
11

DOPAMINE-RELEASING AGENTS

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11.1 INTRODUCTION

Dopamine-releasing agents are compounds that induce efflux of dopamine from the dopamine transporter (DAT) containing neurons [1–5]. Through this action, dopamine releasers elevate synaptic levels of neurotransmitter. These increases are similar to changes induced by dopamine-uptake inhibitors, which also elevate synaptic levels of dopamine, but differ mechanistically. Releasers elevate neurotransmitter by direct efflux, whereas uptake inhibitors indirectly elevate neurotransmitter by preventing normal synaptic clearance. Both mechanisms lead to similar stimulant

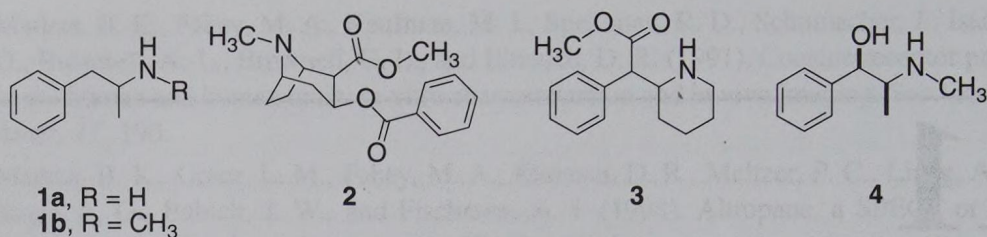


Figure 11-1 Dopamine releasers and uptake inhibitors.

behaviors, as evidenced by the parallel behaviors observed between the best known examples (Fig. 11-1): the releasers amphetamine (**1a**) and methamphetamine (**1b**), and the uptake inhibitors cocaine (**2**) and methylphenidate (Ritalin, **3**). All four compounds are highly addictive, presumably due to their action on dopaminergic neurons, and are abused around the globe.

The earliest known dopamine releaser is probably ephedrine (**4**), the active ingredient in naturally occurring plants such as *Ephedra sinica*, also known as the Chinese herb *ma huang* [6,7]. These herbs were used for centuries for a variety of purposes, including stimulation, asthma, decongestion, and appetite suppression. Ephedrine was first isolated and identified in 1885 by Nagai Nagayoshi from *Ephedra vulgaris*. The clinical usefulness of these herbal extracts, and identification of the active ingredient, created interest in the synthesis of ephedrine (and analogs), possibly leading to the first synthesis of amphetamine shortly thereafter, in 1887 (**1a**) [8]. Methamphetamine (**1b**) was first synthesized in 1893 by Nagayoshi, using a route starting with ephedrine. Amphetamines were some of the first medicinally active compounds not derived from natural products. It should be noted that amphetamine, methamphetamine, and several additional analogs have been isolated from *Acacia berlandieri* and *A. rigidula*, a group of shrubs found in Texas [9–11].

Release does not occur just with dopaminergic neurons; the same process is found in serotonergic and noradrenergic neurons [12]. The most commonly discussed serotonin releasers (Fig. 11-2) are the empathogenic/psychedelic 3,4-methylenedioxy-methamphetamine (**5**, MDMA) [13], also known as the street drug “ecstasy,” and the anorectic fenfluramine (**6**) [14]. Corresponding serotonin-(re)uptake inhibitors include antidepressants such as paroxetine (Paxil, **7**) and fluoxetine (Prozac, **8**) [15]. Little is known about compounds that induce norepinephrine release, but fenfluramine and metabolites have been found to release norepinephrine [16], and norepinephrine release has been implicated in the stimulant properties of releasers along with their dopaminergic activity [17].

