothalamus, PH: posterior nucleus of the hypothalamus, Pir: piriform cortex, Pn: pontine nuclei, Pnr: pontine reticular nucleus, PO: paraolivary nucleus, Po: posterior thalamic nuclear group, PPTg: pedunculopontine tegmental

nucleus, PR: prerubral field, Pr5: principal sensory trigeminal nucleus, PrS: presubiculum, PV: paraventricular nucleus of the thalamus, PVN: paraventricular nucleus of the hypothalamus, RMC: red nucleus, magnocellular part, RMg: raphe magnus nucleus, RR: retrorubral nucleus, Rt: reticular nucleus of the thalamus, RtTg: reticulotegmental nucleus of the pons, S: subiculum, SC: superior colliculus, SCh: suprachiasmatic nucleus, SI: substantia innominate, SN: substantia nigra, SO: supraoptic nucleus, Sol: nucleus of the solitary tract, Sp5: spinal trigeminal nucleus, STh: subthalamic nucleus, Su5: supratrigeminal nucleus, SuMM: supramammillary nucleus, TCx: temporal cortex, TT: tenia tecta, Tu: olfactory tubercule, Tz: nucleus of the trapezoid body, VCN: ventral cochlear nucleus, VDB: nucleus of the vertical limb of the diagonal band, VM: ventromedial nucleus of the thalamus, VMH: ventromedial nucleus of the hypothalamus, VPL/M: ventral posterolateral/posteromedial nuclei of the thalamus, VTA: ventral tegmental area, ZI: Zona incerta.

*Oprd1*transcripts are prominentlyexpressed in cortical regions, including whole neocortex (frontal, parietal, temporal and occipital), where expression is preferentially detected in median layers, cortical regions of the amygdala (basolateral, cortical, and medial nuclei – BLA, CoA and MeA, respectively), claustrum (Cl), endopiriform (En) and entorhinal (Ent) cortices, subiculum (S), presubiculum (PrS) and parasubiculum (PaS), as well as dorsal and ventral hippocampus (HPC) and dentate gyrus (DG). This is consistent with previously demonstrated implication of DORs in high order cognitive functions, such as decision making and associative learning(Laurent et al. 2015; Le Merrer et al. 2013)and emotional processes such as anxiety (Filliol et al. 2000; Perrine et al. 2006).

In the subcortical forebrain, hotspots of *Oprd1* expression are found in the medial septum (MS) and diagonal band of Broca (ventral: VDB and horizontal: HDB, see Figure 1) and striatum (caudate putamen and nucleus accumbens – CPu and NAc, respectively), with a remarkable punctiform distribution strikingly matching this of mRNAs coding for choline acetyltransferase (*Chat*), an enzyme necessary for the synthesis of acetylcholine (Ach). Puncta of high *Oprd1* mRNA levels in these regions indeed correspond to cholinergic interneurons (striatum) or projecting cholinergic neurons (MS, VDB and HDB)(Bertran-Gonzalez et al. 2013; Gazyakan et al. 2000; Le Moine et al. 1994; Scherrer et al. 2006). In the striatum, however, *Oprd1* expression is not restricted to these puncta, in agreement with expression in other cell types(Jiang and North 1992; Scherrer et al. 2006). Expression in the MS and diagonal band of broca suggests that DOR activity can fine-tune cholinergic projections to the hippocampus, further supporting a role in associative (spatial) learning. High levels of *Oprd1* transcripts in striatal regions point to a role of DORs in locomotion, motor coordination, motor skill learning and impulsivity (CPu), motivation and reward (NAc). Interestingly, a third region enriched in *Oprd1* transcripts is the pons, with high levels of expression detected in the pontine nucleus (PN)and adjacent reticulotegmental nucleus (RtTg). These two nuclei receive information from the motor regions of the cortex and project to the deep cerebellar nuclei (CrbN, where *Oprd1* mRNA expression is also high), which in turn project to

thecerebellar cortex (CrbCx, where *Oprd1* transcripts are detected in the external layer of gray matter, in the surroundings of Purkinje cells),and thus contribute to motor control and motor skill learning.Finally, mRNAs coding for DORs are found particularly abundant in the lateral reticular nucleus (LRt), a brain stem nucleus receiving inputs from dorsal spinal cord and projecting to the cerebellum, also critically involved in motor function(Alstermark and Ekerot 2013). Together these anatomical data thus suggest thatDORs play a major role in motor control.

High levels of*Oprd1* mRNAs are detected all along the olfactory tract, including olfactory bulbs (OB), anterior olfactory nucleus (AON), taenia tecta (TT), piriform cortex (Pir), olfactory tubercle (Tu), MeA,vendromedial nucleus of the hypothalamus (VMH) up to the entorhinal cortex. Such location suggests a role for DORs in odor perception and processing. Similarly, *Oprd1* transcripts are also present along the auditory pathway, in the cochlear (CN) nucleus, in the nucleus of the trapezoid body (Tz), the superior olivary nucleus (SO), the lateral lemniscus (LL), the inferior colliculus (IC) and finally the medial geniculate nucleus (MG). Thus DORs are very likely involved in the control of auditory perception and processing. In line with a role of DORs in sensory processing, *Oprd1* mRNAs can be detected throughout the midbrain and brain stem in the origin nuclei of cranial nerves (cranial nerve III: oculomotor nucleus - 3N; IV: trochlear nucleus - 4N; V: motor trigeminal nucleus - Mo5, principal sensory nucleus - Pr5, spinal trigeminal nucleus - Sp5; VI: abducens nucleus - 6N; VII: facial nucleus - 7N; X: dorsal motor nucleus of vagus - 10N; XII: hypoglossal nucleus – 12N, but not ambiguusnor solitarius nucleus – Amb and NTS, respectively), all parts of the parasympathetic system and thus sharing a cholinergic nature. Of note, DOR thus appears frequently and highly expressed in cholinergic neurons. Lastly, *Oprd1* mRNAcan be found in the cuneate nucleus whichcarries proprioceptive information from the upper body as part of the posterior column-medial lemniscus pathway, further pointing toa participation in sensory perception.

In the midbrain, *Oprd1* transcripts are present in the substancianigra (SN) and ventral tegmental area (VTA), red nucleus (magnocellular part, RMC), deep mesencephalic nucleus (DpMe), periaqueductal gray (PAG) and dorsal raphe nucleus (DR).Among these, SN, RN and DpMe are involved in motor control(Rodriguez et al. 2001), VTA and DR in motivation and reward, and PAG in anxiety and pain processing. The lowest levels of *Oprd1* expression are detected in the diencephalon. *Oprd1*is expressed in the paraventricular and reticular nuclei of the thalamus (PV), as well as zona incerta and subthalamic nucleus, another key structure for motor control. *Oprd1* transcripts are more abundant in the hypothalamus, with hot spots detected in the VMH and arcuate nucleus (Arc). Regions of low but detectable expression include the magnocellular preoptic nucleus (MCPO), the lateral, periventricular

and posterior hypothalamicnuclei (LH, Pe and PH), the supraoptic(SO) and supramammillary (SuMM) nuclei, and mammillary bodies (MB). Interestingly, several of these regions are involved in the control of sexual behavior (MCPO, LH, Pe,VMH), endocrine function (Arc, SO, Pe), reward (LH, SuMM) and memory (MB), arguing for a role of DORs in these different functions.

Altogether, anatomical data draw a remarkable picture of DORlocation in the brain, suggestive of major roles in controlling cognitive, learning and memory processes, motor function, motivation and reward, anxiety and sensory/pain processing. Interestingly, this distribution pattern is original among opioid receptors, although overlaps exist with mu and kappa opioid distributions (Erbs et al. 2015; Le Merrer et al. 2009;Mansour et al. 1995), pointing to a unique, distinct role for DORs in brain function.

3. Delta opioid receptors and place/associative learning

Abundant expression of DOR in the hippocampus and tightly connected structures such as subiculum, entorhinal cortex or septal area(Figure 1) points towards a crucial role of these receptors in hippocampus-dependent place/associative learning. Pharmacological data have strongly supported the notion that stimulating or inactivating delta opioid receptors impacts memory performance. Delta opioid receptor agonists administered peripherally either facilitate (Martinez et al. 1984; Pavone et al. 1990; Yang et al. 2003) or impair (Jutkiewicz et al. 2003; Martinez et al. 1984; Schulteis and Martinez 1990; Ukai et al. 1997)avoidance or operant learning, while the preferential delta antagonist ICI 174,864 improves retrieval of avoidance conditioning in mice (Ilyutchenok and Dubrovina 1995; Schulteis and Martinez 1990). These studies, however, have not addressed the role of DORs in different learning paradigms, such as place/associative learning versus conditioning or motor skill learning, known to rely on distinct neurobiological mechanisms and brain substrates. Moreover, a major concern when using pharmacology is the possible cross-reactivity of delta agonists and antagonists with other opioid receptors, especially mu opioid receptors (Hutcheson et al. 2001; Scherrer et al. 2004). In this context, gene knockout, either total or partial, represents a unique tool to address the physiologic role of delta opioid receptors.We will summarize here what the study of mice lacking the *Oprd1* gene and other genetically modified animals has taught us about the role of DOR in modulating spatial/associative learning and memory processes and discuss about the neurobiological substrates underlying this role. We will focus on hippocampus-dependent behavioral responses, having in mind that brain regions directly or indirectly connected to the hippocampus are likely to also contribute to these behaviors.

