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Meta description (<300 char/~50 words)	This is an update of the pharmacology and potential interactions combining stimulants such as amphetamine, methylphenidate, and modafinil with MAOIs.

CNS Stimulants and MAOIs 1

Abstract

This commentary reviews papers updating knowledge about how dopamine is handled in the neuronal synapse and how reuptake inhibitors influence those processes from a theoretical and clinical point of you view. Methylphenidate, bupropion, and modafinil are discussed.

Introduction

The CNS ‘stimulants’ (used therapeutically) that are considered here are, (Part 1) **methylphenidate, (ar)modafinil, bupropion***, and (Part 2) **amphetamine, ephedrine, pseudoephedrine, adrenaline, pramipexole, midodrine, caffeine**, and **Part 3**, (not used therapeutically) **3,4-methylenedioxy-methamphetamine (MDMA)**. I will also mention NA/DA re-uptake-mediated reactions, especially since there may be some cross-over, as well as mentioning 5HT-mediated ones (i.e., ST), which I have dealt with in great detail in other commentaries.

A wide variety of drugs with **dissimilar mechanisms of action** are described as stimulants, these include numerous (essentially) non-therapeutic agents: Cocaine, methamphetamine, MDMA, khat (a herbal cathinone), nicotine, caffeine, and other cathinones (mephedrone (4-MMC), M-CAT), methylone, meth-cathinone, buphedrone, pyrovalerone etc. Most effect dopamine in some way, and most drugs that effect dopamine levels are described as stimulants, possibly except for L-Dopa. Some sources include steroids as stimulants.

The term ‘stimulant’ should be eschewed, one should now follow the new recommendations for neuroscience-based nomenclature of drugs [1-3].

* Bupropion is considered a cathinone-derivative

Amphetamines act as releasers (previously called ‘indirectly acting sympathomimetic amines’), whereas methylphenidate acts as re-uptake inhibitor, midodrine and others are direct receptor agonists. These were previously described by the imprecise term ‘directly acting sympathomimetic amines’ — but agonists at which receptors? Alpha 1 or 2, beta 1, 2, or 3. And where does that leave beta receptor partial agonists?

Note that noradrenaline is a weaker agonist than adrenaline at beta-2 adrenoceptors [4].

These three different mechanisms of action determine the type and magnitude of any drug interaction, as illustrated in the [serotonin toxicity triangle in the introduction to ST](#).

To discuss them all under one heading of ‘stimulant’ is to confuse the different pharmacological mechanisms and different types of pharmaco-dynamic interactions with different implications — not enlightening, not helpful.

The words stimulant and ISA will not be used further in this commentary except when referring to pre-existing literature.

The term stimulant is redundant, one should follow the new recommendations for neuroscience-based nomenclature of drugs

About dopamine — A snapshot

Nothing in biology makes sense, except in the light of evolution.
[Theodosius Dobzhansky](#),

Here is a snapshot of recent molecular-level research findings about DA, its evolution, and its regulation. It draws especially on Sulzer and Reith [5-8]. It is a complex subject, but here are some key issues and fascinating new findings.

Dopamine has played an essential role in the biology of organisms throughout evolution, from the earliest plants where it plays a role in, *inter alia*, disease resistance [9].

Dopamine ([structure](#)), 3,4 Dihydroxyphenethylamine, is a reactive and potentially toxic molecule which is only stable at a pH below physiological pH. In plants it is involved in the browning reaction when plant tissue is damaged. It is light-sensitive and oxidizes in air, as in the browning of a cut banana or avocado. Browning is caused by conversion to melanin-compounds, which may have antimicrobial properties.

Dopamine is only stable at a pH well below physiological pH

Human intra-neuronal mono-amine storage vesicles — which have the **vesicular monoamine transporter (VMAT)** on their surface-membrane — maintain a high concentration gradient of hydrogen ions compared to the cytosol (cellular fluid), having a pH of around 5.6, compared to the cytosol at 7.2. This gradient is kept up by H⁺-ATPase, which pumps protons into the vesicles.

The **vesicular monoamine transporter (VMAT)** is genetically related to, and derived from, the primitive bacterial anti-porters (which expel with a wide range of toxic substrates from uni-cellular organisms). It was probably acquired by higher organisms from bacteria later in evolution by gene transfer [10]. It transports a range of noxious compounds to the cell’s exterior in bacteria: the human VMAT is also non-specific in that it removes all these (structurally different) neuro-transmitters, NA, DA, 5HT, Hist, Ach, and trace amines, from

the cytoplasm into intracellular storage compartments (vesicles), ready for release into the synapse via **exocytosis***.