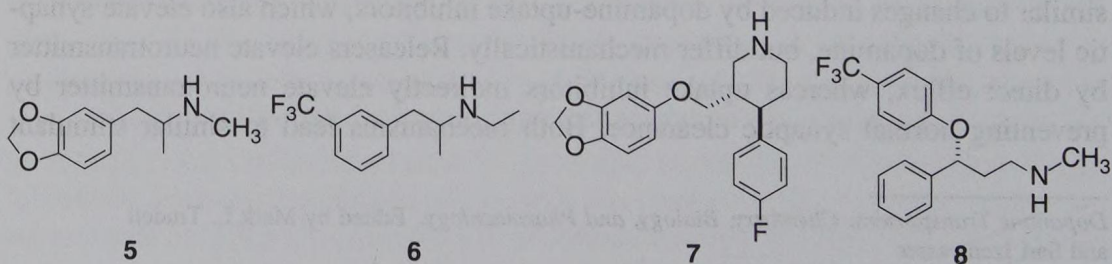


Figure 11-2 Serotonin releasers and uptake inhibitors.

11.2 RELEASE MECHANISM

Several groups have focused on the mechanism of action of releasers, due to both the importance of research on abused releasers (amphetamine and MDMA) and to curiosity about transporter mechanisms in general [1,2,18–21]. The most important finding has been that releasers are substrates of the transporters, and that this translocation is required for neurotransmitter efflux [2]. Other mechanistic hypotheses for efflux initiation have included membrane diffusion, internal release of vesicular neurotransmitter, and a chemical chaperoning mechanism. Most evidence now suggests that releasers act as substrates and induce efflux once inside the neuron or in a translocation state past substrate recognition. The delineation between dopamine release and uptake inhibition is important because the kinetics of neurotransmitter change differ dramatically, and these changes result in differences in feedback and receptor/transporter regulation. A releaser dumps neurotransmitter directly into the synapse, regardless of endogenous tone. An uptake inhibitor acts indirectly and relies on normal synaptic vesicular release to increase neurotransmitter, which may be considered a feedback mechanism.

Yu et al. have devised a bioassay screening strategy aimed at binning releasers and uptake inhibitors, and have used this strategy to identify new dopamine releasers [22]. Releasers, such as methamphetamine, are often thought of as having both releaser and uptake inhibitor activity, but the latter is an artifact of the assay. Neurotransmitter uptake inhibition and release assays measure the same endpoint: exogenous neurotransmitter. Each assay independently cannot differentiate the two types of compounds, but when combined, compounds can be binned as uptake inhibitors or releasers. Uptake inhibitors are active in uptake inhibition assays, but not in release (superfusion) assays, since the neurotransmitter is preloaded. The synaptosomes (or cells) in uptake inhibition assays do not undergo the normal neuronal vesicular release process required for an uptake inhibitor to elevate neurotransmitter. On the other hand, releasers are active in both assays, which led people to assume that releasers have both activities. These differences have been exploited to bin compounds as releasers (substrates) or uptake inhibitors (nonsubstrates). An electrochemical method has also been reported by Sonders et al. taking advantage of the electronic differences between compounds that do and do not transport [1].

The transporter-induced efflux mechanism remains controversial [2]. Initially, it was assumed that efflux occurs by a reversal of the process that causes influx. However, recent evidence suggests that this assumption may be incorrect. Evidence suggests that releaser-induced efflux may occur by a transporter oligomerization event followed by transporter-mediated neurotransmitter outflow. Seidel et al. concatenated a serotonin and GABA (*r*-aminobutyric acid) transporter and loaded cells with GABA [23]. Introduction of a serotonin releaser induced GABA release. Kahlig et al. have recently reported that transporter-mediated efflux may occur by a channel-like mechanism [24].

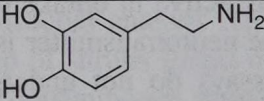
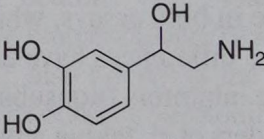
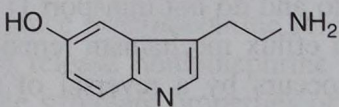
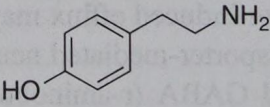
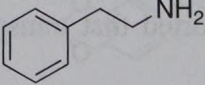
The term *dopamine releaser* suggests that a compound is able to release a specific neurotransmitter, but this may not be the case. The term is more likely to be meant to refer to compounds that induce neurotransmitter efflux via a dopamine transporter. Similarly, *serotonin releaser* and *norepinephrine releaser* refer more accurately to