3.1. Spatial navigation andplace learning

We explored learning and memory abilities in mice lacking the delta opioid receptor gene, *Oprd1*$^{-/-}$ animals(Filliol et al. 2000). We used behavioral tasks known to challenge hippocampal function to assess associative learning performance(Le Merrer et al. 2013). In a three phase-novel object recognition paradigm, we evidenced that *Oprd1* gene deletion impairs selectively recognition of object location and spares novel object recognition. Such selective impairment suggests hippocampal dysfunction (Ennaceur et al. 1997; Mumby et al. 2002;Oliveira et al. 2010). Importantly, acute peripheral administration of the delta opioid receptor antagonist naltrindole (0.3 mg/kg) similarly impaired recognition of object location in WT mice, indicating that deficient spatial abilities in *Oprd1*$^{-/-}$animals results primarily from absent DOR signaling and not from developmental adaptations. In a dual solution cross-maze task, mutant mice performed at similar levels as their WT counterparts but took longer to adopt an allocentric strategy, another behavioral landmark of hippocampal dysfunction in rats and mice (Deipolyi et al. 2008; Packard 2009; Packard and McGaugh 1996). Together, these data clearly point for a crucial role of DOR activity in mediating spatial learning and memory processes, which are known to depend on hippocampal functional integrity.

Remarkably, behavioral data collected from a completely distinct mouse line, animals lacking the orphan receptor GPR88 (*Gpr88*$^{-/-}$), further support the hypothesis of such a role for DORs. GPR88 is a striatal-enriched gene critically involved in modulating dopamine neurotransmission and striatal physiology (Logue et al. 2009; Quintana et al. 2012). We created a Gpr88$^{-/-}$ mouse line and investigated the impact of Gpr88 gene deletion at multiple levels. We examined several molecular and cellular end points and revealed increased [35S]-GTPγS binding mediated bythe selective delta agonist SNC-80 in the striatum of *Gpr88*$^{-/-}$ mice, suggestive of facilitated DOR function, at least in this region. We also explored a vast repertoire of behavioral responses in *Gpr88*$^{-/-}$ mice using extensive phenotyping(Meirsman et al. 2016). We noticed that behavioral features of these mutants remarkably oppose several aspects of *Oprd1*$^{-/-}$ mice phenotype, notably regarding spatial navigation/learning. Indeed, when freely exploring a Y-maze, GPR88-lacking animals showed a trend toward higher spontaneous alternation and returned significantly less into the same arm, indicative of less perseverative errors. In a three-phase novel object recognition paradigm, these mutants performed better in recognizing object location. In a dual solution cross-maze task, *Gpr88*$^{-/-}$ mice not only shifted sooner from an allocentric to an egocentric strategy but also reached higher levels of performance than WT controls. Moreover, when *Gpr88*$^{-/-}$ mice were promptedto reverse their choice in the cross-maze, they learnt this novel rule more rapidly than control animals. Together, the data suggest facilitated hippocampus-dependent place learning in mutant animals.To test the involvement of DOR (hyper)activity in such phenotype, we evaluated whether

chronic inhibition of DORs using the antagonist naltrindole (0.3 mg/kg subcutaneous) would normalize behavior in GPR88 null mice. During Y-maze exploration, chronic naltrindole normalized spontaneous alternation in *Gpr88*$^{-/-}$ mice, by increasing significantly the number of same arm returns. This result suggests that excessive DOR signaling participates in facilitating spatial learning in these mutants.Altogether, behavioral and pharmacological data collected from *Oprd1*$^{-/-}$ and *Gpr88*$^{-/-}$ animals thus indicate that,under physiological conditions, DOR activationeases spatial navigation and place learning.

3.2. Drug-context associations

Interestingly, deficient spatial learning in mice lacking DORscould account for their impairmentindrug-induced conditioned place preference (CPP) when spatial cues are prominent (Chefer and Shippenberg 2009; Le Merrer et al. 2012; Le Merrer et al. 2011), by precluding drug/context associations(Luo et al. 2011). Involvement of DOR in drug reward and seekingwill be discussed in a later section (4.2.3.). Place conditioning is a form of stimulus–outcome learning commonly used to assess the motivational effects of psychoactive drugs. It is based on the observation that animals will learn to approach or avoid distinct spatial environments that have previously been associated with rewarding (place preference-CPP) or aversive (place aversion) drug effects, respectively(Cunningham et al. 2011).Others and we showed that CPP induced by morphine administration is reduced in *Oprd1*$^{-/-}$ animals (Chefer and Shippenberg, 2009; Le Merrer et al, 2012b; Le Merrer et al, 2011). Accordingly, peripheral pre-treatmentwith the DOR antagonist naltrindole (0.3 mg/kg) before conditioning sessions was shown to abolish morphine-induced CPP (Chefer and Shippenberg 2009). These results indicate disruptive effects of DOR blockade on morphine-induced place conditioning. Several pieces of evidence argued at this stage for deficient drug/context associations rather than reduced morphine reward in DOR null mice. First, deficient place conditioning was also observed in these mutantswhen using an aversive stimulus, lithium chloride injections (3mEq/kg), indicating that such deficit was not reward specific. Second, *Oprd1*$^{-/-}$animals were able to display place preference or aversion when tested under the effects of the drug used for conditioning (morphine or lithium, respectively), signifying state dependency (Le Merrer et al. 2012; Le Merrer et al. 2011). State-dependency qualifies a behavioral response that can only be retrieved when the animal experiences thesame (drug) state as during the acquisition of this response (Overton 1978). Interoceptive drug cues (internal state induced by drug exposure) can then function as conditioned stimuli and contribute to contextual information together with external cues. State dependent morphine- or lithium-inducedplace conditioning in*Oprd1*$^{-/-}$mice thus indicates that these animals, and

not their WT counterparts,need both internal and external cues to express place preference or aversion. As long as such cues are available, however, DOR null micecan express preference for morphine-paired environment, indicating that they indeed experience morphine reward.Consistent with this, they were able to acquire intravenous (Le Merrer et al. 2011) as well as intra-VTA (David et al. 2008) morphine self-administration.

Interoceptive drug cues,interestingly,are not the only cues that DOR knockout animals can use to overcome their deficit inplace conditioning. We showed that circadian time or auditory cues, whether predicting morphine injection or feeding (in food-deprived animals), could alsoserve *Oprd1*$^{-/-}$animals as contextual triggers to express place conditioning(Le Merrer et al. 2012). Of note, circadian, drug and auditory cues share a non-spatial nature, and as such should not require hippocampal functional integrity. These data further support our demonstration of deficient hippocampal-dependent learning in *Oprd1*$^{-/-}$mice by evidencing their blunted ability to form drug-context associations and/or retrieve such associations, and the alternative strategies they can use to express their preference.Accordingly, place conditioning to nicotine is also impaired in DOR null animals(Berrendero et al. 2012). No modification of cannabinoid-induced CPP was detected in these animals, though, possibly due to higher number of conditioning sessions (Ghozland et al. 2002) that may have facilitated drug/context associations.

Consistent with place conditioning data, studies investigating other types of context-induced conditioned responses to drugs further support the hypothesis of deficient drug-context associations in mice lacking DORs. Indeed, when *Oprd1*$^{-/-}$ animals were re-exposed to an experimental context previously paired with morphine injections (see protocol in (Faget et al. 2012)), they failed to demonstrate context-induced somatic signs of withdrawal (Figure 2).High global score in vehicle-treated mutants likely reflected elevated basal levels of anxiety in these animals (Filliol et al. 2000). Regarding context-induced locomotion, however, DOR null mice, as well as micetreated with a DOR antagonist, show increased sensitization to the locomotor effects of morphine (Chefer and Shippenberg 2009), demonstrating preserved drug-context associations. In these experiments, however, the animals were tested under the effects of the drug, and thus likely displayed a state-dependent locomotor response to morphine. Conditioned activity (locomotor activity induced by exposure to the drug-paired context, in the absence of the drug) would need to be assessed in these animals to verify this point. Of note, increased locomotor sensitization to morphine in mutants may reflect enhanced motivation for the drug, as suggested by increased breaking points when tested (drug-free) for extinction of morphine self-administration(Le Merrer et al. 2011).Regarding context-induced drug seeking, we review and discuss

relative experimental data in a later section (4.2.2). Together, previous data concur to demonstrate that drug/context associationsare impaired in *Oprd1*$^{-/-}$mice, likely due to hippocampal dysfunction.