The VMAT is related to the other [anti-porter family](#) members, e.g., P-glycoprotein, which is the transporter responsible for resistance to anti-cancer cyto-toxics. Their similar genetic sequences demonstrate their phylogenetic relationships. Human cells expressing VMAT are resistant to neurotoxins, which are sequestered into the vesicles by VMAT.

Many facets of medicine can be understood better through the lens of evolution

Synthesis and storage

Dopamine synthesis occurs in the neuronal cytosol, it is transported to, and concentrated in, **synaptic vesicles (SVs)** via VMAT by ~100,000-fold to a concentration of ~0.1M at a pH of 5.6.

Vesicles are assembled in the Golgi apparatus and then transported down the neuron to the terminal which involves proteins called kinesins, once in the terminal bouton, vesicles are recycled within the nerve terminal — they are divided into three phases/groups; 1) storage (reserve) vesicles, 2) recycling vesicles, and 3) resting pool, 4) immediate release vesicles, also called the readily releasable pool (juxtaposed with the cell membrane).

Exocytosis (SV release into the synapse) can be synchronous or asynchronous, each have different SV recycling pathways.

Recycling of SVs after exocytosis into the synapse is faster than de novo synthesis of SVs in the cell body; also, axonal transport of SVs to the synapse is probably too slow to sustain high rates of discharge.

If I tried to explain, and understand, any more about this SV cycle my head might explode, so if you wish to know more consult Chanaday [11] and other references above — but at least that gives glimpse of the extraordinary detail in which these processes are now being resolved.

Vesicles (in mice), contain ~30,000 DA molecules; this content is modulated by drugs such as amphetamine and L-DOPA — indeed L-DOPA increases quantal size by 300%.

Vesicular DA stores are regulated in part by DAT functionality. Emerging evidence suggests that brain derived neurotrophic factor (BDNF) also plays a part in regulating DA release.

Evidence supports a role for DAT substrates, like amphetamine, in inducing DAT internalization. Trafficking of DAT across the cell **surface†** may be the predominant mechanism of acute DAT regulation.

Activation of D2 auto-receptors (probably the short isoform D2 receptor) decreases release by mechanisms that include inhibiting DA synthesis, enhancing DA uptake by the DAT, and regulating VMAT expression.

In the dorsal and ventral striatum **nicotinic acetylcholine receptors (nAChRs)** are expressed densely on the DA axons and ACh released from striatal **Cholinergic Inter-neurons (ChI)** effects DA release-probability, and its dynamic short-term plasticity through action at nAChRs and **muscarinic acetylcholine receptors (mAChRs)**.

* Exocytosis is the process by which vesicles fuse with the neuronal cell membrane and then open to the exterior, discharging the contents into the synaptic cleft.

† This describes how the active site of the transporter is switched from facing outside the cell, to facing inside the cell — if it is facing inside the cell it cannot function as a reuptake mechanism unless it is switched back again.

In the striatum, recycling of released DA by re-uptake probably plays a major role in determining the releasable pool of DA.

In the prefrontal and cingulate cortex, hippocampus, and VTA dopamine is also cleared by the NAT [6, 12]. In the low DAT pre-frontal cortex phasically fired DA may be cleared mostly by COMT, and diffusion may play a role in DA clearance. In the striatum, DA uptake is the primary mechanism for the clearance of DA ($T_{1/2}$, 60 ms), in prefrontal cortex fewer release and uptake sites lead to slower DA clearance ($T_{1/2}$, 2 s). In DA-poor regions like prefrontal cortex DAT inhibitors are less effective in slowing DA clearance.

Striatal postsynaptic D1 and D2 receptors are distant from DA synapses, at extra-synaptic locations along dendritic membranes, often with a higher density in the peri-synaptic zone of synapses formed by glutamate terminals on the heads of dendritic spines. It may be necessary for DA to spill over from release sites to activate its receptors, meaning DA transmission is mainly extra-synaptic. Indeed, striatal DA uptake sites are rarely found on the DA synaptic membrane and, rather, may be distributed throughout the membrane of DA fibers.

Sulzer [6] summarises it thus:

The net DA concentration at any point in time results from a dynamic equilibrium between release and uptake. Both are regulated by mechanisms that range from DA neuron firing to local intracellular and intercellular regulatory signals within target regions. Tonic activity of DA neurons translates into tonic [DA]_o, whereas burst activity apparently translates into transiently enhanced [DA]_o, which is also locally **regulated**^{*}. Overall, the moment-to-moment interplay among firing, release, uptake, and auto- and hetero receptor dependent modulation is not only dynamic, but state and region-dependent.