a compound-inducing efflux via serotonin and norepinephrine transporters, respectively (SERT and NET). The compounds undergoing efflux may not be limited to the primary transporter neurotransmitter, and may include other accumulated neurotransmitters within the neuron or cell. This possibility is intriguing, especially in the case of neurons expressing multiple transporter types. A dopamine releaser acting on a neuron expressing both SERT and DAT may induce both dopamine and serotonin efflux.

11.3 NEUROTRANSMITTERS AND RELEASE

While amphetamine and methamphetamine are widely known as dopamine releasers, neurotransmitters such as dopamine (**9**), norepinephrine (**10**), serotonin (**11**), tyramine (**12**), and β -phenethylamine (**13**) also cause DAT-induced efflux of dopamine [4] (Table 11-1). Dopamine was found to be a DAT releaser, albeit far weaker than amphetamine, with an EC_{50} value of 86.9 nM. β -Phenethylamine ($EC_{50} = 39.5$ nM) was found to be more potent as a DAT releaser, and tyramine ($EC_{50} = 119$ nM) was roughly equipotent. Norepinephrine ($EC_{50} = 869$) and serotonin

TABLE 11-1 Comparison of the DAT-, NET-, and SERT-Releasing Activity of Endogenous Neurotransmitters

Compound	Name	Structure	EC_{50} (nM)		
			DAT	NET	SERT
9	Dopamine		86.9	66.2	Inhibitor
10	Norepinephrine		869	164	Inactive
11	Serotonin		1960	Inhibitor	44.4
12	Tyramine		119	40.6	2775
13	β -Phenethylamine		39.5	10.9	Inactive

Source: DAT, NET, and SERT data from Rothman et al. [4].

($EC_{50} = 1960$ nM) were found to be dopamine releasers but were far weaker than dopamine. Self-release also occurs with serotonin ($EC_{50} = 44.4$ nM) and norepinephrine ($EC_{50} = 164$ nM).

Neurotransmitter-induced efflux is not limited to the dopamine transporter. Dopamine induces NET release ($EC_{50} = 66.2$ nM) more potently than does norepinephrine ($EC_{50} = 164$ nM), but is a weak serotonin uptake inhibitor ($IC_{50} = 6489$ nM), suggesting that dopamine is a NET substrate but not a SERT substrate. Tyramine is the only monoamine neurotransmitter that induces neurotransmitter efflux through all three transporters (DAT, NET, and SERT), meaning that it is a substrate of all three transporters. The real significance of these observations is not clear, but may imply that efflux is a common neurotransmitter regulatory mechanism induced by any transporter substrate, possibly as a protective mechanism.

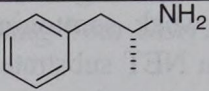
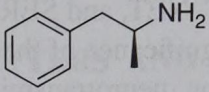
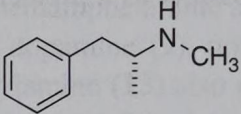
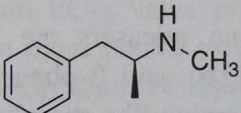
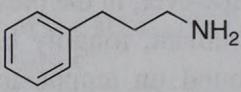
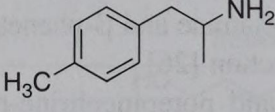
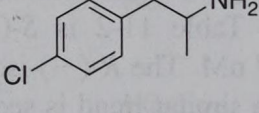
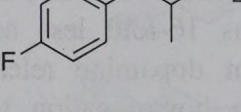
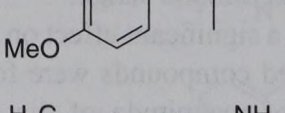
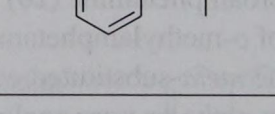
11.4 AMPHETAMINES