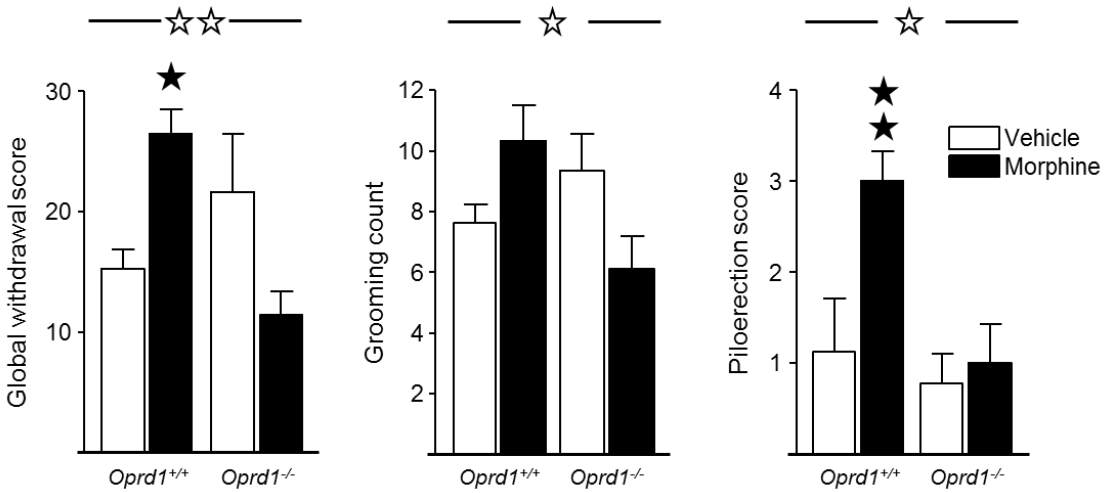

Figure 2. Conditioned signs of withdrawal from morphine in *Oprd1*$^{-/-}$ and their WT controls. The animals (*Oprd1*$^{+/+}$: n=8-10 per treatment, *Oprd1*$^{-/-}$: n=8 per treatment) received daily injections of morphine (30 mg/kg) for 6 days and were immediately placed in Plexiglas transparent boxes, as previously described (Faget et al. 2012). Mutant mice fail to display somatic signs of withdrawal when exposed to the morphine-paired context under drug-free conditions. Global withdrawal score - genotype x treatment: $F_{1,32}$= 758.7, p<0.01. Grooming count - genotype x treatment: $F_{1,32}$= 69.5, p<0.05. Piloerection – Genotype: $F_{1,32}$= 8.6, p<0.01, Treatment: $F_{1,32}$= 7.9, p<0.05, genotype x treatment: $F_{1,32}$= 6.2, p<0.05. Black stars: treatment effect; open stars: treatment x genotype interaction.

3.3. Hippocampal DORs: implications for associative learning

3.3.1. Functional role of DORs in the hippocampus

Anatomical and pharmacological data concur to demonstrate that DORs can locallymodulate hippocampal function. These receptors are indeed abundantly expressed in the hippocampus (Crain et al. 1986; Le Merrer et al. 2009; Mansour et al. 1995),in GABAergic interneurons (Rezai et al. 2012; Scherrer et al. 2006; Svoboda et al. 1999) where they act presynaptically to inhibit GABA release (Piskorowski and Chevaleyre 2013; Rezai et al. 2012) and consequently favor disinhibition of principal glutamatergic cells (Lupica 1995). Further electrophysiological studies have shown that pharmacological activation of DORs induces long-term depression of parvalbumin-expressing GABA interneurons within CA2 (Piskorowski and Chevaleyre 2013) and inhibits the excitatory temporoammonic pathway from the entorhinal cortex to CA1 (Rezai et al., 2013). Accordingly, enkephalins, among endogenous ligands of DORs, are released in the lateral perforant path(Chavkin et al. 1985), where DOR activation contributes to high frequency-induced long-term potentiation (LTP),possibly by transiently reducing GABA

transmission (Bramham et al. 1991),and thusto hippocampal-dependent learning. Furthermore, DORs also play a role in the induction of LTP in dentate granule cells (Xie and Lewis 1995). Thuspharmacological or genetic inactivation of DORs in the hippocampus seems to prevent their endogenous ligands from inhibiting GABAergic interneurons, which makesinhibition of pyramidalcellsmore likely and thus reduces probability for LTP, a plausible mechanism for impaired associative learning.Under physiological conditions, activation of DORs in the hippocampus, conversely, would ease hippocampal function and facilitate spatial/associative learning.

Interestingly, this proposition is in agreement with gene expression data showing increased transcription of *Oprd1* in the hippocampus of rats trained for a spatial discrimination task (Robles et al. 2003). Moreover, when re-exposingDOR e-GFP mice to an environment previously paired with repeated morphine injections, we observed somatic signs of withdrawal, indicating drug-context association, and activation of hippocampal DORs as visualized by their internalization *in vivo*(Faget et al. 2012). Theseexperiments unravel a recruitmentofhippocampal DORs during the processing of spatial cues.

3.3.2. DORS and hippocampal gene expression

To identify potential molecular mechanisms underlying impaired associative learning in *Oprd1*$^{-/-}$ mice, we quantified the expression of 67 genes of interest in the dorsal hippocampus of mutants as compared to wild type controls using quantitative real time Polymerase Chain Reaction (qRT-PCR). Interestingly, transcript levels of *Grin1* and *Grin2a,* coding for GluN1 (NR1) and GluN2A (NR2A) subunits of NMDA glutamate receptors, respectively, were low in *Oprd1*$^{-/-}$ mice(Le Merrer et al. 2013). These two subunits are crucial for spatial learning in mice (Bannerman et al. 2008; Korotkova et al. 2010; Place et al. 2012).We also detected low hippocampal mRNA levels of several genes known for their enriched expression in medium spiny neurons (MSNs - *Bcl11b/Ctip2*, *Arpp21*, *Foxp1*, *Gpr6*, *Hpca*, *Pde10a*, *Penk*, *Pdyn*, *Tac1*). Among them, *Pdyn, Penk*and*Tac1* code for neuropeptides (dynorphin, enkephalin, substance P, respectively) participating in the control of hippocampal activity (McDermott and Schrader 2011; McQuiston 2011; Ogier et al. 2008). *Bcl11b/Ctip2* is involved in postnatal neurogenesis and granule cell differentiation, and its deletion in the forebrain impairs spatial learning (Simon et al. 2012). *Hpca*encodes a calcium binding protein, hippocalcin, that contributes to neuronal plasticity (Jo et al. 2010). The functional roles of *Arpp21*, *Foxp1*,*Gpr6* and*Pde10a*in the hippocampus have not been explored yet or remain poorly understood(Giralt et al. 2013)despite demonstrated expression in this structure (low for *Gpr6*, see Allen Brain Atlas). In contrast, increased expression of several genes such as *Grm1* (coding metabotropic glutamate receptors mGluR1) and *Chat* (coding for the Ach synthesizing

enzyme choline acetyltranferase) may reflect compensative processes aiming at restoring hippocampal function (Aiba et al. 1994). Together, these data indicate that DOR deletion significantly impacts gene expression in the dorsal hippocampus, and these transcriptional modifications likely contribute to impair hippocampal function in mutant mice.

We similarly explored gene transcription in the dorsal CA1 of *Gpr88*$^{-/-}$ mice. *Gpr88* expression is too low to be detected in the hippocampus(Allen Brain Atlas). Nevertheless, deletion of this gene resulted in modified levels of transcripts for a few genes in the CA1: expression of *Ache* (coding the Ach degrading enzyme acetylcholinesterase) was down regulated, whereas expression of*Gabra4* (alpha4 subunit of the GABA receptor)*, Foxp1* (forkhead box P1*), Wfs1* (wolframin)and *Oprd1* wereupregulated(Meirsman et al. 2015). Interestingly, decreased levels of acetylcholinesterase(Hasselmo and Sarter 2011) and increased expression of wolframin(Kitamura et al. 2014; Sutt et al. 2010) may contribute to facilitate hippocampus-dependent associative learning in *Gpr88*$^{-/-}$ mice. Most importantly, increased *Oprd1* expression could also contribute to this facilitation, in agreement with augmented transcription in the hippocampus of rats trained for a spatial task (Robles et al. 2003). Moreover, pharmacological blockade of DORs normalized spatial alternation rates in *Gpr88*$^{-/-}$ mice, pointing to excessive DOR activity in these animals as an underlying mechanism of their increased spatial memory performance, although involvement of striatal DORs should not be excluded. In conclusion, these data provide further evidence for a crucial role of hippocampal DORs in underlying spatial/associative learning processes.

3.3.3. Extra-hippocampal DORs and associative learning

Not only DORs in the hippocampus canplay a role in modulating hippocampus-dependent place and associative learning but also DORs in other regions.Indeed, these receptors are highly expressed in several direct or indirecthippocampal input or output regions, such as the enthorinal, perirhinal and prefrontal cortices, subiculum and septal area, all key brain sites for learning and memory(Dickerson and Eichenbaum 2010; White and McDonald 2002). DOR expression is also particularly high in the striatum, which functionally competes with the hippocampal formation to drive behavior (Ghiglieri et al. 2011; Packard 2009).However, although hippocampal lesion/inactivation facilitates dorsal striatal function (Middei et al. 2004; Schroeder et al. 2002), striatal lesion/inactivation fails to conversely facilitate hippocampus-dependent spatial learning (Castane et al. 2010; De Leonibus et al. 2007; Jacobson et al. 2012). This lack of reciprocity may result from differential implication of subpopulations of striatal medium spiny neurons (MSNs). Indeed, striatal deletion of the adenosine A2a receptor (*Adora2a*) gene, which expression is significantly enriched in D2R-MSNs(Heiman et al. 2008), decreases D2R-MSN

excitability and facilitates spatial learning (Wang et al. 2006; Wei et al. 2011; Zhou et al. 2009). However stimulation of DORs in the dorsal striatum seems to repress D1R-MSN activity instead (see section 4.3.1.), making unlikely their involvementin facilitating hippocampus-dependent processes.

