Dopamine D1-D2 receptor heteromer signaling pathway in the brain: emerging physiological relevance

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Abstract
Dopamine is an important catecholamine neurotransmitter modulating many physiological functions, and is linked to psychopathology of many diseases such as schizophrenia and drug addiction. Dopamine D1 and D2 receptors are the most abundant dopaminergic receptors in the striatum, and although a clear segregation between the pathways expressing these two receptors has been reported in certain subregions, the presence of D1-D2 receptor heteromers within a unique subset of neurons, forming a novel signaling transducing functional entity has been shown. Recently, significant progress has been made in elucidating the signaling pathways activated by the D1-D2 receptor heteromer and their potential physiological relevance.

Background
Dopamine plays a key role in the regulation of various physiological functions of normal brain including reward, locomotion, behavior, learning, and emotion. It is not then surprising that the dysregulation of the dopaminergic system has been linked to pathophysiology of many diseases, such as Alzheimer’s disease, schizophrenia, Parkinson’s disease, attention deficit hyperactivity disorder, depression and drug addiction [1-3], leading to the clinical use of drugs that target dopamine neurotransmission in the treatment of these disorders.

Five subtypes of dopamine receptors (D1R-D5R), belonging to the G-protein-coupled receptor (GPCR) superfamily have been cloned, through which dopamine transduces its various effects. Dopamine receptors are subdivided into D1-like (D1, D5) and D2-like (D2, D3, D4) receptor subclasses [1-3], with the D1 and D2 receptors being the major subtypes. The most studied dopamine signaling pathway is the modulation of cyclic AMP production, with D1-like receptors activating cyclic AMP production through Gs/olf, and D2-like receptors inhibiting adenyl cyclase (AC) activity through Gi/o proteins [2]. This results in a bidirectional modulation of this pathway and related proteins, such as protein kinase A (PKA) and DARPP-32 (dopamine and cAMP regulated protein) [4]. Other important dopamine signaling pathways have also been reported, including the modulation of the Akt-GSK3 pathway [5] and the activation of the PAR4 signaling pathway [6].

For some actions of dopamine, such as the control of motor behavior [7] or dopamine-mediated reward processes in nucleus accumbens [8], a concomitant stimulation of D1 and D2 receptors is required, a phenomenon known as the “requisite” D1/D2 synergism [9]. In this type of synergism, D1 and D2 receptor-specific drugs potentiate the effect exerted by each other when delivered together, but are ineffective when administered separately [9]. The combined, but not separate, administration of a selective D1 and a selective D2 agonist was shown to be necessary for the dopamine-stimulated expression of immediate-early gene c-fos in striatal neurons [10] and in electro-physiological studies where both receptors were indeed responsible for GABA release in striatum [11]. The participation of both D1 and D2 receptors was also required for evoking neural and behavioral sensitization to cocaine [12] and for evoking the changes in behavior and basal ganglia output [13,14]. All these observations are other evidence for the presence of not only a synergism between dopamine D1 and D2 receptors, but an obligatory participation of both receptors to generate this synergism.

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One explanation for why the well documented synergistic effects seen between D1 and D2 receptors [15,16] may be achieved is through the formation of heterooligomers between the two receptors, as it has been shown for many GPCRs [17-19]. Dopamine receptors, all subtypes included, in addition to their ability to exist as homomers, were shown to form different heteromeric complexes with other receptors (reviewed in 20). The presence of D1-D2 receptor heteromers with unique functional properties was first shown in transfected cells using different methods [21-24] as described below. Initially, the notion of heteromerization observed for many GPCRs and its functional relevance was not completely clear in physiological conditions and was in some cases regarded with a degree of skepticism, but at least for the D1-D2 receptor heteromer we have shown evidence of occurrence under physiological conditions in native tissues with emerging important functional relevance.

For D1 and D2 receptors, the presence of two anatomically segregated sets of neurons, forming the striatoni gral D1-enriched direct pathway and the striatopallidal D2-enriched indirect pathway is commonly recognized, with D1R localizing to the dynorphin (DYN)-expressing neurons, and D2R localizing to the enkephalin (ENK)-expressing neurons [25,26]. Recent studies emanating from fluorophore-tagged promoter elements of D1R and D2R in bacterial artificial chromosome (BAC) transgenic mice [27] allowed an evaluation of the proportions of striatal neurons expressing D1R, D2R, or both [28-32]. There were, however, variations in the levels of expression of EGFP between one line and another [32], resulting in incomplete labeling of a significant proportion of striatal medium spiny neurons (MSNs) [28]. While this method supported the segregation between the D1-enriched direct pathway and the striatopallidal D2-enriched indirect pathway, a certain fraction of MSNs (~17%) expressing both receptors was predicted in the NAc shell, whereas only ~5-6% of MSNs were calculated to co-express both receptors in the dorsal striatum [30-32]. These BAC-calculated colocalization data are consistent with our data and the numerous other reports indicating a colocalization of D1R and D2R in neurons in culture or in situ with higher D1R and D2R co-localization observed in cultured striatal neurons (60 to 100%) than in the adult striatum [33-40].