The most commonly studied dopamine releasers are amphetamines, including amphetamine (**1a**), methamphetamine (**1b**), and β -phenethylamine (PEA, **13**) [4]. β -Phenethylamine is not a methamphetamine-like stimulant because of rapid metabolism by monoamine oxidase (MAO). However, in the presence of an MAO inhibitor, PEA is a potent dopamine-releasing stimulant, roughly equipotent to amphetamine [25]. The additional α -methyl group found on amphetamines blocks MAO metabolism. Amphetamine-based compounds have been found to be good MAO inhibitors, suggesting that even though both amphetamine and β -phenethylamines bind to MAO, the α -methyl group blocks enzyme function [26].

Table 11-2 shows the dopamine- and norepinephrine-releasing properties of a series of amphetamine analogs varying in substituent and substitution location [27]. The most potent compound in Table 11-2 is *S*-(+)-amphetamine, which releases dopamine with an EC_{50} of 8.7 nM. The *R*-(-)-isomer is threefold weaker, at 27.7 nM (EC_{50}). Although weaker, a similar trend is seen for the optical isomers of methamphetamine. *S*-(+)-methamphetamine releases dopamine with an EC_{50} of 24.5 nM, while the *R*-(-)-isomer was 16-fold less active at 416 nM (EC_{50}). Phenethylamine (**13**) is also a potent dopamine releaser, with a potency of 39.5 nM (EC_{50}). A one-carbon chain homologation to phenpropylamine (**14**) reduces potency significantly to the micromolar range.

Aromatic substitution changes have a significant effect on amphetamine potencies. Chloro-, fluoro-, and methyl-substituted compounds were found to have dopamine-releasing potencies within an order of magnitude of that of amphetamine. EC_{50} values ranged from 11.8 nM for *m*-chloroamphetamine (**20**) to 68.2 nM for *p*-chloroamphetamine (**16**), with the exception of *o*-methamphetamine (**23**), which was substantially weaker ($EC_{50} = 127$ nM). The *meta*-substituted compounds were found to be more potent than their corresponding *ortho* or *para* analogs. The *para*-substituted compounds were the weakest for chloro and fluoro substitution, but the *ortho* analog was the weakest for methyl substitution. Methoxy substitution caused a dramatic decrease in potency. *m*-Methoxyamphetamine (**22**) was found to have an EC_{50} of

TABLE 11-2 Comparison of the DAT- and NET-Releasing Activity of a Series of Amphetamines

Compound	Structure	EC ₅₀ (nM)	
		DAT	NET
R(-)-1a		27.7	9.5
S(+)-1a		8.7	10.2
R(-)-1b		416	28.5
S(+)-1b		24.5	12.3
14		1491	222
15		44.1	22.2
16		68.5	23.5
17		51.5	28.0
18		867	166
19		33.3	18.3

(Continued)

TABLE 11.2 Continued

Compound	Structure	EC ₅₀ (nM)	
		DAT	NET
20		11.8	9.4
21		24.2	16.1
22		103	58.0
23		127	37.0
24		62.4	19.1
25		38.1	24.1
26		1478	473

Source: DAT and NET data from Rothman et al. [4]. Some of the data were presented by Blough et al. [27].

103 nM, but the *para* and *ortho* analogs (**18** and **26**) were far worse, generating EC₅₀ values of 867 and 1478 nM, respectively. These data show that dopamine-releasing potencies can vary depending on aromatic substituent and point of attachment.