4. Delta opioid receptors, motor function, response learning, motivation and reward

*Oprd1*gene is highly expressedinmultiple brain regions involved in motor control, including the striatum (CPu and NAc), motor cortical areas, STh, GP, SN, PN, RtTg, RN, LRt and cerebellum (Figure 1). Such distribution clearly designates DORs as key actors of motor function. Their role, however, appears complex, as suggested by the diverging effects of DOR ligands on motor responses. Indeed, DOR agonist SNC80 stimulates locomotor activity while other agonists fail showing such effect (Jutkiewicz et al. 2005; Le Bourdonnec et al. 2008; Le Bourdonnec et al. 2009; Nozaki et al. 2012; Saitoh et al. 2011). DOR antagonists were shown to relieve dyskinesias induced by chronic L-DOPA administration or neuroleptics (Henry et al. 2001; McCormick and Stoessl 2002). Conversely, DOR agonists were shown to improve dyskinesia in 6-hydroxydopamine (6-OHDA)hemilesioned rats, although depending on the dose (Mabrouk et al. 2009; Mabrouk et al. 2014). Discrepancies would notably lie in the brain structures primarily targeted by pharmacological compounds, such as GP versus SN (Mabrouk et al. 2009), andin differential affinity of the compounds for presynaptic versus postsynaptic receptors.

Besides their presence in motor circuits, DORs are also highly expressed in multiple brain regions modulating motivation and reward, such as the medial prefrontal cortex, NAc, VP, VTA, SuMMand LDTg (Figure 1), suggesting that DORs contribute to these processes. Consistent with this, pharmacological data have long suggested that MORs and DORs would play overlapping roles in mediating reward processes (Le Merrer et al. 2009). Major evidences were that DOR agonists can elicit CPP(Longoni et al. 1998; Morales et al. 2001; Shippenberg et al. 1987; Suzuki et al. 1997) and increase consumption of palatable substances (Baldo and Kelley 2007), whereas antagonists alter cocaine and nicotine self-administration (Ward and Roberts 2007), attenuate CPP to cocaine, methamphetamine or morphine (Chefer and Shippenberg 2009; Menkens et al. 1992; Suzuki et al. 1994) and reduce heroin and cocaine self-administration (Martin et al. 2000). In these studies, however, DORligandsmay have produced part of their effects via activation of MORs(Hutcheson et al. 2001; Scherrer et al. 2004).In this context, genetically modified mice proved to be useful by allowing researchers to assess the consequences of DOR inactivation independently from that of MOR.

In this section, we will focus primarily on data obtained from mice lacking DOR or other genetically modified animals and compare with pharmacological data whenever pertinent. We will discuss the

consequences of invalidating DOR on various behavioral responses for which functional integrity of the striatal regions, CPu and/or NAc, is necessary,although not sufficient, as these responseslikely involve other brain sites within motor or reward circuits where DORs are also abundant.

4.1. Locomotion and motor function

4.1.1. Basal locomotion and interest for novelty

Striatal regions are key brain sites involved in controlling locomotion and exploration(Do et al. 2012; Palmiter 2008). Deletion of the *Oprd1* gene or chronic pharmacological blockade of DOR leads to hyperlocomotion in mice (Filliol et al. 2000; Le Merrer et al. 2013). This hyperactivity fails to habituate over repeated testing (Filliol et al. 2000), although mutant mice perform as well as wild-type animals at recognizing novelty. Indeed, *Oprd1*$^{-/-}$ mice displayed similar preference for, and hyperactivity in,the novel versus familiar compartment of a place conditioning apparatus (Le Merrer et al. 2011). Furthermore, mutants visited the novel object more often during the object phase in a three-phase paradigm of object recognition (Le Merrer et al. 2013). Such facilitated novel object recognition suggests that novelty is more attractive to DOR null mice(Ennaceur 2010). Consistent with this idea, under low light conditions (15 lux), when levels of anxiety in the elevated plus-maze were similar between WT and mutant animals, *Oprd1*$^{-/-}$ mice made more head dips (Le Merrer et al. 2013), suggestive of increased novelty seeking and risk-taking behavior in these mutants. Therefore, increased locomotor activity in mice lacking DORs could result from impaired habituation, a landmark of hippocampal deficit, together with increased interest for novelty, pointing towards facilitated striatal activity.

4.1.2. Response and motor skilllearning

Striatal regions are critically involved in mediating procedural/response and motor skill learning(Graybiel 2008; Packard 2009;Packard and McGaugh 1996). Strikingly, such learningprocesses had been poorly explored in *Oprd1*$^{-/-}$ mice, despite high levels of expression in striatum. We thus examined whether DOR deletion would affect striatum-dependent learning by performing two behavioral assays. We first used a single solution response task in the cross-maze, which solely requires a striatal-dependent egocentric strategy (response learning)(Packard 2009). Second, we tested WT and mutant mice in an accelerating rotarod task to assess skill motor learning, a form of procedural learning that was shown to tightly depend on dorsal striatum functional integrity (Dang et al. 2006; Durieux et al. 2009).

In the cross-maze,*Oprd1*$^{-/-}$ mice developed a response strategy more rapidly than WT animals under a single-solution response paradigm. This result suggests that the control of response learning is facilitated in mutants (Packard 2009; Packard and McGaugh 1996), most likely via the lateral dorsal striatum (Lovinger 2010). However, increased motivation to gain a food reward might have contributed to improve performance of mutants in this task (see 4.2.1). We thus further assessed striatal-dependent behavior using a motor skill learning task, which does not engage food seeking. *Oprd1*$^{-/-}$ mice indeed performed better than controls on the accelerating rotarod. Lateral dorsal striatal circuits are critically involved during motor skill learning (Lovinger 2010; Yin et al. 2009). Therefore our data concur to indicate that dorsal striatal function is facilitated in mice lacking delta opioid receptors.

We also assessed striatum-dependent behaviors in *Gpr88*$^{-/-}$ mice, which display elevated striatal DOR activity. Interestingly, they failed to acquire a motor skill learning taskon the accelerating rotarod, demonstrating a major impairment in striatal function (Meirsman et al. 2015; Quintana et al. 2012). Chronic administration of the DOR antagonist naltrindole alleviated this motor skill learning deficit,butat an early stage only, when motor learning depends on the D2 dopamine receptor-bearing medium spiny neurons (D2R-MSNs) of thedorsal striatum(Durieux et al. 2012).This particular time course of naltrindole effects suggests that excessive DOR activity in *Gpr88*$^{-/-}$ mice could compromise motor skill learning by affectingthe activityof striatal D2R-MSNs. Together, behavioral data from *Oprd1*$^{-/-}$and *Gpr88*$^{-/-}$ mice consistently point to an inhibitory influence of DORs on striatum-dependent response and skill learning processes.

4.2. Motivation, decision making and reward

4.2.1. Motivation for food, food reward and decision making

Dorsal and ventral striatum play a crucial role in regulating reward and motivation for food (Richard et al. 2013). Whereas the involvement of MORs in these processes has been extensively explored, little is known about a potential role of DORs, although the prevailing idea seems to be that MORs and DORs mayplay overlapping roles(Bodnar 2004; Nogueiras et al. 2012).Consistent with this, pharmacological studies have shown that DOR agonists increase the intake of palatable substances (Baldo and Kelley 2007). However, DOR antagonists, injected systematically or locally in brain areas, fail to consistently decreasepalatable food intake(Bodnar et al. 2005; Katsuura and Taha 2014; Khaimova et al. 2004; Levine et al. 1994; Miner et al. 2012). In this context, the study of mice bearing genetic invalidation of *Oprd1*wasuseful to disentangle DOR from MOR function in motivation for food and food reward.

Weassessed motivation for food in *Oprd1*$^{-/-}$ mice using two behavioral tests(Le Merrer et al. 2013). In a runway task, latency to reach sucrose reward tablets was not modified in mutant animals as compared to WT controls when the mice were confined in the end box for 20s. When this confinement was omitted, however, knockout mice obtained more sugar pellets than WT mice, by eating and coming back faster to the start box. This result suggests increased food seeking in mutants. Of note, we omitted confinement in this experiment to reduce anxiety levels, elevated in *Oprd1*$^{-/-}$ mice (Filliol et al. 2000). We propose that, in these animals, high levels of anxiety (avoidance) compete with high motivation for food (approach) to drive behavior(Aupperle and Paulus 2010; Montgomery 1955;Powell et al. 2004). By reducing anxiety in the straight alley test, we may have unmasked the latter. Consistent with this, in a novelty-suppressed feeding (NSF) experiment, *Oprd1*$^{-/-}$animals took as long as WT controls to start eating in the arena, but approached food pellets (lab chow) more often, and retreated, revealing conflicting avoidance and approach behaviors (Powell et al. 2004). Moreover, in the same task, *Dlx5/6*-CreX*Oprd1*$^{fl/fl}$(Dlx-DOR) mice, which do not express DOR in GABAergic neurons of the forebrain, and do not display high levels of anxiety (maybe due to preserved DOR expression in the amygdala), started quicker than controls to eat food in the arena (Chu Sin Chung et al. 2015).We have previously shown that latency to eat in the NSF test tightly correlates with Fos expression in the CeA, whereas the amount of food consumed when back in the home cage clusters with Fos immunostaining in the VTA (Becker et al. 2014), which illustrates, at neurobiological level, conflictual avoidance/approach behaviors in this task. Interestingly, after the NSF assay, Fos expression was reduced in the CeA (as well as BLA) and tended to be increased in the VTA (significantly increased in the NAc) of Dlx-DOR mice, suggesting that removing DORs in GABAergic neurons of the forebrain both reduced avoidance (anxiety levels) and increased approach (motivation/reward). Together, these data suggest that DORs' activity, notably in the forebrain, represses motivation for food (palatable or not).

