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NEUROLOGY AND PRECLINICAL NEUROLOGICAL STUDIES - ORIGINAL ARTICLE

Apomorphine differentially engages the cAMP and β-arrestin signaling pathways relative to dopamine at human dopamine receptors

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Abstract

Apomorphine is the only dopamine agonist used to treat Parkinson disease with similar efficacy to levodopa. Its original characterization as a dopamine agonist was based on its receptor binding profile and capacity to recruit G proteins; however, current knowledge of G protein-coupled receptors highlights the importance of β-arrestin signaling to dopamine receptor functionality and expression. This study systematically compared the activity of apomorphine and dopamine across the range of dopamine receptor subtypes using biosensor assays that assessed its functional effects on both the cAMP and β-arrestin signaling pathways. Apomorphine facilitated cAMP signaling at both D1 and D2 family receptors with similar efficacy to dopamine but greater potency except at D3 receptors, where it exhibited similar potency. Apomorphine also recruited β-arrestin at all dopamine receptors similar to dopamine but with lower maximal effects at D1, D4, and D5 receptors. The potent efficacy of apomorphine on cAMP signaling at all dopamine receptor subtypes may explain its similar efficacy to levodopa. The clinical impact of the β-arrestin effects requires further study but is likely to influence its pharmacodynamic effects, including differences in adverse event profile compared to levodopa and D2-preferring agonists.

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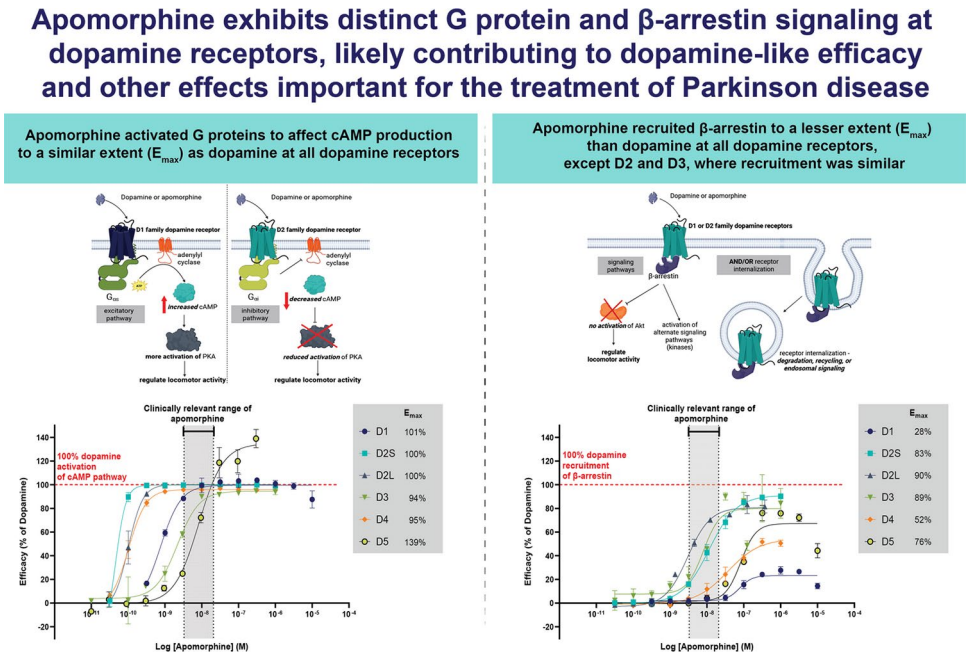
Graphical Abstract



Keywords Apomorphine · Dopamine · Dopamine receptors · G protein coupled receptor · Beta-arrestin · Parkinson's disease

Introduction

While few would disagree that apomorphine binds to all dopamine receptors (Beaulieu et al. 2023), there is currently little understanding of what that means with regards to its therapeutic profile. For example, it is often hypothesized that the 'levodopa-like' efficacy of apomorphine is related to its ability to act on all dopamine receptors (Jenner and Katzenschlager 2016), but this is mainly based on its receptor binding profile and functional activity experiments measuring its ability to modulate the G protein-coupled receptor (GPCR) cyclic adenosine monophosphate (cAMP) pathway.