Although the above is complex and potentially confusing, I hope it gives some illumination and insight into the interesting and amazing advances in the molecular-level understanding of these extraordinary mechanisms. It is relevant to clinical medicine. For instance, it suggests that reuptake inhibitors may attenuate the effects of amphetamines.

Re-uptake inhibitors

Methylphenidate

Methylphenidate is a dopamine reuptake inhibitor (DRI), a weak NRI, but has **no significant potency as an SRI** (see table below).

There have been a couple of PET Studies done in humans which both showed similar findings of modest blockade (40-70%) of the DAT at therapeutic doses [14, 15]

dose-dependent blockade of dopamine transporter; means=12% (SD= 4%) for 5 mg, 40% (SD=12%) for 10 mg, 54% (SD=5%) for 20 mg, 72% (SD=3%) for 40 mg, and 74% (SD=2%) for 60 mg.

Clinical

Methylphenidate and MAOIs have been in use together for 50 years, it would be astonishing if many people had not ingested the combination by now: neither death, nor even morbidity, from such an event has been reported (while it has been, many times, with amphetamine).

Methylphenidate is most widely used as a treatment for attention-deficit hyperactivity disorder (ADHD) in children, and more recently in the treatment of melancholic depression [16]. It has been supposed by some to have serotonergic

^{*} Tonic and burst firing is another world of functional plasticity, again beyond the scope of this commentary, see Shao [13]

effects; but if that were so it would carry a risk of precipitating fatal serotonin toxicity with MAOIs, and it does not. There are no case reports indicating ST with methylphenidate in combination with MAOIs, or other serotonergic drugs [17, 18], and most certainly no fatalities [19].

Also, as with mirtazapine, trazadone, and amitriptyline, methylphenidate does not produce serotonergic side effects, or signs of serotonin toxicity in over-dose [20, 21], nor significant interactions with other **drugs*** [22].

It does not raise prefrontal cortex 5-HT levels, but modestly raises NA and DA [24-26].

The occurrence of serotonin-mediated side effects, and signs of ST in over-dose, or if combined with MAOIs, are a measure of a drugs' clinically significant serotonin-mediated effect in humans. If these effects are not produced, then clinically significant ST is most unlikely [27-30].

Methylphenidate is safe in combination with MAOIs

Methylphenidate is safe in combination with MAOIs; see Feinberg's review of MAOIs and CNS stimulants [31], which found, in agreement with my database on ST:

no documented reports [...] of hypertensive crises or fatalities occurring when the stimulant was cautiously added to the MAOI.

and also, see [32, 33].

The above is in keeping with its negligible 5-HT transporter affinity (>10,000 nM), absence of releaser effect, and apparent inability to cause even small increases in brain serotonin levels. Rothman's data does not include methylphenidate, thus there is no releaser potency data. If methylphenidate did act as a releaser of 5-HT in humans then it would be predicted that this effect would be lessened by selective serotonin reuptake inhibitors (**SSRIs**)[†], and interaction with MAOIs would cause severe ST: none of those things are the case, thus, we can be sure it has no significant serotonin-mediated effects.

Since its selectivity for DAT/NAT is almost 10/1 it is reasonable to describe it as selective dopamine reuptake inhibitor

Methylphenidate Human cloned receptor affinities (HCR)

DAT 40 nM,

NAT 350 nM

SERT >10,000 nM

Bupropion

Bupropion is considered to produce its mild antidepressant effects via DAT blockade, but PET studies show that at clinically relevant doses (up to 450 mg/day) the drug occupies only about 25% of DAT binding sites [34-36] and increases extracellular dopamine levels only slightly [37]. Its metabolite, hydroxy-bupropion (which may be the active moiety anyway), has a similarly weak effect [38]. Although higher occupancies are often considered necessary for therapeutic effects — cf. the 80% rule [39] — it is, nevertheless, notable that in dopamine pathways small changes can have significant behavioural effects.

* The Sherman case was not serotonin toxicity, but blood pressure elevation [23].

† As explained in the commentary that sets out the 'serotonin toxicity triangle' model, remember that all releasers need to enter the pre-synaptic nerve in order to produce an effect; if the relevant transporter is blocked they cannot do that.

This correlates with clinical experience where patients who get an improvement with tranlycypromine, who have previously had bupropion, recognise that it is a pale reflection of TCP in terms of improving energy and motivation.

