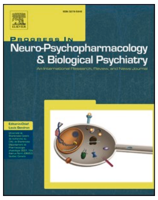
Progress in Neuropsychopharmacology & Biological Psychiatry 127 (2023) 110784

Contents lists available at ScienceDirect

Progress in Neuropsychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp



It's all about making new contacts: How being metabotropic and phasicity help D1-like receptors promote LTP in the PFC

David Quispe Escudero[1]

Departamento de Psicobiología, Facultad de Psicología, Universidad Complutense de Madrid, Madrid E-28040, Spain

ARTICLE INFO

Keywords:
Dopamine
Long term potentiation
Prefrontal cortex
Cognition
Methamphetamine

ABSTRACT

D1-like receptors have two important qualities, they are all metabotropic and they activate with phasic dopamine. After analyzing the molecular implications of each of these qualities separately and then combining them for the specific case of the prefrontal cortex, we propose a model that explains why long term potentiation in this cortical area depends on the amount of contact between D1-like receptors and dopamine. This simple model also explains why in order to promote long term potentiation, dopamine transporters should be scarce in the prefrontal cortex. Additionally, it explains why stimulants like methamphetamine could have such detrimental cognitive effects on regular substance consumers.

All dopamine (DA) receptors are G-protein coupled receptors (GPCR). They are divided into D1-like receptor family (D1R) and D2-like receptor family (D2R) (Beninger and Miller, 1998). D1R includes D1 and D5 receptors, which have in common the fact they are receptors for phasic DA (Mishra et al., 2018). Phasic DA means the receptor must adapt quickly to *changes in its environment* (in this case, to the levels of DA) and these receptors are activated only when they perceive such changes (Binder et al., 2009). Burst firing, which is a pattern of relatively high intensive firing then followed by pauses, is typically observed in the phasic firing of spontaneously active DA neurons (Dreyer et al., 2010).

Molecularly speaking, for a receptor there are only two options: it is either bound (associated) to its substrate or it is not (dissociated). Therefore, for D1R the *change of environment* is equivalent to the brief moments during which a DA molecule is binding to the receptor. Upon binding to its substrate, the receptor is quickly activated. Only *upon binding* to it, not while it *remains bound*. **Therefore, what is important for the D1R activation is that "new" bindings are always happening**. Only this way is the DA phasicity in these receptors fulfilled. This can be guaranteed when at least one of the next three conditions occurs.

Condition 1: When there is a large amount of DA molecules in the synaptic cleft, which increases the likelihood of new bindings.

In Eq. (1), "q" symbolizes the amount of extracellular DA.

Condition 2: Whenever a single DA molecule associates and dissociates a receptor in repeated times.

It is also possible that just one DA molecule manages to bind and unbind fast enough and on several occasions. If this is what actually occurs, the requirement of change is also met for the receptor's phasicity even with a single DA molecule. **Here we propose a way this could occur**. It is known that a ligand occupies the binding site of its receptor for a certain period, the residence time. This residence time depends on the kinetics of the receptor-ligand complex (Schuetz et al., 2018). Eventually, the DA molecule must dissociate, as this is the only way for the neurotransmitter to at last diffuse away from the neuroreceptor. D1-like receptors have a 10- to 100-time lower affinity for DA than D2-like receptors (Martel and Gatti McArthur, 2020). It is this weak affinity* what makes the dissociation of a DA molecule from D1R much more likely (Hikida et al., 2010). Once unbound, there is no particular reason DA would then head straight away to a transporter protein to be removed from the extracellular space. Thus, this recently-dissociated DA molecule could likely re-associate with a receptor.

There is another factor that contributes to this dissociation. The fact that there is always a flux of molecules in the aqueous cleft makes synapses not a calm place at all (Zuber et al., 2005), they resemble the ocean during a thunderstorm. Molecules are jostling around and bumping into each other all the time. The bound neurotransmitter is constantly jostled and bumped, and every so often it gets knocked loose due to D1R having a lower affinity (Wall et al., 2011). Therefore, we suggest the greater this **traffic of molecules** in the synaptic space, the more likely a bound neurotransmitter will dissociate. We decided to name the level of synaptic traffic as "S", akin to entropy because molecular traffic also has a component of randomness. Since this traffic

---

E-mail address: dquisp01@ucm.es.

[1] Present Address: 10 Balmy St., San Francisco, CA, 94410.

https://doi.org/10.1016/j.pnpbp.2023.110784
Received 6 December 2022; Received in revised form 23 April 2023; Accepted 4 May 2023

favors DA binding and unbinding, we can argue that a greater "S" favors a greater activation of D1R.