First used to treat Parkinson disease (PD) in the 1950's (Schwab et al. 1951), much of the pharmacological characterization of apomorphine precedes our current understanding of the full complexity of how dopamine receptors signal intracellularly, interacting with other receptors via coordinated pathways. While apomorphine has been assessed for binding or activity at select (predominately D2) dopamine receptors, a characterization of its effects relative to dopamine at even the best-known signaling cascades (cAMP and β-arrestin) across all dopamine receptors is lacking. Consequently, the evidence for its receptor profile has been piecemeal or primarily focused on its receptor binding profile. A more precise pharmacological characterization is the first step to understanding why its therapeutic profile differs from D2-receptor preferring dopamine agonists, which are largely falling out of favor in PD due to lower efficacy relative to levodopa and concerns related to the risk of impulse control disorders (ICDs) (Pringsheim et al. 2021). Historically, the first evidence of dopamine receptors came from experiments in the 1970's showing dopamine's stimulation of adenylyl cyclase activity in brain tissue (Kebabian and Greengard 1971). It was later shown that the D1-family receptors (D1, D5) activate $G\alpha_s$ to increase cAMP levels, while D2-family receptors (D2S, D2L, D3, D4) activate $G\alpha_{i/o}$ to decrease cAMP levels (Fig. 1). However, it is now known that dopamine agonists may differentially activate secondary messenger systems at dopamine receptors, which may have clinical relevance for its distinct efficacy and adverse events profile. Aside from canonical cAMP signaling, one of the best characterized pathways is the β-arrestin pathway (Caron and Barak 2019). Both D1 and D2 family receptors recruit β-arrestin proteins, which can desensitize these GPCRs and cause internalization, leading to degradation, recycling, or endosomal signaling. β-arrestin can also activate alternative signaling pathways (e.g., kinases) at the cell membrane (Wootten et al. 2018). Research has