This reminds me of the quotation from Samuel Johnson, which Boswell recorded when they were at dinner with the famous artist, Sir Joshua Reynolds. There was a discussion about the status of claret wine — in those days it was pale and weedy stuff. One of the party stated that Claret was for boys, and port was for men. Whereupon Johnson interjected, 'No Sir, claret is for boys, port is for men, but Brandy is for heroes.'

It has no untoward interactions with MAOIs. See [separate commentary](#) specifically about this drug for further details.

Modafinil, armodafinil

One detailed review says many studies suggest that modafinil must target an intracellular protein or receptor, not an extracellular site, for it to bring about its many and various effects [40]. It does have effects via moderately strong re-uptake inhibition of DA and weak inhibition of NA, but its mechanisms are complex, uncertain, and yet to be clearly elucidated.

It is probably justified to include it in this category of reuptake inhibitors, since that is either its major effect, or one of its prominent effects. I do not presently have recourse to Stephen Stahl's latest edition of the great book, my 'review copy' is yet to arrive. I am sure he will have adopted neuroscience classification principles; I await news of how it is classified! I am sure there will be a pretty picture with lots of little coloured receptors on it!

PET studies demonstrate it does significantly block the DAT in humans at clinically relevant doses (200-400 mg/day) to about the same extent as methylphenidate [41, 42].

A study in Rhesus monkeys produced similar data [43].

Armodafinil (the R-enantiomer) seems to take longer to reach peak levels and has a longer half-life, which are desirable properties and may be an improvement. PET studies show 250 mg occupied striatal DAT by about 60%, accompanied by small parallel increases in extra-cellular dopamine [41].

It activates the orexin pathway thus promoting vigilance, and increases histamine (remember, blocking H1 receptors causes sedation).

It promotes vigilance, at least in part, via dopamine related mechanisms.

There is a difference between *in vitro* profile and *in vivo* findings. Modafinil does increase extracellular DA and NA (microdialysis reports are convincing — personal communication, Professor Stanford). Because the NA transporter has a higher affinity for DA than NA, inhibition of DA uptake causes an indirect effect (competitive inhibition of NA uptake) [8, 44]. These produce only small changes in neurotransmitter levels that are unlikely to be of consequence in terms of serious adverse interactions, but they may be sufficient to confer a clinical benefit.

Rapid and transient stimulation of DA levels in brain are indicative of abuse potential for drugs, e.g., DAT blockers like cocaine, and amphetamines. Modafinil and armodafinil dose-dependently increased DA efflux with a slower, longer-lasting effect [45].

A recent review over 1600 overdoses of modafinil indicated no major adverse effects, which makes one wonder exactly what it is doing [46] — **no clinical effects were observed in 723/1616 of the exposures to modafinil.**

It produces slower, longer-lasting, and less potent stimulation of DA release than cocaine or methamphetamine

There is no suggestion that it significantly increases serotonin and there are no reports of it provoking serotonin toxicity or any substantial increase in blood pressure with MAOIs, although clinical use suggests it may help to lessen postural hypotension in some patients.

Modafinil does not provoke serotonin toxicity

Perhaps we should think of it as a ‘nudge-drug’.

Pharmacological Profile for 5-HT/NE/DA Release/Re-uptake

See full table in Rothman [47]

Sertraline, for comparison, not from Rothman

	5-HT		NE		DA	
	Release (EC50 nM)	Uptake (Ki nM)	Release (EC50nM)	Uptake (Ki nM)	Release (EC50 nM)	Uptake (Ki nM)
Amphetamine	1765	3830	7	39	25	34
Methamphetamine	736	2137	12	48	24	114
Ephedrine	>10,000	>50,000	72	225	1350	4398
Tyramine	2800	1550	41	73	120	106
Fenfluramine	52	150	300	1300	10,000	22,000
MDMA	57	238	77	462	376	1572
Cocaine	>10,000	304	>10,000	780	>10,000	478
Desipramine	>10,000	350	>10,000	8.3	>10,000	
Citalopram	>10,000	2.4	>10,000		>10,000	
Fluoxetine	>10,000	9.6				
Sertraline	--	0.29*				

And lastly: Cocaine

In view of cocaine’s potency at the DAT it is unexpected that there are no clear reports of cocaine toxicity in combination with MAOIs.

I found one study where cocaine was given to mice in conjunction with MAOI which did not report any apparent toxicity, e.g., hyperthermia [48].

Perhaps that reveals something about the subtle differences in cocaine’s mechanism of action in relation to the latest findings about DA transport, outlined at the beginning of this commentary.

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