*Affinity (in the form of the dissociation variable, K_d) could be included as a variable in Eq. (1). However, my intention is to show how the dynamics of an independent variable (when it increases or decreases) affect the dependent variable. Since K_d of DA for D1R is actually a constant, meaning no increases or decreases, I decided to omit it in the model.

Condition 3: When there are no transporters in the immediate vicinity of a D1R.

Finally, for a molecule to perform this binding and unbinding as many times as possible, it must physically remain in the synaptic cleft as long as possible. The main protein responsible for this is the dopamine transporter (DAT). DAT's function is to "clean" the synapse by reuptaking DA into the presynaptic neuron (Varrone and Halldin, 2014). Thus, the more DAT proteins present around a D1R, the less activation for the receptor.

With these three conditions, we can formally express D1R phasic activation like this:

$$D1R_{act} = f(\ \underset{+}{q},\ \underset{+}{S},\ \underset{-}{DAT}\ ) \qquad (1)$$

Where the positive sign means a direct relationship with the dependant variable, and a negative sign represents an inverse relationship with the activation of D1R.

Aside from being a family of phasic DA receptors, D1R promotes long term potentiation (LTP) (Gurden et al., 2000). This occurs because these receptors are coupled to a G_s protein. The "s" stands for stimulator because once D1Rs are activated their G protein will stimulate adenylyl cyclase, which in turn increases the level of the secondary messenger cyclic AMP (cAMP) in the postsynaptic neuron (Bhatia et al., 2019; Mishra et al., 2018). The greater levels of cAMP in the neuron activate a protein cascade that ultimately increases the levels of AMPA receptors in the neuron's membrane. By installing additional AMPAs in the synapse, the postsynaptic neuron can also ensure the activation of the vital NMDA receptors, which are the ones that are permeable to Ca^{+2}. It is the calcium ion the one that ultimately leads the process of activating growth factors in the neuronal nucleus, which synthesizes more synapses, therefore strengthening the connection (Dai et al., 2008; Speranza et al., 2021). This is the basis of synaptic plasticity, which is responsible for LTP.

Thus, we can argue that the more activation of D1Rs, the more synaptic plasticity, and the more LTP:

$$LTP = f(\ \underset{+}{D1R_{act}}\ ) \qquad (2)$$

Since $D1R_{act}$ is present in both equations, we can just replace (1) into (2), which results in*:

$$\begin{tikzcd} D1R_{act} = f(\ \underset{+}{q},\ \underset{+}{S},\ \underset{-}{DAT}\ ) \arrow[rr, bend right] & ; & LTP = f(\ \underset{+}{D1R_{act}}\ ) \arrow[r, Rightarrow] & LTP_{D1R} = f(\ \underset{+}{q},\ \underset{+}{S},\ \underset{-}{DAT}\ ) \end{tikzcd} \qquad (3)$$

*Probably there are other variables that are relevant to LTP but for this model we will focus only on the ones mentioned in order to avoid making the equation too complex.

With this basic formal representation, we intend to reinforce the idea that either through the nature of the dopaminergic receptor (the fact that this family is activated by phasic DA rather than tonic), or through the internal configuration of the postsynaptic neuron which triggers a stimulating protein cascade, for both situations in order to obtain the D1R activation it is **essential the greatest amount of contact between DA and its receptor**. This is what will finally result in an LTP.

LTP plays a huge role in cognitive functions (Lynch, 2004; Shors and Matzel, 1997). And it is known that cognitive functions such as long term memory and decision making are a role of the prefrontal cortex (PFC) (Euston et al., 2012; Wang et al., 2018). Additionally, PFC has other peculiarities. It lacks (or has a minimal amount of) DATs (Morón et al., 2002). And also, the majority of the prefrontal DA receptors belong to D1R (Anastasiades et al., 2019), which as we said before are activated by phasic DA. Therefore, we can rearrange (3) for the specific case of the PFC, yielding us:

$$LTP_{PFC} = f(\ \underset{+}{q},\ \underset{+}{S},\ \underset{-}{\cancel{DAT}}\ ) \Rightarrow LTP_{PFC} = f(\ \underset{+}{q},\ \underset{+}{S}\ ) \qquad (4)$$

Thanks to (3) and (4) we can appreciate what the advantages of not possessing DATs mean for the PFC. Before, scientists proposed the fact that DA must "stay out" longer in the PFC's synapse could play a role in the region's unique function of cognition (Stahl, 2003a). With Eq. (4) this is clearer. Because the DA receptors in the PFC are overwhelmingly D1R, it means that for their activation the receptor needs at least one DA molecule always physically present in the synapse to do the binding and unbinding. Possessing a protein that physically removes the same DA molecules from the synapse (DAT) is totally counterproductive to this principle. Therefore, it could be suggested that scarce (or null) DATs in the PFC are the result of an adaptation that ultimately derived in the acquisition of cognitive abilities.