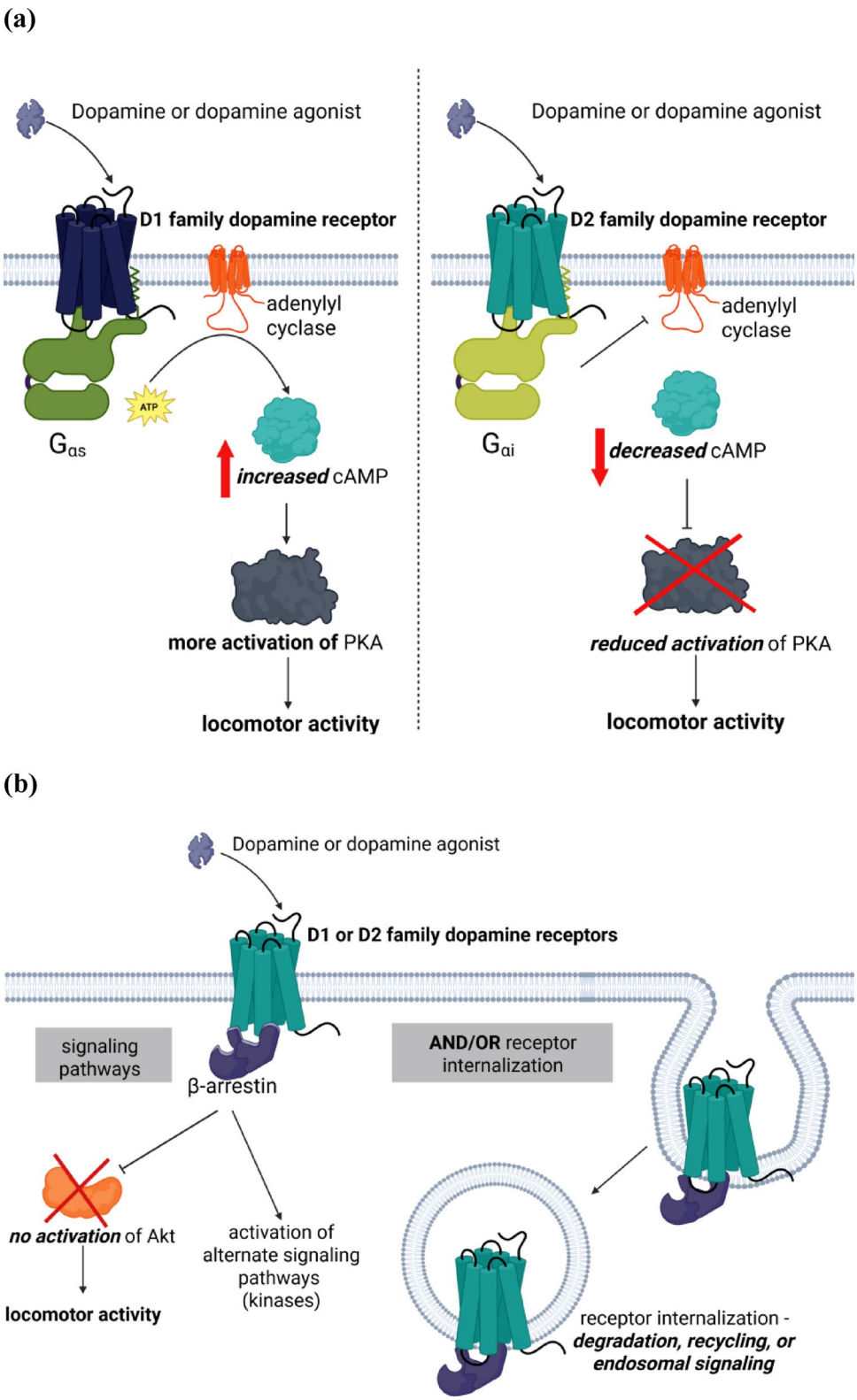


Fig. 1 Secondary messenger pathways at the D1 and D2 family of receptors including (**a**) G protein-dependent cAMP signaling and (**b**) G protein-independent signaling pathways including β-arrestin signaling. Figure generated in Biorender

shown that β-arrestin2 knockout mice exhibit reduced locomotor improvement and increased dyskinesia in response to levodopa (Urs et al. 2015). In contrast, β-arrestin2 overexpression or selective activation enhances levodopa-induced locomotion – though less than dual cAMP and β-arrestin engagement – and reduces dyskinesia, indicating

that β-arrestin signaling modulates both therapeutic and side effects of levodopa treatment (Del'guidice et al. 2011; Donthamsetti et al. 2020; Rose et al. 2018; Urs et al. 2015).

For the first time, we assess the relative functional activity of apomorphine compared to dopamine on the cAMP pathway and the β-arrestin pathway across all dopamine receptors. Using commercially available technology, we report that apomorphine is active at all dopamine receptor subtypes with a profile akin to dopamine but with greater potency. Importantly, we show that apomorphine differentially engages the cAMP and β-arrestin signaling pathways relative to dopamine at human dopamine receptors.

Methods

All dopamine receptor assays were undertaken using commercially available technology (Eurofins Cerep, Celle l'Evescault, France and Eurofins DiscoverX, Fremont, California, United States). Apomorphine (U.S. Pharmacopeia lot #R166G0 diluted in DMSO) was tested across 10 concentrations with half log serial dilutions for determination of EC_{50} values (concentration producing a half-maximal response). Apomorphine and dopamine were assessed in duplicate, except for the D3 and D5 cAMP assays, in which dopamine was completed as singlets. Three independent replicates were obtained for the D1 assays.

cAMP secondary messenger pathway

For D1, D2S (D2 short isoform), D2L (D2 long isoform), and D4 receptors, cAMP functional assays were performed according to manufacturer protocols utilizing a proprietary cell line. Human isoforms of the D1, D2S, D2L, and D4 receptors were expressed in cAMP-Hunter™ cells and were seeded (total volume of 20 µL) into 384-well plates. Downstream release of cAMP via GPCR activation was measured using the HitHunter cAMP XS^+ chemiluminescent assay (Discover X, Fremont, CA), which detects the production of cAMP after receptor activation, based on Enzyme Fragment Complementation (EFC) technology using β-galactosidase (β-gal) as a functional reporter. This technology uses cAMP coupled to a β-gal fragment as an enzyme donor (ED), with a complementary fragment of β-gal functioning as the enzyme acceptor (EA). Exogenous cAMP, fused to an ED, competes with endogenous cAMP for binding to an anti-cAMP antibody. Complementation of the ED and the EA forms an active EFC enzyme, which is able to hydrolyze the substrate to produce a luminescence signal, that is proportional to cellular production of cAMP and read by a PerkinElmer Envision™ microplate reader. For the G_s agonist assay (D1), apomorphine (0.3–10,000 nM) was added to cells and incubated for 30 min at 37 °C. For the G_i agonist assay (D2, D4), after adding 5 µL of apomorphine (0.03–1,000 nM) to the cells, 5 µL of EC_{80} forskolin diluted in HBSS/HEPES was added and incubated for 30 min at 37 °C. Cells were then incubated with 5 µL cAMP XS + Ab reagent followed by 20 µL cAMP XS + ED/CL lysis cocktail for one hour at room temperature and read for chemiluminescent signal. Concentrations of the reference compound dopamine varied across dopamine receptors, with a range of 0.03–1,000nM.