11.5 MDMA ANALOGS AND METABOLITES

MDMA (**5**) is normally labeled a serotonin releaser, but it also releases dopamine [4] (Table 11-3). This 3,4-methylenedioxy-substituted amphetamine is much weaker than amphetamine as a DAT releaser. MDMA (**5**) releases dopamine with an EC₅₀ value of 278 nM, compared to the more potent compound amphetamine (**1a**, EC₅₀ = 8.7 nM). Interestingly, the potency of MDMA at the DAT appears to fall between the *meta*- and *para*-methoxyamphetamine analogs, which release with EC₅₀ values of 103 and

TABLE 11-3 Comparison of the DAT- and NET-Releasing Activity of MDA, MDMA, and Metabolites

Compound	Name	Structure	EC ₅₀ (nM)	
			DAT	NET
5	MDMA		278	110
R(-)-5	(-)-MDMA		3682	564
S(+)-5	(+)-MDMA		142	136
27	MDA		190	108
R(-)-27	(-)-MDA		900	287
S(+)-27	(+)-MDA		98.5	50.0
28	HHMA (N-Me-α-Me-DA)		1729	77
29	HHA (α-Me-DA)		3485	33
30	HMMA		607	625
31	HMA		1450	694

Source: DAT and NET data from Rothman et al. [4]. The metabolite data were presented by Bauman et al. [28].

867 nM, respectively. As was observed with both amphetamine and methamphetamine, the *S*-(+) isomer ($EC_{50} = 142$ nM) is more potent than the *R*-(-) isomer ($EC_{50} = 3682$). The same trends were observed with the N-demethylated compound MDA (**27**). N-Methylation appears to reduce dopamine-releasing activity, but the effect was not as great as with amphetamine and methamphetamine.

MDMA metabolizes to MDA by N-dealkylation [13]. Both MDMA and MDA metabolize further by conversion of the methylenedioxy group to a catechol, followed by methoxylation of the *meta*-hydroxyl by catechol-*O*-methyltransferase (COMT). The two catechol metabolites, HHMA (**28**) and HHA (**29**), are dopamine analogs and have much weaker activity as dopamine releasers; however, they are both potent releasers of norepinephrine [28]. Methoxylation of the catechol, forming HMMA (**30**) and HMA (**31**), causes a slight increase in DAT activity, but reduces activity dramatically as a norepinephrine releaser and suggests that methoxylation of endogenous catechols is an important regulatory mechanism.

11.6 OTHER DOPAMINE RELEASERS

Several other compounds are known to induce dopamine release, originally identified by their stimulant activity in behavioral assays [4] (Table 11-4). 1-Benzylpiperazine (BZP, **32**) is also an abused stimulant recently scheduled by the DEA [29,30]. BZP has been used in combination with the selective serotonin releaser *m*-trifluoromethylphenylpiperazine (TFMPP, **33**) to create "legal X" [31,32]. Phenmetrazine (**34**), a stimulant known to act by releasing dopamine, was clinically used as an anorectic but removed due to abuse [33]. The N-methylated analog phendimetrazine (Adipost, **35**) is currently used in the clinic as an anorectic and is probably effective due to metabolism to **33**. The appetite suppressant aminorex (**36**) is another compound found to release dopamine and have stimulant activity [4,34,35]. All of these compounds are secondary cyclic amines, and have much weaker activity than that of amphetamine.

Another general class of dopamine-releasing agents are the aminoacetophenones, such as cathinone (**37**), the principal active compound in the stimulant *Catha edulis* (known as Khat) [4,22,36]. Cathinone was found to release both dopamine and norepinephrine. In contrast to the amphetamine analogs, N-methylation to methcathinone (**38**) [4,22,37] increased DAT activity from an EC_{50} value of 83.1 nM to 50 nM [27]. N-Ethylation to **39** caused the compound to become an uptake inhibitor with an IC_{50} of 1067 nM. Interestingly, the latter compound retains norepinephrine-releasing properties, albeit somewhat weaker. As noted earlier, (-)-ephedrine (**4**) is a dopamine releaser and is essentially methcathinone with a reduced ketone.