The fact that DORs likely decrease motivation for food does not necessary imply that they influence food reward in the same direction. Indeed, preference for sucrose reaches similar levels in *Oprd1*$^{-/-}$mice and WT controls (Olmstead et al. 2009). Ceiling effect (about 95% preference), however, likely made difficult to detect increased preference inmutants. In contrast with genetic deletion, pharmacological blockade of DORs in the ventral pallidum was shown to increase saccharine palatability and consumption(Inui and Shimura 2014), while DOR inhibition in the NAc increased consumption of a sucrose solution under an anticipatory contrast paradigm(Katsuura and Taha 2014). DORs may thus exert an inhibitory control on food reward as well, especiallythose expressed in the ventral pallidum and NAc.

Interestingly, *Oprd1* deletion fails to significantly impact operant learning for food. *Oprd1*$^{-/-}$animals are able to acquire an instrumental task to earn food or sucrose reward with similar levels of performance as WT controls (Gutierrez-Cuesta et al. 2014; Laurent et al. 2012; Olmstead et al. 2009).Also, Dlx-DOR mutants performed similarly to controls in acquiringchocolate-flavored pellet self-administration (Chu Sin Chung et al. 2015). Surprisingly, however, they displayed lower breaking points under a progressive-ratio schedule of reinforcement, suggestive of decreased motivation to work for this palatable food.Interestingly, *Oprd1*$^{-/-}$ mice similarly displayed a marked tendency for decreased breaking points when tested for their motivation to earn sucrose pellets under aprogressive-ratio paradigm (Gutierrez-Cuesta et al. 2014).Of note, this was unlikely to result from deficient hippocampal function, as lesioning the HPC instead produces an increase in breakpoints for food(Schmelzeis and Mittleman 1996). How to reconcile increased approach of food in NSF and straight alley with decreased breakpoints for a sweet reward under a progressive ratio schedule of reinforcement in total or conditional DOR null mice will require further investigation.

Once instrumental learning for food reward was acquired, DOR null mice were tested for impulsivity. Remarkably, these animals showed difficulties in withholding their motor response to obtain sucrose reward(Olmstead et al. 2009). This result could have reflected increased motivation for food, as evidenced previously(Le Merrer et al. 2013). Strikingly, however, comparable difficulties in waiting for a defined temporal interval to elapse were observed in rats with hippocampal lesions (Bannerman et al. 1999). Indeed, hippocampus is involved in controlling temporal memory (in the sense of temporal processing - succession of events -, not circadian cues), likely through an inhibitory influence on the dorsal striatum (Yin and Meck 2014; Yin and Troger 2011). Remarkably, *Oprd1*$^{-/-}$ miceunderestimated 15 s and 45 s target durations in a bi-peak procedure,as evidenced by proportional leftward shifts of the peak functions, and similarly to mice with cytotoxic lesions of the dorsal hippocampus (Yin and Meck 2014). These results support the hypothesis of altered hippocampal function in DOR null mice and indicate that these animals may have difficulties in performing operant tasks when accurate timing is required, by triggering premature responses. In conclusion, impaired timing performance in DOR null mice is a more convincing candidate explanation for their increased motor impulsivity than increased motivation for food, although the latter cannot be ruled out.

Finally, DOR activity seems necessary for a previous reward experience to influence decision making. Pavlovian incentive learning, which mediates the excitatory and inhibitory effects of conditioned stimuli (CS) based on learned associations, can influence instrumental performance. The behavioral test called pavlovian to instrumental transfer (PIT) allows assessing the impact of such influence(Corbit and Balleine

2015). When tested in this paradigm, *Oprd1*$^{-/-}$ mice failed to increase their instrumental responding during presentation of the specific outcome-predicting stimulus (CS), proving a significant deficit in PIT (Laurent et al. 2012). Consistent with this, the DOR antagonist naltrindole abolished outcome-specific PIT in rats when injected systematically or into the shell, but not the core,of the NAc (Laurent et al. 2014; Laurent et al. 2012). Remarkably, DOR-eGFP knock-in mice trained for predictive pavlovian responding displayed more DOR at the somatic membrane of cholinergic interneurons (CINs) of the NAc shell. This increase correlated positively with conditioned response and later PIT performance, as well as with increased variance in action potential firing ofCINs in the NAc shell (Bertran-Gonzalez et al. 2013). Connections between BLA and NAc shell are likely to be involved in this process, as their interruption causes severe impairment in outcome-specific PIT (Shiflett and Balleine 2010). Of note, BLA is one of the brain regions where DORs are the most intensively expressed (Allen Brain Atlas: http://www.brain-map.org/, (Mansour et al. 1995; Scherrer et al. 2004). Together, these results thus point to a key role of DORs in modulating ongoing goal-directed behavior based on previous reward exposure.

As a conclusion, data collected from DOR null micesuggest thatDOR exertsan inhibitory influence on motivation to obtain a food reward and possibly on food reward *per se*, but facilitate the influence of previous pavlovian reward learning on instrumental choice performance. Invalidation of the *Oprd1* gene in restricted brain regions or neuronal populations would be useful to further explore the role of DORs in these processes. Interestingly, the notion that DOR activity may, under certain conditions, antagonize MOR-mediated effects on reward has emerged in the literature, and questions the role of the former in drug addiction.

4.2.2. Drug reward and seeking

Animal studies using multiple models of drug exposure have drawn a complex, sometimes inconsistent, picture of DORs' role in drug reward and seeking. The dominant view appears to be that DORs would play a similar, although less critical, role than MORs in mediating these processes(Klenowski et al. 2015; Le Merrer et al. 2009). However two major concerns should be acknowledged that may have rendered functional dissociation between MORs and DORs in these processes particularly challenging. First, pharmacological tools available to target opioid receptors often lack specificity (Hutcheson et al. 2001; Scherrer et al. 2004). Second, a major difficulty when assessing drug reinforcement in animal models lies in the tight intertwining of reward and learning processes. Indeed, most animal models used to evaluate the rewarding properties of drugs also assess conditioned learning abilities (Stephens et al. 2010), and as such may notably involve hippocampus-dependent processes (Luo et al. 2011). Thus

discrepancies between reports regarding the involvement of DORs in drug reward may reflect differential recruitment of learning processes depending on the experimental paradigm. We previously discussed the case of place preference studies, relying on drug/context associations, impaired in *Oprd1*$^{-/-}$ animals. Such impairment, however, does not exclude an effect on drug reward *per se*. We will discuss in this section the case of self-administration and drug seeking experiments. The formerrely on operant learning, preserved in mice lacking DORs, and may thus provide useful information regarding the effects of DOR inactivation on drug reward. The latter involves both motivation for the drug and conditioning to various cues, and thus may illustrate the integrative role of DORs in these processes.

As regards self-administration studies, pharmacological investigations have evidenced a role for DORsin drug reinforcement/reward that depends on the drug tested (cocaine, nicotine, opiates or alcohol), the route of administration (systemic, intracerebroventricular, intracerebral) and, when relevant, the targeted brain region (Klenowski et al. 2015). Studies using DOR null mice confirmed discrepancies depending on the drug. Indeed, *Oprd1*$^{-/-}$ mice showed difficulties in acquiring cocaine or nicotine self-administration under a fixed ratio schedule of reinforcement (FR3 and FR1, respectively), reaching lower final rates of administration, and consistently achievedlower breakpoint under a progressive ratio schedule(Berrendero et al. 2012; Gutierrez-Cuesta et al. 2014). However, *Oprd1* deletion did not prevent animals from self-administering morphine either systematically(Le Merrer et al. 2011) or into the VTA(David et al. 2008).Instead, increased breakpoints for intravenous morphine self-administration under a progressive-ratio schedule of reinforcement suggest a higher motivation for the drugin these animals (Le Merrer et al. 2011). Finally, *Oprd1*$^{-/-}$ mice self-administered more alcohol in a two-bottle choice paradigm (Roberts et al. 2001). Together, these studies suggest that cocaine and nicotine, and not morphine or alcohol, have diminished reinforcing properties in DOR null mice as compared to WT controls.Differences in drug-induced anxiety may account for these discrepancies. Cocaine and nicotineshare psychostimulant properties, and as such can increase anxiety levels. These effects may detour *Oprd1*$^{-/-}$animals, which are highly anxious under basal conditions(Filliol et al. 2000), from consuming these drugs but not narcotics, such as morphine or alcohol. Consistent with this hypothesis, a positive correlation was found between voluntary alcohol consumption in mutants and their levels of anxiety(Roberts et al. 2001). This result suggests that DOR null mice would self-administer alcoholat least in part to relieve their excessive anxiety. In this context, the study of Dlx-DOR mice (conditional DOR deletionin forebrain GABAergic neurons) represents a promising tool to disentangle increased motivation for drugs from relief of anxiety after *Oprd1* deletion, as these animals display low levels of anxiety as compared to controls but high motivation to reach food in the NSF test (Chu Sin

Chung et al. 2015). Further studies using local/population-specific invalidation of *Oprd1*would be needed to better understand the role of DOR in drug self-administration.