For the D3 and D5 receptors, cAMP functional assays were conducted in CHO and GHR4 cells, respectively, as previously reported. Human isoforms of the D3 receptor were expressed in CHO cells (Missale et al. 1998) and apomorphine (0.03–1,000 nM) was incubated with the cells for 30 min at 37 °C. Signal was detected via homogenous time-resolved fluorescence (HTRF), and 300 nM of dopamine served as a reference compound. Human isoforms of the D5 receptors were expressed in GHR4 cells (Sunahara et al. 1991), and apomorphine (0.3–10,000 nM) was incubated with the cells for 30 min at room temperature. Signal was detected via HTRF, and 1 µM dopamine served as a reference compound.

β-Arrestin secondary messenger pathway

The PathHunter β-arrestin assay (DiscoverX, Fremont, CA) was used to characterize apomorphine and dopamine activation of the β-arrestin secondary messenger pathway across all dopamine receptors. The assay used the PathHunter™ cell line that overexpresses a Prolink-tagged dopamine receptor (enzyme donor) and EA-tagged β-arrestin2. Activation of the receptor stimulates the recruitment of β-arrestin2 and produces EFC signal. According to manufacturer protocol, cells were seeded in a total volume of 20 µL into 384-well microplates and incubated at 37 °C. Apomorphine (D1 and D5: 0.3–10,000 nM, D2–D4: 0.03-1,000 nM) or dopamine (0.05-30,000 nM) was added to cells and incubated for at least 120 min at room temperature or 37 °C. PathHunter Detection reagents (15 µL; 50% v/v) were added and incubated for one hour at room temperature. Using a PerkinElmer Envision™ instrument, the chemiluminescent signal was detected and quantified.

Receptor internalization via the endocytosis pathway

Following the observation that apomorphine displayed only weak partial agonism at the D1 receptor β-arrestin pathway,

Table 1 Pharmacological activity of apomorphine in engaging cAMP and β-arrestin pathways relative to dopamine at human dopamine receptors

	Dopamine EC_{50} (nM)	Apomorphine EC_{50} (nM)	E_{max} relative to dopamine
cAMP assays			
D1	4.28	0.78	101%
D2L	1.86	0.10	100%
D2S	1.07	0.07	100%
D3	2.60	2.20	94%
D4	4.11	0.10	95%
D5	12.50	5.34	139%
β-arrestin assays			
D1	545.75	92.97	28%
D2L	61.48	6.35	83%
D2S	61.98	11.55	90%
D3	3.13	9.40	89%
D4	146.88	36.92	52%
D5	128.61	96.45	76%
Internalization assay			
D1	238.60	30.29	38%

we performed an additional receptor internalization assay for the D1 receptor. This assay also uses EFC technology in PathHunter cells, which express the untagged receptor of interest and EA-arrestin, with ED localized to the surface of early endosomes (DiscoverX, Fremont, CA). Enzymatic activity is restored upon GPCR activation and arrestin-mediated trafficking to early endosomes. In this assay, cells were seeded in a total volume of 20 µL into 384-well microplates. Apomorphine or dopamine (0.3–10,000 nM for both) was added to cells and incubated at 37 °C or room temperature for 90–180 min. Assay signal was generated through the addition of PathHunter Detection reagent cocktail (50% v/v) and quantified using the PerkinElmer Envision™ instrument.