However, just because there are no DATs present in the PFC it does not mean DA molecules there are not reuptaken. This eventually occurs through the norepinephrine transporters (NET). Actually, NETs have a higher affinity for DA than for norepinephrine (NE) (Morón et al., 2002). Thus, Eq. (4) could be reformulated as:

$$LTP_{PFC} = f(\ \underset{+}{q},\ \underset{+}{S},\ \underset{-}{NET}\ ) \qquad (5)$$

There is a catch, nonetheless. In order to find a NET in the PFC, a DA molecule needs to navigate over a greater area. This is because noradrenergic neurons in the PFC do not innervate the same areas as dopaminergic neurons (Stahl, 2003b; see Fig. 1). This type of neuronal communication in which the transmitter needs to travel further than usual is referred to as volume transmission (Wiencke et al., 2020). The negative effect of transporters on LTP is valid only when they are in the vicinity of a D1R (see the underlined phrase in Condition 3). Since the "immediate-proximity principle" is not met in the case of NETs in the PFC, we can disregard the effect of these transporters in the following fashion:

$$LTP_{PFC} = f(\ \underset{+}{q},\ \underset{+}{S},\ \underset{-}{\cancel{NET}}\ ) \Rightarrow LTP_{PFC} = f(\ \underset{+}{q},\ \underset{+}{S}\ ) \qquad (4)$$

Which again takes us back to Eq. (4). This means that, regardless of the presence of NETs, their effect on LTP is negligible simply because none of them are in the vicinity of D1Rs. This does nothing but strengthens the fact that the PFC is an area very well adapted to perform