As regards drug seeking, systemic pharmacological blockade and complete *Oprd1* knockoutboth result in decreased drug reinstatement. Systemic DOR antagonist administrationreduced alcohol-seeking behavior elicited by drug-associated environmental stimuli in rats (Ciccocioppo et al. 2002; Marinelli et al. 2009), discrete cues (Marinelli et al. 2009) oryohimbine injections (Nielsen et al. 2012). Accordingly,*Oprd1*$^{-/-}$micedisplayeddiminished cue-induced reinstatementof cocaine seeking following extinction. Furthermore, the enhancement of Fos expression triggered by cocaine reinstatement was attenuated in the dorsal striatum (CPu) and CA1 of these animals(Gutierrez-Cuesta et al. 2014). Thesedata furtherdocumenthippocampal dysfunction in *Oprd1*$^{-/-}$ mice and suggest that DOR activity in the hippocampus facilitates the influence of drug-paired cues to induce reinstatement of drug taking. DOR in the NAc, however, may play a different role. Indeed, intra-NAc administration of naltrindole failed to inhibit cocaine-primed reinstatement of cocaine seeking after extinction (Simmons and Self 2009)and significantly increased cue-induced cocaine-seeking behavior in rats following 24-hr abstinence(Dikshtein et al. 2013).After 30 days of abstinence, DOR blockage had no longer effects on cocaine seeking by itself, but was able to prevent β-endorphin from repressing such seeking (Dikshtein et al. 2013). These last results unravel a braking activity of NAc DOR on motivation to obtain a drug of abuse, in agreement with data suggesting a similar effect on motivation for food(Le Merrer et al. 2013). Additional studies will however be required to further explore the role of different brain populations of DOR in modulating motivation for natural or drug reinforcers.

4.3. DOR in the striatum: implications for motor function, response learning, motivation and reward

4.3.1. Functional role of DORs in the striatum

Striatal regions, dorsal (CPu) and ventral (NAc), display high levels of DOR expression (see Figure 1). In the mouse striatum, DOR transcripts were predominantly found in cholinergic interneurons (CINs),where receptor expression appears confined to the soma and proximal dendrites (Bertran-Gonzalez et al. 2013; Le Moine et al. 1994;Scherrer et al. 2006). Activation of DOR on these neurons produces a decreaseinAch release(Gazyakan et al. 2000). A small proportion of striatal DORcan also be detected in GABAergic (inter)neurons (Scherrer et al. 2006)and in presynaptic glutamatergic terminals (Jiang and North 1992). Finally, molecular phenotyping of medium spiny neurons (MSNs) expressing either D1 or D2 dopamine receptors (D1R and D2R, respectively) revealed a significant enrichment in *Oprd1* transcripts relative to

the rest of the brain, but no difference between these two populations of MSNs (Heiman et al. 2008). DOR in the striatumis thus also present on MSNs, where they can fine-tune dopamine transmission (Figure 3).Such distribution makes difficult to understand the functional consequences of DOR activation in the striatum, namely facilitation or inhibition ofstriatal outputs, and, eventually, which of these outputs, D1R-bearing striatonigral or D2R-bearing striatopallidal pathway, is affected. Genetically modified animals provided some cues to answer these questions.

Mice lacking DOR acquired faster a response strategy in a cross-maze and a motor skill on the accelerating rotarod(Le Merrer et al. 2013), suggesting that dorsal striatum activity would be eased in these animals (Durieux et al. 2012; Lovinger 2010). DOR activity in this region would therefore exert a braking influence on striatal function. Dorsal striatum, however, exerts a population-selective control over locomotion and motor control, D1R- and D2R-bearing MSNs being involved in distinct aspects of these functions. In order to test the reactivity of the striatonigral and striatopalllidal pathways in *Oprd1*$^{-/-}$ mice, we assessedthe effects of D1/D5 or D2/D3 dopamine receptors agonist administration on locomotor activity (that recruits preponderantly the dorsal part of the striatum and the NAc core) in these animals and their WT controls. We observed higher sensitivity to the locomotor stimulating effectsof theD1/D5 agonist SKF-81297 in mutants. Together, our resultssuggest that dorsal striatal function in DOR null mice is biased towards facilitated D1R-expressing striatonigral output. Importantly, chronic naltrindole administration similarly facilitated the locomotor stimulant effects of SKF-81297 in WT animals, indicating that blocking DOR signaling is sufficient to facilitatestriatonigral activity, independently from neurodevelopmental adaptations(Le Merrer et al. 2013).Finally, the locomotor effects of SKF-81297 were also found increased in Dlx-DOR mice, confirming the involvement of forebrain DOR in these processes(Chu Sin Chung et al. 2015). Together, these data point to an inhibitory role of DOR in the dorsal striatum on D1R-bearing MSNs, likely through DOR activation at postsynaptic level (resulting in D1R-MSN hyperpolarization)although inhibition of excitatory glutamatergic afferencesshould also be considered (see Figure 3). Of note, an effect at D2R-expressing MSNs cannot be excluded (Le Merrer et al. 2013).

The picture isdifferent as regards DORs in the NAc, and notably in the shell sub-region. Remarkably, pavlovianconditioning increased DOR expression within the somatic membrane of CINs in the NAc shell of DOR-eGFP mice. This effect correlated with the level of conditioned responding and was accompanied by higher irregular/burst firing in CINs but no change in their action potential frequency (Bertran-Gonzalez *et al*., 2013). Increased burst firing variability would result in decreased Ach release at MSNsand thus reduce the Ach-induced bias toward cortical activation of D2R-bearing MSNs(Ding *et al*.,

2010). Activation of DOR in the NAc shell following pavlovian training could then indirectly facilitate the activity of D1R-bearing MSNs. Moreover, genetic deletion of *Oprd1* and systemic or intra-NAc shell injection of naltrindole abolished pavlovian to instrumental transfer (PIT) in mice and rats, respectively (Laurent et al. 2014; Laurent et al. 2012). PIT was similarly suppressed by intra-NAc shell pharmacological blockade of D1Rs, showing its dependence on D1R-bearing MSNs(Laurent et al. 2014). These results indicate that, under conditions where DOR is highly expressed on CINs, their activation biases NAc shell function towards facilitated D1R-bearing MSN output. Which DOR tone, at CINs or at post-synaptic MSNs, prevails under basal conditions or following other forms of learning, however,remains to be explored.

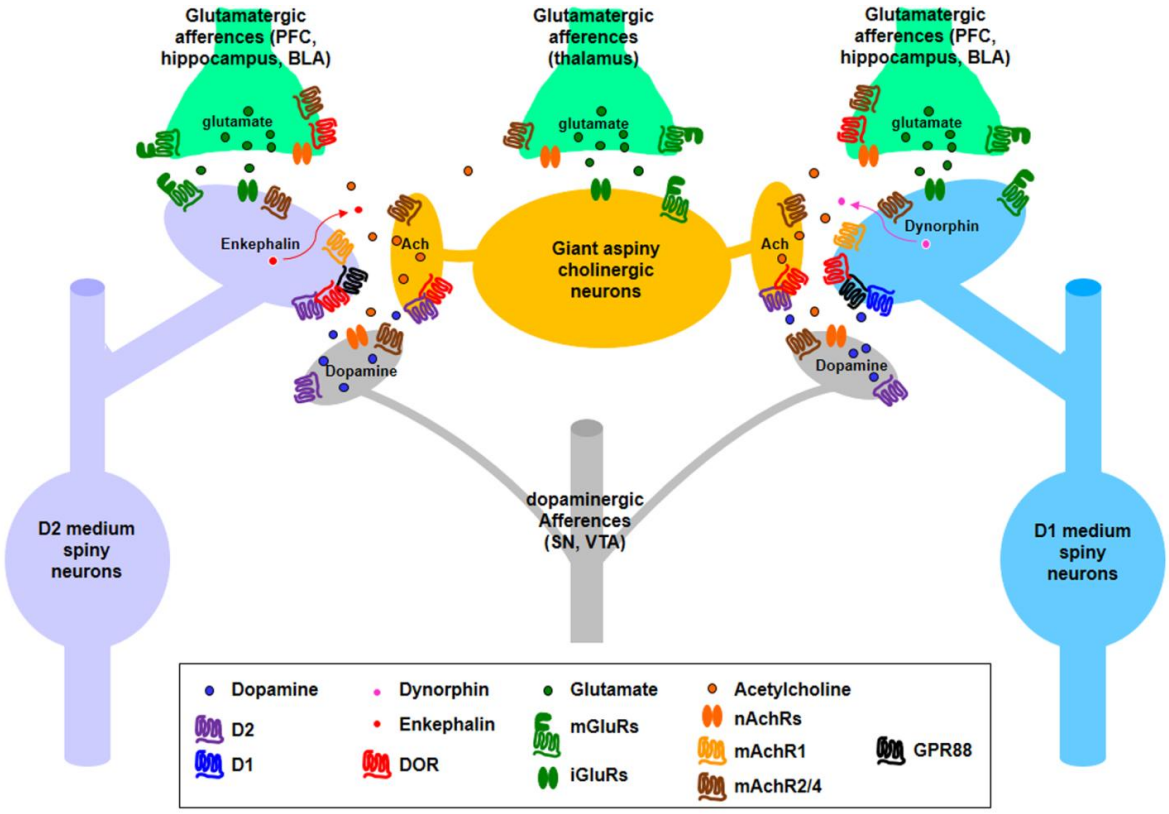

Figure 3.Schematic representation of the localization of DORs and some potential GPCR partners within local striatal microcircuitry.DORs are expressed at pre- or post-synaptic levels in most cellular types in the striatum, where they can interact functionally and/or physically with multiple other GPCRs, such as dopamine (D1R or D2R), muscarinic cholinergic (mAchRs) or GPR88 receptors. BLA: basolateral amygdala; iGluRs: ionotropic glutamate receptors, mGluRs: metabotropic glutamate receptors, nAchRs: nicotinic cholinergic receptors, PFC: prefrontal cortex; SN: substantia nigra; VTA: ventral tegmental area.