Data analysis

To evaluate relative potency, apomorphine EC_{50} values were determined by non-linear regression analysis of the concentration-response curves generated with mean replicate values using Hill equation curve fitting:

$$Y = D + \left[\frac{A - D}{1 + \left(\frac{C}{EC_{50}}\right)^{nH}}\right]$$

where Y = response, A = left asymptote of the curve, D = right asymptote of the curve, C = compound concentration, EC_{50} = half-maximal effective concentration, and nH = slope factor.

The agonist effect (E_{max}) of apomorphine at dopamine D1, D2S, D2L, D3, D4, and D5 receptors was calculated as a percentage of the control agonist (dopamine) response at each signaling pathway. For D1, D2S, D2L, and D4 assays, mean values of the duplicates (per concentration point) of the relative luminescence units (RLU) were used for all calculations. The vehicle control for the assay included the buffers and reagents only (without agonist).

For β-arrestin and G_s agonist mode, percentage activity was calculated as follows:

$$\%\ Activity = 100\% * \frac{(mean\ RLU\ of\ test\ sample - mean\ RLU\ of\ vehicle\ control)}{(mean\ RLU\ of\ MAX\ control\ agonist - mean\ RLU\ of\ vehicle\ control)}$$

For G_i agonist mode assays, the following formula was used:

$$\%\ Activity = 100\% * \left(1 - \frac{(mean\ RLU\ of\ test\ sample - mean\ RLU\ of\ MAX\ control\ agonist)}{(mean\ RLU\ of\ vehicle\ control - mean\ RLU\ of\ MAX\ control\ agonist)}\right)$$

For D3 and D5 cAMP assays, the results were expressed as a percent of control agonist (dopamine) response, with

$$\%\ Activity = 100\% * \frac{(measured\ response)}{(control\ agonist\ response)}$$

.For the D1 internationalization assay, agonist activity was expressed as a percentage using the following formula

$$\%\ Activity = 100\% * \frac{(mean\ RLU\ of\ test\ sample - mean\ RLU\ of\ vehicle\ control)}{(mean\ RLU\ of\ MAX\ control\ agonist - mean\ RLU\ of\ vehicle\ control)}$$