11.7 DOPAMINE RELEASE VS. NOREPINEPHRINE RELEASE

Dopamine releasers also release norepinephrine, and surprisingly, in all cases more potently [17,38,39]. Most of the trends evident for dopamine release are also true for norepinephrine release, but the differences between compounds tend to be

TABLE 11-4 Comparison of the DAT- and NET-Releasing Activity of Selected Non-Phenethylamine Dopamine Releasers

Compound	Name	Structure	EC ₅₀ (nM)	
			DAT	NET
32	1-Benzylpiperazine		307	62.2
33	3-Trifluoromethylpiperazine		Inactive	Inactive
34	Phenmetrazine		131	50.4
35	Phendimetrazine		Inhibitor	Inhibitor
36	Aminorex		49.4	26.4
37	Cathinone		83.1	23.6
38	Methcathinone		49.9	22.4
39	N-Ethylaminopropiophenone		Uptake inhibitor	99.3
4	(-)-Ephedrine		236	43.1

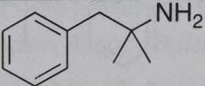
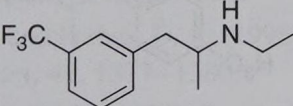
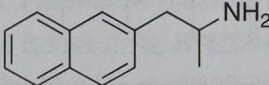
Source: DAT and NET data from Rothman et al. [3], Rothman and Baumann [4], Yu et al. [22], and Blough et al. [27].

much smaller. Most historical studies on releasers do not report norepinephrine release, possibly because researchers concentrated on behavioral endpoints, such as stimulant activity, and assumed that such activity was solely a dopaminergic effect. Tseng et al. [40] studied the three methoxyamphetamine analogs (**18**, **22**, **26**) and is the only group known to have included information about the releasing activity of all three transporters. The general trend that dopamine releasers induce NET-induced efflux, and more potently, is an important discovery, due to the potential problems associated with elevations of norepinephrine, such as cardiotoxicity [41]. Concurrent norepinephrine release has also made it difficult to find a truly selective dopamine releaser.

11.8 SEROTONIN-RELEASE MODULATION

Serotonin-releasing activity has been found to modulate the effects of dopamine release [3,4,42]. Compounds releasing dopamine without significant serotonin activity, such as amphetamine, are potent stimulants. Compounds releasing dopamine but with significant serotonin activity are not. This is most evident in the activity of the releaser anorectic Fen-phen, a combination of the dopamine and norepinephrine releaser phentermine (**40**) and serotonin releaser fenfluramine (**41**) [12,43–45] (Table 11-5). Phentermine is a known stimulant, but when combined with fenfluramine does not show significant stimulant activity [46,47]. These observations suggest that the serotonergic activity attenuates stimulant activity and thus the effects of dopamine release. The effects of serotonin release on stimulant activity can also be seen in the development of PAL-287 (**42**) as a potential addiction cessation agent [48]. Initial reports on the activity of PAL-287 suggested that it was inactive

TABLE 11-5 Comparison of the DAT-, NET-, and SERT-releasing Activities of Selected Compounds

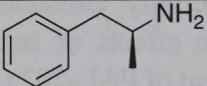
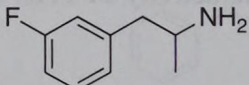
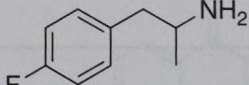
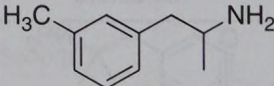
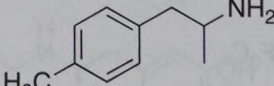
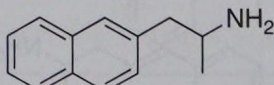
Compound	Name	Structure	EC ₅₀ (nM)		
			DAT	NET	SERT
40	Phentermine		262	39.4	3511
41	Fenfluramine		Inhibitor	739	79.3
42	PAL-287		12.6	11.1	3.4

Source: DAT, NET, and SERT data from Rothman et al. [4] and Rothman et al. [48].

because it failed to induce locomotor stimulation [49]. Rothman et al. [48] have found PAL-287 to be a potent dopamine releaser but to lack potent stimulant activity, presumably due to its activity as a serotonin releaser.