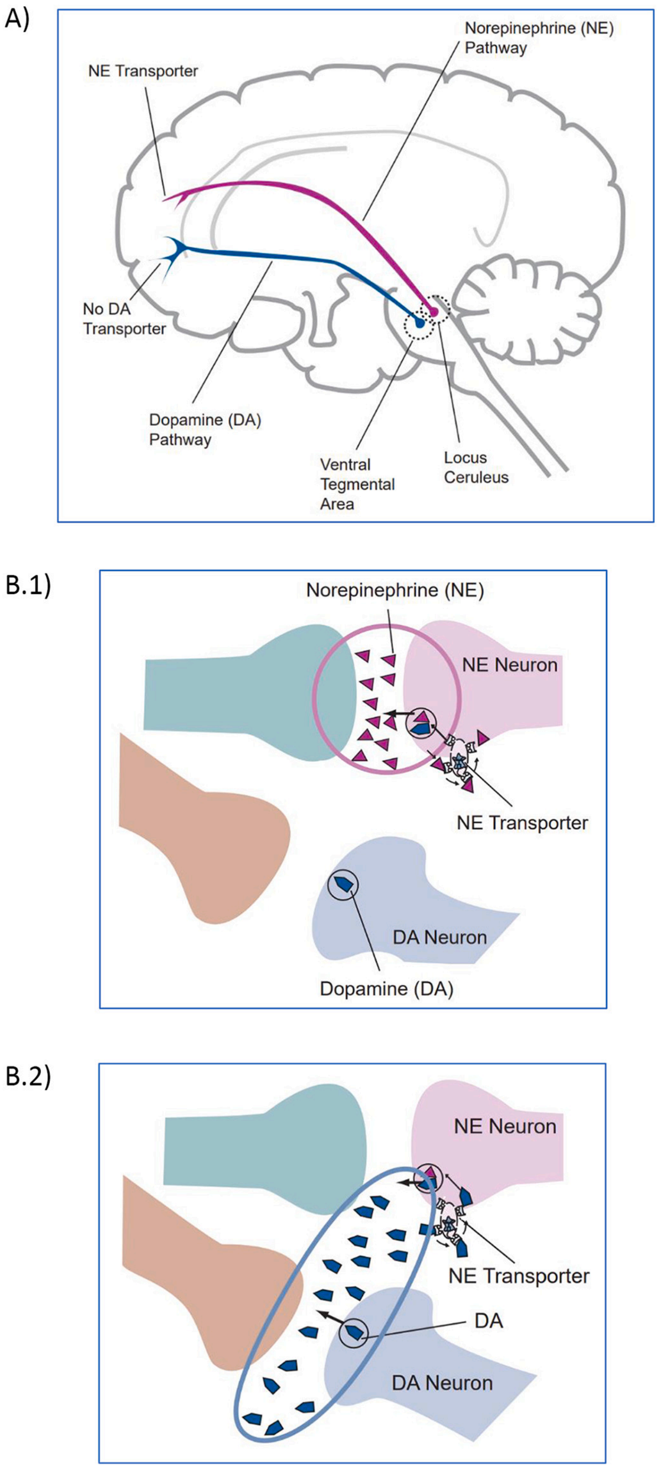


Fig. 1. A) Dopaminergic and Noradrenergic projections to the PFC. Both DA and NE in the PFC originate from midbrain nuclei, the ventral tegmental area (VTA) and the Locus Ceruleus (LC), respectively. However, VTA and LC do not project into precisely the same cortical spots. Another difference is that the dopaminergic innervation does not possess transporters (or only extremely few).

B.1) Prefrontal NE release. Because noradrenergic neurons possess transporters, prefrontal NE does not diffuse far from its synapse in order to be reuptaken. The purple circle represents the area of neurotransmitter diffusion.

B.2) Prefrontal DA release. The opposite happens to dopaminergic neurons. DATs are scarce (or non-existent) in the PFC; therefore, in order to be reuptaken DA molecules need to travel a greater area until they reach a NET. The blue ellipse represents the area of transmitter diffusion (compare it with the purple circle of Fig. B.1). Since the principle of "immediate proximity" of transporters is not met in this case, we can just discard the effect of NETs in Eq. (5).

Note: all figures are from "Neurotransmission of cognition, part 3. Mechanism of action of selective NRIs: both dopamine and norepinephrine increase in prefrontal cortex" by S. M. Stahl, 2003. *The Journal of clinical psychiatry*, *64*(1), 4–5.

LTP: the prefrontal area lacks DATs, while the other transporters (NETs) are not really close enough to the D1Rs. Therefore, there are no proteins in the proximity to remove DA molecules, which effectively allows DA to stick around longer to do their binding and unbinding. This could be the reason why the PFC is essential when it comes to functions that require extensive LTP, like cognition.

Now, let's turn our attention to Methamphetamine (Meth). It is known that when Meth is consumed in acute and small amounts, it actually has positive effects on some cognitive functions (reaction time, vigilance, learning/memory) (Hart et al., 2012). This blatant contradiction perhaps makes no sense to the general population and could be challenging to explain when it comes to drug addiction prevention: how come the same substance that scientists and health care providers claim has such devastating cognitive effects produces the exact opposite when consumed in medicated doses? With this simplified model we suspect we could help clear the confusion. From (4) we can deduce that an increase in the amount of extracellular DA has a beneficial effect on LTP. And that is exactly what even an acute dose of Meth does: due to its pharmacology, Meth forces the presynaptic neuron to flood the synapse with DA (Courtney and Ray, 2014; Karila et al., 2010; Pereira et al., 2006; Branch and Beckstead, 2012). This explains the improvement in cognitive abilities for people who consumed the drug in clinical settings like Hart and colleagues reported (similar to what occurs with other amphetamines, like Adderall). However, when the consumption of Meth is not of a small dose, DA is quickly depleted (Sulzer et al., 2005). This is because, as with any other finite resource, the presynaptic neuron cannot endlessly produce enough DA, therefore the "q" in Eq. (4) gradually becomes smaller (or null, depending on how much Meth is consumed). When the neuron runs out of DA to release, then simply there are no more ligands for D1R receptors to bind, which leads to no more LTP in the PFC. This is what explains why people who abuse Meth score so poorly in cognitive tests.

Funding information

All research in this publication was self-funded by the author.