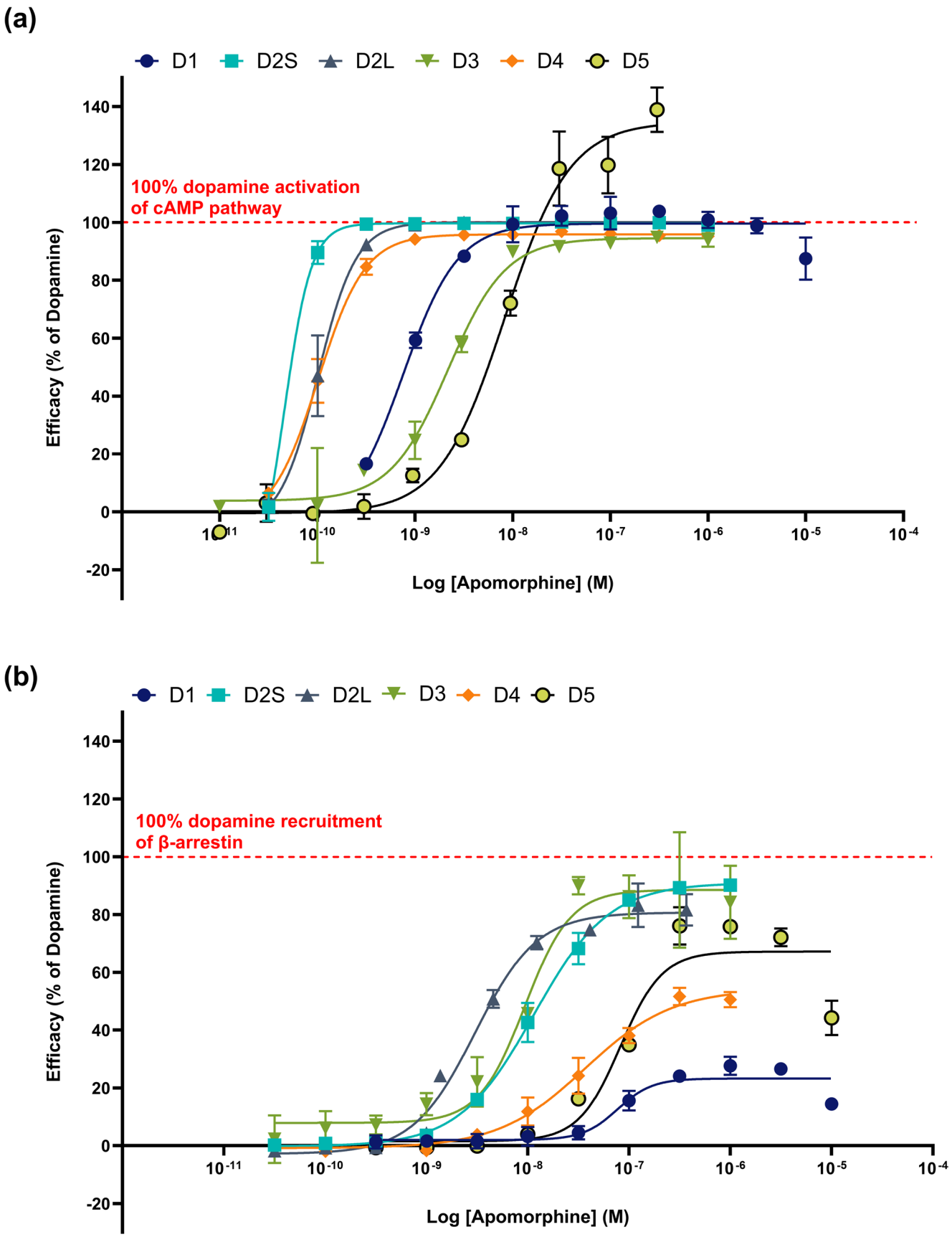


Fig. 2 Concentration-response curves for apomorphine in engaging (**a**) cAMP and (**b**) β-arrestin signaling across all dopamine receptors. Efficacy was determined as a percentage of the reference compound, dopamine, with 100% activation shown as a dotted red line in the figures

.Results

Across all assays, apomorphine hydrochloride displayed agonism at all dopamine receptor subtypes (Table 1).

Relative to dopamine, apomorphine had greater potency (lower EC_{50} values) in cAMP assays at all dopamine receptors except D3, where it was similar to dopamine. Further, apomorphine's agonist activity at the D3 and D5 receptors was weaker compared to its cAMP pathway activity at other dopamine receptor subtypes. EC_{50} values (nM) for apomorphine vs. dopamine, respectively, were 0.78 vs. 4.28 for D1, 0.10 vs. 1.86 for D2L, 0.07 vs. 1.07 for D2S, 2.20 vs. 9.40 for D3, 0.1 vs. 4.11 for D4, and 5.34 vs. 12.50 for D5 receptors. Figure 2a shows the intrinsic activity curves for apomorphine relative to dopamine for the cAMP pathway. Relative to dopamine, apomorphine displayed maximal engagement of downstream cAMP signaling for all dopamine receptors (E_{max}: 94–139%).

Similarly, for β-arrestin recruitment, apomorphine showed greater potency relative to dopamine, except at D3 receptors, where it was slightly less than dopamine. EC_{50} values (nM, apomorphine vs. dopamine) were: 92.97 vs. 545.75 for D1, 6.35 vs. 61.48 for D2L, 11.55 vs. 61.98 for D2S, 9.40 vs. 3.13 for D3, 36.92 vs. 146.88 for D4, and 96.45 vs. 128.61 for D5 receptors. Whereas apomorphine demonstrated relatively similar β-arrestin recruitment as dopamine at D2 (E_{max}: 83–90%) and D3 receptors (E_{max}: 89%), it demonstrated sub-maximal recruitment of β-arrestin at D1 (E_{max}: 28%), D4 (E_{max}: 52%), and D5 receptors (E_{max}: 76%; Fig. 2b). Consistent with lower recruitment of β-arrestin, apomorphine also showed sub-maximal internalization of the D1 receptor (E_{max}: 38%), despite its greater potency (EC_{50}: 30.29 nM) relative to dopamine (EC_{50}: 238.60 nM) in this assay.