Wee et al. looked at the reinforcing properties of a series of amphetamine analogs [PAL-353 (**21**), PAL-303 (**17**), PAL-314 (**19**), and PAL-313 (**15**)] in rhesus monkeys which varied in DAT- and SERT-releasing potencies (Table 11-6). These compounds vary from 80-fold selective for dopamine over serotonin (PAL-353) to nearly equipotent (PAL-313) [50]. Dopamine-selective compounds were found to be more reinforcing than were less selective compounds. The 18-fold dopamine selective releaser PAL-303 was also found to be a stimulant in rats, similar to amphetamine [51]. PAL-287 (**42**) was also not strongly reinforcing [48]. Similar effects were observed by Negus et al. while studying similar compounds in cocaine- and food-maintained responding experiments in primates [45]. Amphetamine and methamphetamine showed reduction of cocaine but not food self-administration. The addition of serotonergic activity caused reduction in both behaviors.

TABLE 11-6 Comparison of the DAT- and SERT-Releasing Activity of Selected Phenethylamines

Compound	Name	Structure	EC ₅₀ (nM)		DAT Selectivity
			DAT	SERT	
(+)-1a	(+)Amphetamine		8.0	1756	219
21	PAL-353		24.2	1937	80
17	PAL-303		51.5	939	18
19	PAL-314		33.3	218	6.5
15	PAL-313		44.1	53.4	1.2
42	PAL-287		12.6	3.4	0.27

Source: DAT and SERT data from Rothman et al. [4], Rothman et al. [48], and Wee et al. [50].

11.9 CONCLUSIONS

This review by no means covers all of the recent literature on amphetamines and releasers. Some of the most exciting work is mechanistic in nature and is beyond the scope of this chapter. Absolute releaser potencies may differ between laboratories to a small degree, depending on the specific assay conditions. The intention here was to show how structural changes affect activity based on the same assay conditions. Although dopamine releasers have been known for over a century, modern pharmacology continues to uncover their potential as pharmacotherapies as well as experimental tools for the study of dopaminergic neurons and neural networks.

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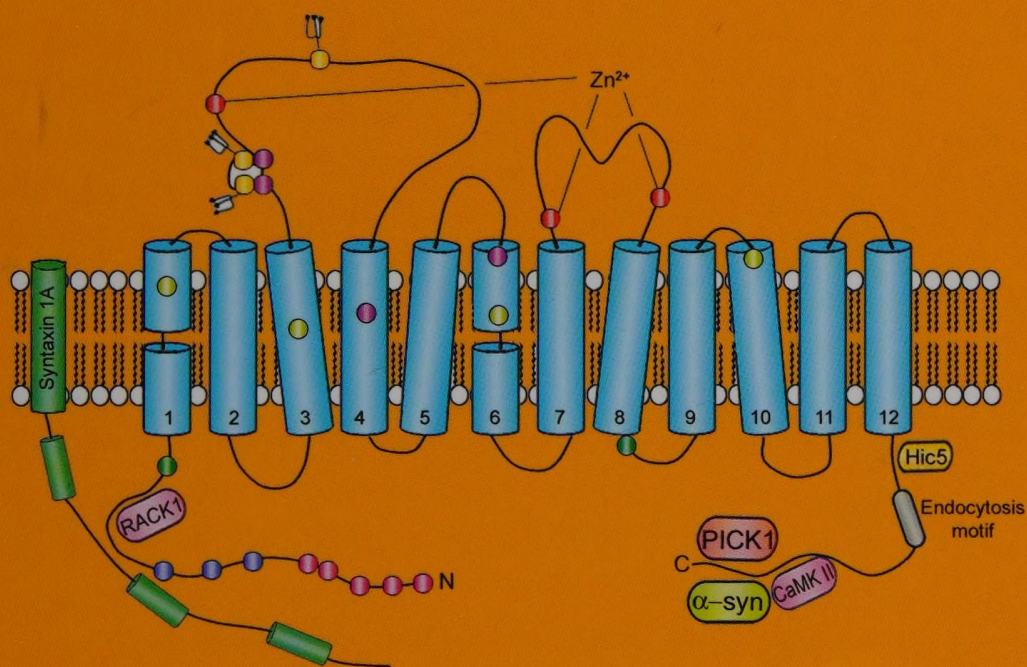
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