In *Gpr88*$^{-/-}$ mice, DOR signaling is facilitated in the striatum (CPu and NAc), together with cholinergic and MOR activities (Meirsman et al. 2015).These animals thus represent a unique tool to assess the consequences of excessive DOR activity in this region. In the cross-maze, GPR88 null mice acquired earlier and better an allocentric strategy in a dual solution task and shifted sooner to a response strategy. After this shift had occurred, however, their performance started to decrease, suggesting that response learning was impaired in these animals. On the accelerating rotarod, *Gpr88*$^{-/-}$ micecompletely failed to acquire a motor skill, consistent with blunted activity of D1R-expressing MSNs (Durieux et al. 2012). Chronic treatment with naltrindole restored acquisition of a motor skill in mutant mice, but surprisingly only at early stages, pointing to a restoration of D2R-bearing MSN activity under DOR blockade. Failure to maintain a high level of performance at later stages suggests that DOR blockade in this experiment was not sufficient to completely rescue D1R-bearing MSN function. Finally, *Gpr88*$^{-/-}$ micewere less sensitive to the locomotor stimulating effects of a D1R agonist, consistent with a repressive effect of DOR on D1R-bearing MSNs(Quintana et al. 2012). Together, data from *Gpr88* mutant mice suggest that excessive DOR signaling in the striatum inhibits the activity of D1R-expressing MSNs, and probably affects the D2R-expressing population of MSNs as well. Further investigation will be needed to assess NAc-dependent behavioral responses in these animals, such as motivation for food or drug reward.

4.3.2. Interactions with other striatal GPCRs

The study of *Oprd1*$^{-/-}$, *Dlx5/*6-Cre x *Oprd1*$^{fl/fl}$and*Gpr88*$^{-/-}$micesuggests that dorsal striatal DOR inhibit the activity of D1R-expressing MSNs and may also affect the activity of D2R-bearing striatal outputs. These effects could be mediated through interactions at the level of striatal microcircuitry (Figure 3), but may also involve direct interactions between DOR and D1R or D2R in neurons where they are co-expressed. We challenged the existence ofsuch interactions using Bioluminescence resonance energy transfer (BRET) in heterologous cells. Remarkably, DOR appears to interact closely with D2R, suggesting the existence of potential heterodimers between these two GPCRs, but not with D1R (Figure 4). DOR and D2R co-localize in CINs and in D2R-bearing MSNs (Figure 3)(Ambrose et al. 2006; Calabresi et al. 2014; Heiman et al. 2008;Le Moine et al. 1994). Additional experiments will be needed to assess the pharmacological consequences of DOR and D2R co-expression. However, the rescue of D2R-MSN dependent early motor skill learning that we observed after naltrindole administration in *Gpr88*$^{-/-}$mice points to a direct inhibitory influence of DOR on D2R signaling. This inhibition could occur at CINs by preventing D2R activation from repressing ACh release and/or directly at postsynaptic MSNs by

counteracting the hyperpolarizing effect of D2R stimulation. Interestingly, a similar mechanism couldaccount for a trend in reduced inhibitory effects of a D2R agonist on locomotion in *Oprd1*$^{-/-}$ mice (Le Merrer et al. 2013).Further work will be required, though, to understand the molecular substrate of DOR/D1R-D2R interactions and their role in striatal function.

Dopamine receptors are obviously not the only GPCRs likely to interact directly with DORs at striatal level. Importantly, DOR signaling was shown to modulate cholinergic tone in this region. Indeed, presynaptic DOR can inhibit Ach release in the rat striatum (Mulder et al. 1984). DOR are also abundant on CINs, where their activation should similarly reduce Ach release by hyperpolarizing these neurons. The pharmacological blockade of DOR in the shell of the NAc was shown to suppress D1R-dependent PIT in mice (Laurent et al. 2014), likely by facilitating Ach release and, consequently, D2R-MSN activity (Ding et al. 2010). Interestingly, this inhibitory effect of intra-NAc shell naltrindole on PIT was prevented by systemic administration of the M4 muscarinic cholinergic receptor (mAchR4) antagonist MT3. Although this effect of MT3 could involve postsynaptic competition for adenylate cyclase recruitment (Laurent et al. 2014), one should not exclude possible direct interactions between DOR and cholinergic GPCRs (mAchRs). We thus assessed the existence of such interactions withmAchR1 or mAchr4, both highly expressed in the striatum, in heterologous cells. We were not able to detect direct interactions (Figure 4). However, the remarkably high levels of BRET measured between DORs and mAchr1s suggest that these receptors may randomly co-localize (not as heterodimers) in the same confined cellular compartment.Suchclose cellular proximity suggests that these two receptorsmay likely interact at functional level to modulate striatal activity.

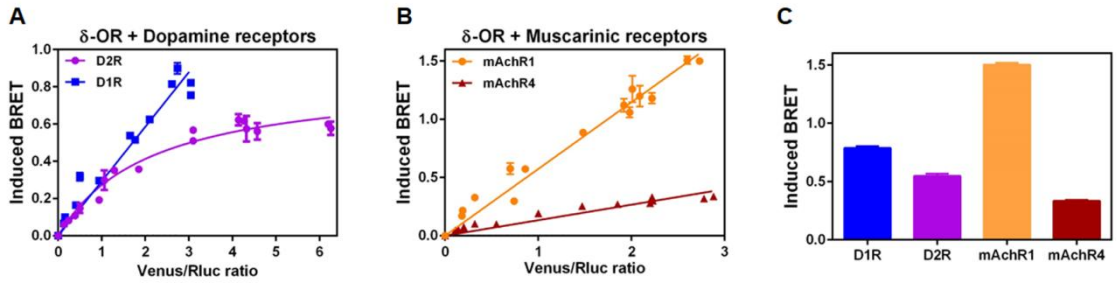

Figure 4.Interaction between DOR and dopaminergic and cholinergic GPCRs. 20 ng of DOR-Rluc8-pcDNA3 plasmids were co-expressed with increasing amount (10-120 ng) of GPCRs-Venus-pcDNA3 plasmids (n=3 per condition) in HEK293FT cells to study the physical interaction of DOR with GPCR partners by Bioluminescence Resonance Energy Transfer (BRET). (A) BRET signals displayed specific and saturated curves with DOR-D2R whereas signals remained unsaturated with DOR-D1R co-expression. (B) BRET signals were not saturated with cholinergic mAchR1 or mAchR4. (C) DOR and mAchR1 co-expression results in remarkably

high levels of energy transfer, suggesting that these receptors randomly (not as heterodimers) co-localize in the same confined cellular compartment.

Finally, GPR88 may also represent a direct molecular partner of DOR. These orphan receptors are among the most densely expressed GPCRs in the striatum(Ghate et al. 2007; Logue et al. 2009;Massart et al. 2009). *Gpr88* transcripts are detected in MSNs(Massart et al. 2009),with significant enrichment in D2R-bearing projections(Heiman et al. 2008).In *Gpr88*$^{-/-}$ mice, we evidenced increased DOR signaling in membrane preparations from striatal samples and a remarkable normalization of most of their behavioral features by systemic blockade of DOR (Meirsman et al. 2015). These results suggest that, under physiological conditions, GPR88 act as a brake on DOR activity to regulate behavior. GPR88 influence at DOR activity could operate either at circuit level, or through functional competition at the level of downstream effectors within neurons, or via direct, possibly physical, interactions between these receptors. Preliminary data in our lab suggest the existence of such direct interactions. Future work will aim at assessing the pharmacological consequences of DOR/GPR88 co-expression in cells and try to understand how their interaction could contributetothe influence of DORs on striatal output balance.