Comparing the signaling pathways, apomorphine had higher potency (lower EC_{50}) in recruiting the cAMP pathway relative to the β-arrestin pathway at all dopamine receptor subtypes, except for the D3 receptor where its potency was relatively similar. At D1, D4, and D5 receptors apomorphine appeared to exhibit biased agonism towards cAMP pathway activation (ful engagement: E_{max} ~100%) relative to partial recruitment of β-arrestin (E_{max} D1: 28%, D4: 52%, and D5: 76%). More balanced agonism was seen at D2L, D2S, and D3 receptors where again there was full engagement of the cAMP pathway (E_{max} ~100% at all receptors) and nearly full recruitment of β-arrestin (E_{max} D2L: 83%, D2S: 90%, D3: 89%). Due to the similar efficacy values between β-arrestin recruitment and internalization of D1 receptors, it is likely that β-arrestin is significantly contributing to D1 receptor internalization following apomorphine activation.

Discussion

The results of this study show that apomorphine facilitates cAMP signaling at both the D1 and D2 family of receptors with similar efficacy yet greater potency than dopamine, except at D3 receptors, at which apomorphine demonstrated similar potency compared to dopamine. Apomorphine also recruited β-arrestin at all dopamine receptor subtypes with greater or similar potency to dopamine but with lower maximal effects at D1, D4, and D5 receptors. Overall, apomorphine displayed full agonism (maximal efficacy) for all dopamine receptor subtypes for the cAMP pathway, with partial agonism (submaximal efficacy) for β-arrestin signaling at D1, D4, and D5 receptors and full agonism for both cAMP and β-arrestin assays at D2 and D3 receptors.

While it has long been theorized that the levodopa-like efficacy of apomorphine reflects its activity at all dopamine receptors, our study further demonstrates that it has greater potency than dopamine at each of these receptors, except for D3 receptors. Dopamine receptors engage a complex array of signaling proteins to exert their effects in the brain. Utilizing pharmacological agents, adeno-associated viral vectors, and knockout animals, it has been consistently found that engagement of both cAMP and β-arrestin pathways contribute to levodopa-induced locomotor effects (Fienberg et al. 1998; Hervé et al. 2001; Beaulieu et al. 2004, 2005; Beaulieu and Gainetdinov 2011; Alcacer et al. 2012; Urs et al. 2015; Rose et al. 2018; Donthamsetti et al. 2020). While the canonical role of dopamine receptor-mediated cAMP signaling in both acute and chronic responses to dopaminergic drugs is well established, there is growing awareness of how these effects are modified by adapter proteins such as β-arrestin. This has sparked interest in developing biased agonists that can preferentially activate specific pathways over others (Park et al. 2020). Interestingly, apomorphine displayed maximal or near maximal engagement of cAMP at all dopamine receptors while having sub-maximal recruitment of β-arrestin at D1, D4, and D5 receptors yet full engagement of β-arrestin at D2 and D3 receptors. It is also pertinent to note here that G protein cAMP assays involve significant amplification of signal and both full and partial agonists can sometimes reach the same maximal response (100% E_{max}) in this assay (Smith et al. 2018). While apomorphine displayed full efficacy at the D1 cAMP pathway in our study, other studies have suggested that apomorphine behaves as a partial agonist in other G protein-dependent readouts downstream of the D1 receptor (Conroy et al. 2015; Sahlholm et al. 2025). Due to these assay limitations, we cannot definitively determine from these experiments whether apomorphine has biased agonism towards G protein signaling compared to β-arrestin recruitment. Regardless, reduced recruitment of β-arrestin at D1 receptors has

been posited as important for preventing receptor desensitization and internalization with repeated drug administration (Sahlholm et al. 2025). The lower effects demonstrated by apomorphine relative to dopamine in the D1 receptor internalization assay are consistent with apomorphine's submaximal recruitment of β-arrestin and suggests that, at least at the D1 receptor, β-arrestin recruitment greatly contributes to receptor internalization. This is relevant because β-arrestin engagement is believed to contribute to the attenuation of efficacy (tolerance) seen with early investigational D1 receptor agonists, which has been a key limiting factor in their development for PD (Pearce et al. 1999; Smith et al. 2002; Gray et al. 2018). The limited effects of apomorphine on β-arrestin recruitment and receptor internalization at the D1 receptor may explain its long-term clinical efficacy in patients. More work is required to understand the potential impact of submaximal recruitment of β-arrestin at D4 and D5 receptors, which have both been shown to play a role in attentional behaviors, cognitive tasks, and decision making (Keck et al. 2019; Ferré et al. 2022).