Presence of dopamine D1-D2 receptor heteromers in brain

Several reports indicated the presence of a D1-like receptor activating IP3 production and/or increasing intracellular calcium in neurons in culture or slices from different brain regions, including striatum, hippocampus, and cortex [41-44]. However, the cloned D1R was devoid of such effects when expressed in different host cells (reviewed in 17 and 20) and persisted in a D1 receptor null mouse model [45]. We then demonstrated that dopamine D1 and D2 receptors form functional heterooligomeric complexes in cells and in vivo [21-23,40,46] and that the mobilization of intracellular calcium was in fact a unique signaling pathway resulting from the activation of this D1-D2 heteromeric receptor complex [21,23,40].

The presence of the D1-D2 receptor heteromer was demonstrated by different techniques including coimmunoprecipitating both receptors from rat striatum, as well as from cells coexpressing D1R and D2R [21,40], and by different methodologies using the fluorescence resonance energy transfer (FRET) technique in cells [22,24], in striatal neurons [40,47] and different brain regions [40,46]. Interestingly, in adult rat brain, coexpressed dopamine D1 and D2 receptors were present in a unique subset of neurons coexpressing both DYN and ENK neuropeptides in different brain regions, including nucleus accumbens (NAc), caudate-putamen (CP), ventral pallidum, globus pallidus (GP), and entopeduncular nucleus [46], with some inter-regional variation. The lowest proportion (~6-7%) of D1R-expressing neurons that coexpress D2R was shown in the CP [40,46], whereas the highest proportion (~59%) of D1R-expressing neurons that coexpress D2R was observed in GP [46]. A substantial number (~20-30%) of D1R neurons that coexpress D2R was also observed in NAc [40,46], consistent with the anatomical findings resulting from BAC transgenic mice [30-32].

The direct interaction of D1R and D2R to form heteromers in brain was shown by confocal FRET technique using two methodologies [40,46,47]. The confocal FRET technique demonstrated clearly and directly the presence of the D1-D2 receptor heteromer in striatal neurons [40,47] and in brain in situ [40,46]. In NAc, acceptor photobleaching-based FRET showed a high FRET efficiency (~21%) [46], in the same range (~20%) as with a second quantitative confocal FRET, that further quantified the parameters of the interaction between D1R and D2R to calculate the FRET efficiency and the assessment of the distance separating both fluorophore-tagged receptors [40,46]. In NAc, interactions between colocalized D1R and D2R (Figure 1) displayed high FRET efficiency (~20%) and a relative distance of 5-7 nm (50-70 Å) (Table 1), synonymous with a close proximity between D1 and D2 receptors and indicative of D1-D2 heteromer formation. In contrast, although an indication of D1-D2 heteromer formation in CP was observed, the parameters, FRET efficiency (~5%) and the relative distance of 8-9 nm (80-90 Å) between the receptors suggested that in CP either D1R-D2R interaction was weaker, or fewer D1-D2 receptor heteromers were formed, and/or lower order of D1-D2 oligomers than in the NAc was present [40,46].
D1-D2 receptor heteromer-induced signaling pathway and its physiologic relevance

The specific activation of the D1-D2 receptor heteromer in postnatal striatal neurons [40], and from cells co-expressing D1R and D2R [21,23] resulted in the intracellular release of calcium from stores sensitive to activation of inositol triphosphate receptors (IP3-R). This rise in intracellular calcium was rapid, transient, independent of extracellular calcium influx, and involved the activation of Gq protein, and phospholipase C (PLC) [21,23,40]. This calcium signal resulted in an increase in the phosphorylated-activated form of CaMKII in postnatal striatal neurons [40] and rat striatum [23]. The use of dopamine D1-/-, D2-/- and D5-/- receptor null mice indicated clearly that the calcium-CaMKII signaling pathway exclusively involved both D1R and D2R within a functional complex [23,40], and was different from the calcium signal generated by the activation of D5R or the D2-D5 receptor heteromer [48,49].

Intracellular calcium plays key roles in many neuronal functions including the regulation of synaptic transmission [50]. The intracellular calcium signaling pathway activated through the dopamine D1-D2 receptor heteromer resulted in CaMKIIα activation and BDNF production in striatal neurons in culture as well as in the nucleus accumbens of adult rats, leading ultimately in cultured postnatal striatal neurons to enhanced dendritic branching [40]. Both CaMKIIα and BDNF have been shown to be involved in synaptic plasticity. While