4.3.3. DORs and striatal gene expression

Using qRT-PCR, we assessed the levels of expression of 67 genes in the CPu and NAc of *Oprd1*$^{-/-}$ mice to identify potential molecular partners of DORs in these regions (Le Merrer et al. 2013). This analysis revealed that *Oprd1* deletion had different transcriptional consequencesin these two regions, with only two genes showing commonly (up)-regulated expression (*Slc6a11* and *Grm4* – coding the GABA transporter mGAT4 and metabotropic glutamate receptor mGluR4, respectively). Interestingly, transcriptional regulations of several genes in the CPu were coherent with behavioral data pointing to facilitated D1R- and blunted D2R-bearing MSN activity in DOR null mice. Indeed, low mRNA levels of *Camk2* and *chrm4* (coding for the alpha isoform of the calcium/calmodulin-dependent protein kinase II and mAchR4, respectively) and high mRNA levels of *grin2b* (NR2B subunit of NMDA glutamate receptors) could facilitatestriatonigral outputs in mutants(Gomeza et al. 1999; Guo et al. 2010; Jocoy et al. 2011; Tzavara et al. 2004). In contrast, increased expression of *Grm4* (metabotropic glutamate receptor mGluR4) and *Pdyn* (prodynorphin) and decreased expression of *Tac1* (substance P) and *Gpr6* (GPR6) would rather inhibitstriatopallidal activity (Govindaiah et al. 2010; Hopkins et al. 2009; Lobo et al. 2007; Perreault et al. 2007). Of note, down-regulated expression of *Blc11b* (*Ctip2*) may represent the triggering factor for decreased expression of other MSN marker genes, such as *Foxp1* and*Chrm4*(Arlotta et al. 2008). In the NAc, and not the CPu, several genes coding major actors of Ach and monoamine

degradation (*Ache*, coding acetylcholinesterase and *Maoa* - monoamine oxidase a) or their extraction from the synaptic cleft(*Slc6a4*, serotonin transporter SERT) displayed up-regulated expression. These results suggest that a brake on Ach/monoamine neurotransmission is lostin *Oprd1*$^{-/-}$ mice, requiring compensatory mechanisms. Therefore, DOR in the NAc appears to exert a tonic inhibition on these systems. Altogether, these data point to a crucial role of DOR in regulating striatal functions that differ between dorsal and ventral regions.

We similarly explored the transcriptional consequences of *Gpr88* genetic invalidation for 92 genes by qRT-PCR (Meirsman et al. 2015). Remarkably, the expression of *Oprd1*was down-regulated in the NAc, and not regulated in the CPu, of *Gpr88*$^{-/-}$ mice, whereas DOR activity, assessed by [^{35}S]-GTPγS binding, was increased in the whole striatum. These results suggest that either increased DOR activity is restricted to the CPu in these animals, and does not involve increased gene expression, or excessive DOR activation triggers a negative feedback mechanism in both the CPu and NAc, the latter being more sensitive than the former. Of note, down-regulated expression of *Rgs4*, coding Regulator of G protein signaling 4 – RGS4,in *Gpr88*$^{-/-}$mutants suggests a close interaction between this protein and GPR88 in the striatum. Interestingly, RGS4 was shown to inhibit opioid signaling (Georgoussi et al. 2006)and may thus participate in mediating the inhibitory effects of GPR88 activation on DOR signaling. Additional investigations will be needed to better assess DOR protein levels in the absence of GPR88, such as radioactive binding using DOR selective compounds for example.

4.3.4. Influence of hippocampal DORs on striatal function

Not only striatal DOR may be involved in the control of striatal-dependent behaviors but extrastriatal DORs as well. Indeed, previous studies have evidenced a functional antagonism between the hippocampal formation and the striatum, with the dorsal hippocampus exerting an inhibitory influence on the dorsal striatum, whereas the ventral hippocampus would facilitate the activity of the ventral striatum (Yin and Meck 2014).Consequently, impaired dorsal hippocampal function in *Oprd1*$^{-/-}$ mice may ease the acquisition of response and motor skill learning tasksby biasing hippocampo–striatal balance in favor of the dorsal striatum (Ciamei and Morton 2009; Packard and McGaugh 1996; Schroeder et al. 2002). Interestingly, behavioral, pharmacological and transcriptional data collected from *Oprd1*$^{-/-}$ and*Gpr88*$^{-/-}$ mice point a critical role for DOR in controlling the hippocampo-striatal balance, with major consequences on hippocampus- versus striatum-dependent learning processes (Figure 5). Whether such role would also applyto a ventral hippocampo-accumbal balance (Hart et al. 2014)will require further investigation.

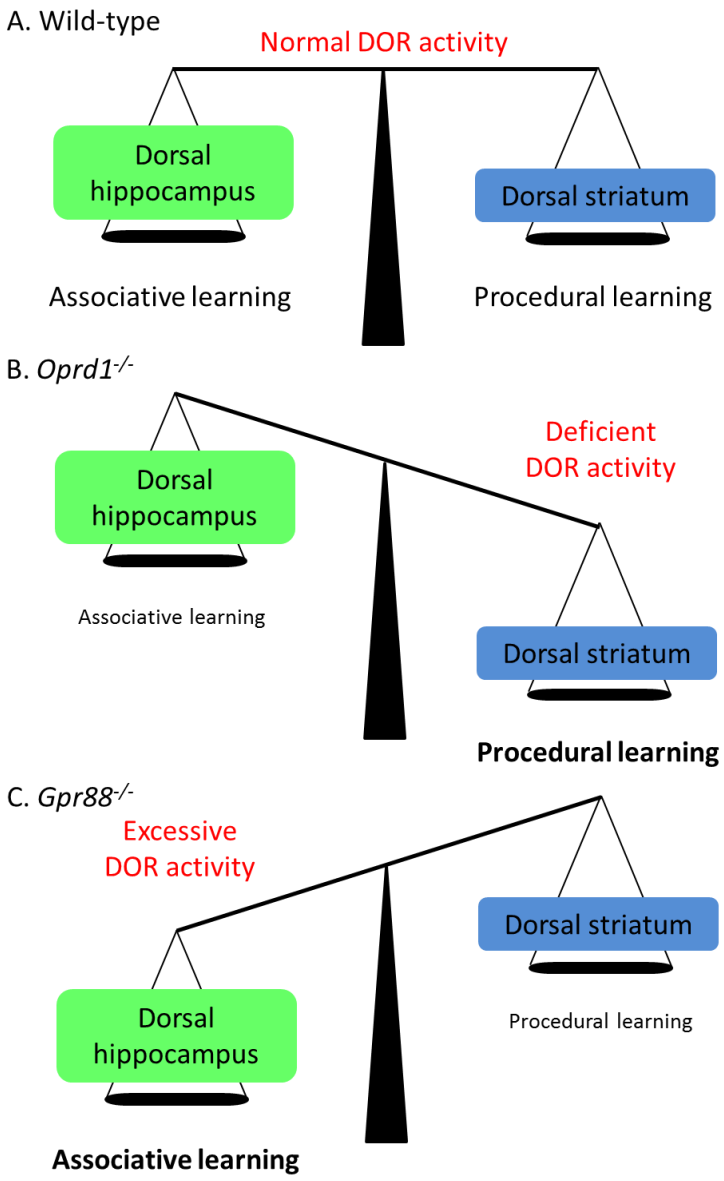

Figure 5. DORs modulate the dorsal hippocampo-striatal balance.(A)Under physiological conditions, hippocampal formation and striatum compete to ensure optimal control over learning processes. (B) In mice lacking delta opioid receptors, hippocampus-striatum balance is tilted towards facilitated striatal function, as revealed by impaired performance in dorsal hippocampus-dependent tasks (associative learning) but facilitated acquisition of dorsal striatum-dependent tasks (procedural learning). (C) Conversely, the hippocampo-striatal balance is biased towards eased dorsal hippocampal-dependent processes (associative learning) and deficient dorsal striatal function (procedural learning) in mice lacking GPR88 receptors, which display increased DOR activity in the striatum. Whether DORs can similarly modulate a more ventral hippocampo-accumbal balance will deserve further investigation.

5. Conclusions and clinical perspectives

Over the last 15 years, *in vivo* pharmacology and genetically modified animals have allowed to identify a unique, original implicationof DOR in high order cognitive processes, motor function, mood and emotional responses. We focused here on the involvement of this receptor in modulating learning and memory processes, motor function and reward/motivation, notably by regulating the balance between hippocampal and striatal functions. At dorsal level, such balance ensures optimal shift between associative hippocampus-dependent and procedural striatum-dependent learning processes, with crucial implications for cognitive performance and motor function. In this context, pharmacological ligands selective for DOR may represent precious therapeutic tools to relieve pathologies where the hippocampo-striatal balance in compromised, such as neurodegenerative diseases affecting either the hippocampal formation or the striatum (Alzheimer disease, Parkinson disease or Huntington disease for example). At ventral level, DORs may contribute to a ventral hippocampus to nucleus accumbens crosstalk. Remarkably, within this circuit, DORs appear less involved in mediating reward processes *per se* than in controlling the consequences of previous reward experience on ongoing behavior. Therapeutic applications in the field of addiction thus involve the development of DOR antagonists to suppress conditioned responses to drug cues, with obvious benefit for the relief of withdrawal symptoms, reduction of drug seeking and prevention of relapse. A caveat should be quoted here, however, as biasing the hippocampo-striatal balance towards one functional system may be detrimental for the other, as seen for spatial versus motor learning in *Oprd1*$^{-/-}$ and *Gpr88*$^{-/-}$animals. Moreover, DORs are also involved in controlling anxiety levels and epileptogenic thresholds (Chu Sin Chung and Kieffer 2013), making them a delicate target to manipulate for therapeutic purpose. These limitations highlight the need for developing innovative pharmacological strategiesto allow the targetingof specific populations of receptors, either in restricted areas of the brain or selected neuronal types,and obtain optimized treatments for CNS diseases.Other promising clinical perspectives lie in the selection of either DOR ligands with biased signaling (Kenakin 2011)or compounds targeting heterodimers of DORs with other GPCRs, to obtain specific therapeutic action with limited side effects.

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