Conversely, apomorphine displayed robust effects on β-arrestin recruitment at the D2 receptors (E_{max}: 83–90%), which aligns with published data (Klewe et al. 2008; Mann et al. 2021). β-arrestin recruitment at D2 receptors has been purported to mediate the motor efficacy of apomorphine and D2-preferring dopamine receptor agonists (Ferraiolo and Hermans 2023), though maximal improvement appears to require concerted engagement of both β-arrestin and cAMP pathways (Fienberg et al. 1998; Hervé et al. 2001; Beaulieu et al. 2004, 2005; Beaulieu and Gainetdinov 2011; Alcacer et al. 2012; Urs et al. 2015; Rose et al. 2018; Donthamsetti et al. 2020). In addition to D2 receptors, apomorphine also engaged both cAMP and β-arrestin signaling pathways at the D3 receptor. The relevance of apomorphine's relatively balanced agonism at the D3 receptor, which would support receptor desensitization and internalization upon extended stimulation, may be important, as these receptors have been implicated in the development of ICDs and neuropsychiatric side effects including hallucinations, as observed with treatment with D2-like receptor preferring agonists (Seeman 2015; Napier and Persons 2019). In this regard, case series and longitudinal evaluations of PD patients suggest that apomorphine might be less likely to induce impulse control disorders than the oral D2-selective agonists and that patients with a history of these neuropsychiatric effects may be able to tolerate apomorphine therapy without symptom recurrence (Borgemeester et al. 2016a; Rosa-Grilo et al. 2016; Houvenaghel et al. 2025; Desjardins et al. 2025). The lower risk of exacerbating pre-existing hallucinations with apomorphine (compared to D2-like receptor agonists) is an important consideration for PD patients who are predisposed to these types of neuropsychiatric symptoms (van Laar et al. 2010; Borgemeester et al. 2016b). In addition to its balanced D3 receptor agonism, apomorphine has weak $5HT_{2A}$ antagonist actions, which may also help guard against development of hallucinations (Millan et al. 2002; Newman-Tancredi et al. 2002).

To our knowledge, this is the first study to systematically compare functional activity of apomorphine on both cAMP signaling and β-arrestin recruitment across all known dopamine receptor subtypes, and our results align with the disparate published studies evaluating individual dopamine receptors (Klewe et al. 2008; Wood et al. 2015; Conroy et al. 2015; Brust et al. 2015; Park et al. 2020; Sahlholm et al. 2025). A potential limitation of our study is that the curve for apomorphine activity for some cAMP functional activity assays was lacking an established bottom to the curve (i.e., D1, D2S, and D4); however, all curves captured the inflection points necessary for calculating an EC_{50}. Because we only assessed cAMP levels (associated with G protein activation) and β-arrestin signaling, our findings should be considered a start to the full characterization of the functional effects of apomorphine at dopamine receptors. Future work should include assays that are more proximal to receptor activation (e.g. bioluminescence resonance energy transfer assays) to better understand and quantify potential biased agonism at dopamine receptor subtypes (Smith et al. 2018), as well as a full characterization of internalization at all dopamine receptor subtypes. Dopamine receptors engage multiple signaling pathways to differentially affect downstream signaling and regulate behavioral output. Continued research on dopamine receptor functional effects will undoubtedly expand our understanding of differential drug actions that contribute to therapeutic efficacy of antiparkinsonian treatments.

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Data Availability Data available from corresponding author upon reasonable request.

Declarations

Conflict of interest Brittney Yegla, Jonathan Rubin, Mindy Grall, and Andrea Formella are employed by Supernus Pharmaceuticals Inc. Peter Jenner reports honoraria for consultancy and advisory boards from AbbVie, Bial, Britannia Pharmaceuticals, Cerevel, Kyowa Kirin, Supernus, and Zambon.

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