Table 1 Confocal FRET analysis of D1 and D2 receptor interaction

| ROI       | Donor of FRET | Acceptor of FRET | PFRET | FRET Efficiency | Distance between donor and acceptor (nm) |
|-----------|---------------|------------------|-------|----------------|-----------------------------------------|
| (1) Donor alone | 13.944       | 0                | 529.703 | 0.357          | 10                                      |
| 2         | 842.685       | 562.542          | 0      | 0              | 5.91                                    |
| 3         | 804.879       | 488.573          | 474.042 | 0.351          | 5.9                                     |
| 4         | 830.377       | 569.241          | 535.203 | 0.353          | 5.924                                   |
| 5         | 720.099       | 436.039          | 410.781 | 0.319          | 6.269                                   |
| 6         | 898.475       | 482.132          | 444.885 | 0.311          | 6.171                                   |
| 7         | 964.916       | 460.029          | 407.186 | 0.247          | 6.875                                   |
| 8         | 1116.854      | 399.85           | 384.365 | 0.234          | 6.632                                   |
| 9         | 951.224       | 324.177          | 314.284 | 0.206          | 7.145                                   |
| 10        | 1076.73       | 341.095          | 326.925 | 0.2            | 7.153                                   |
| 11        | 976.861       | 227.299          | 216.367 | 0.149          | 7.789                                   |
| 12        | 1201.314      | 363.612          | 336.45  | 0.191          | 7.121                                   |
| 13        | 998.373       | 283.121          | 269.621 | 0.187          | 7.197                                   |
| 14        | 1017.225      | 303.213          | 287.876 | 0.2            | 6.987                                   |
| 15        | 816.347       | 166.339          | 156.562 | 0.129          | 8.329                                   |
| 16        | 806.034       | 265.133          | 251.731 | 0.19           | 7.393                                   |
| 17        | 815.063       | 349.81           | 338.709 | 0.252          | 6.792                                   |
| 18        | 833.344       | 485.752          | 382.262 | 0.257          | 6.946                                   |
| (19)Non-Specific | 95.52        | 83.573          | 35.284  | 0.086          | 9.168                                   |
| Average   | 921.8117      | 382.821          | 356.88  | 0.243117       | 6.83958                                 |
| SEM       | 33.82434      | 29.9949          | 27.1577 | 0.018620       | 0.165392                                |

Confocal FRET analysis of figure 1 shows the relative expression of the donor (D2-Alexa 350, green) and acceptor (D1-Alexa 488, red). The analysis also shows the processed FRET (pFRET), the FRET efficiency and the distances separating the two fluorophore-tagged receptors in each microdomain (ROI), with averages and SEM in the bottom of the table. A distance ~10 nm or higher indicates no FRET.
evidence has indicated that CaMKIIα is a critical regulator of synaptic plasticity in neurons [51-54] with 50% of CaMKIIα-deficient mice presenting changes in behavior and learning [55]. BDNF has been shown to modulate the branching and growth of axons, dendrites and spines (reviewed in 56). For example, BDNF was shown to be released from cell bodies and dendrites of cortical neurons and regulated the branching of dendrites in adjacent neurons [57]. The BDNF effect on the dendritic morphology and also on spine morphology (reviewed in 56) would be of great importance in the modulation of neuronal and synaptic function and plasticity [58]. The neurotrophin signaling transduced through BDNF receptor TrkB has been recently reported to be involved in the control of the size of the striatum by modulating the number of medium spiny neurons (MSNs), with deletion of the gene for the TrkB receptor in striatal progenitors leading to the loss of almost 50% of MSNs without affecting striatal interneurons [59]. Also, the BDNF signaling through TrkB was shown to be involved in the induction and the maintenance of synaptic plasticity, through its long-term potentiation (LTP) component [60]. The other component, long-term depression (LTD) was shown to involve BDNF signaling through the receptor p75 in hippocampal slices from p75-deficient mice [61]. BDNF plays also an important role in the modulation of neurotransmitter release, a key step in synaptic plasticity [56]. The release of glutamate for example involves PLC and BDNF through a mechanism involving a rise in intracellular calcium via a release from IP3 receptor-sensitive stores [62,63]. It is very interesting to draw the parallel between these mechanisms by which CaMKII and BDNF modulate synaptic plasticity and the signaling pathway revealed with the dopaminergic system-CaMKII-BDNF, synaptic plasticity and the occurrence of drug addiction and schizophrenia. The finding that the activation of CaMKIIα was necessary for the induction of behavioral sensitization to drugs [68], a physiological phenomenon that also requires the coactivation of D1 and D2 dopamine receptors [14], provides additional evidence of the important role of dopamine D1-D2 receptor heteromer-calcium signal in drug addiction.

After years of some skepticism surrounding the physiological presence and relevance of GPCR homo- and hetero-oligomers, there is ample evidence for the presence in the brain of a unique entity, the D1-D2 heteroreceptor, with a unique signaling pathway different from the signals generated by each receptor homomer, with a physiological relevance and high importance in at least two major pathologies, schizophrenia and drug addiction, making the D1-D2 receptor an interesting therapeutic target for these disorders.

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Authors’ contributions
All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

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