Declaration of Competing Interest

I, David Quispe Escudero, declare that I have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

References

Anastasiades, P.G., Boada, C., Carter, A.G., 2019. Cell-type-specific D1 dopamine receptor modulation of projection neurons and interneurons in the prefrontal cortex. Cereb. Cortex 29 (7), 3224–3242.
Beninger, R.J., Miller, R., 1998. Dopamine D1-like receptors and reward-related incentive learning. Neurosci. Biobehav. Rev. 22 (2), 335–345.
Bhatia, A., Lenchner, J.R., Saadabadi, A., 2019. Biochemistry, Dopamine Receptors.
Binder, M.D., Hirokawa, N., Windhorst, U., 2009. Adaptation of sensory receptors. In: Encyclopedia of Neuroscience. Springer, p. 54.
Branch, S.Y., Beckstead, M.J., 2012. Methamphetamine produces bidirectional, concentration-dependent effects on dopamine neuron excitability and dopamine-mediated synaptic currents. J. Neurophysiol. 108 (3), 802–809.
Courtney, K.E., Ray, L.A., 2014. Methamphetamine: an update on epidemiology, pharmacology, clinical phenomenology, and treatment literature. Drug Alcohol Depend. 143, 11–21.
Dai, R., Ali, M.K., Lezcano, N., Bergson, C., 2008. A crucial role for cAMP and protein kinase A in D1 dopamine receptor regulated intracellular calcium transients. Neurosignals 16 (2-3), 112–123.
Dreyer, J.K., Herrik, K.F., Berg, R.W., Hounsgaard, J.D., 2010. Influence of phasic and tonic dopamine release on receptor activation. J. Neurosci. 30 (42), 14273–14283.
Euston, D.R., Gruber, A.J., McNaughton, B.L., 2012. The role of medial prefrontal cortex in memory and decision making. Neuron 76 (6), 1057–1070.
Gurden, H., Takita, M., Jay, T.M., 2000. Essential role of D1 but not D2 receptors in the NMDA receptor-dependent long-term potentiation at hippocampal-prefrontal cortex synapses in vivo. J. Neurosci. 20 (22). RC106-RC106.
Hart, C.L., Marvin, C.B., Silver, R., Smith, E.E., 2012. Is cognitive functioning impaired in methamphetamine users? A critical review. Neuropsychopharmacology 37 (3), 586–608.
Hikida, T., Kimura, K., Wada, N., Funabiki, K., Nakanishi, S., 2010. Distinct roles of synaptic transmission in direct and indirect striatal pathways to reward and aversive behavior. Neuron 66 (6), 896–907.
Karila, L., Weinstein, A., Aubin, H.J., Benyamina, A., Reynaud, M., Batki, S.L., 2010. Pharmacological approaches to methamphetamine dependence: a focused review. Br. J. Clin. Pharmacol. 69 (6), 578–592.
Lynch, M.A., 2004. Long-term potentiation and memory. Physiol. Rev. 84 (1), 87–136.
Martel, J.C., Gatti McArthur, S., 2020. Dopamine receptor subtypes, physiology and pharmacology: new ligands and concepts in schizophrenia. Front. Pharmacol. 11, 1003.
Mishra, A., Singh, S., Shukla, S., 2018. Physiological and functional basis of dopamine receptors and their role in neurogenesis: possible implication for Parkinson's disease. J. Exp. Neurosci. 12, 1179069518779829.
Morón, J.A., Brockington, A., Wise, R.A., Rocha, B.A., Hope, B.T., 2002. Dopamine uptake through the norepinephrine transporter in brain regions with low levels of the dopamine transporter: evidence from knock-out mouse lines. J. Neurosci. 22 (2), 389–395.
Pereira, F.C., Lourenço, E.S., Borges, F., Morgadinho, T., Ribeiro, C.F., Macedo, T.R., Ali, S.F., 2006. Single or multiple injections of methamphetamine increased dopamine turnover but did not decrease tyrosine hydroxylase levels or cleave caspase-3 in caudate-putamen. Synapse 60 (3), 185–193.
Schuetz, D.A., Bernetti, M., Bertazzo, M., Musil, D., Eggenweiler, H.M., Recanatini, M., Cavalli, A., 2018. Predicting residence time and drug unbinding pathway through scaled molecular dynamics. J. Chem. Inf. Model. 59 (1), 535–549.
Shors, T.J., Matzel, L.D., 1997. Long-term potentiation: what's learning got to do with it? Behav. Brain Sci. 20 (4), 597–614.
Speranza, L., di Porzio, U., Viggiano, D., de Donato, A., Volpicelli, F., 2021. Dopamine: the neuromodulator of long-term synaptic plasticity, reward and movement control. Cells 10 (4), 735.
Stahl, S.M., 2003a. Neurotransmission of cognition, part 1, Dopamine is a hitchhiker in frontal cortex: norepinephrine transporters regulate dopamine. J. Clin. Psychiatry 64 (1), 4–5.
Stahl, S.M., 2003b. Neurotransmission of cognition, part 3. Mechanism of action of selective NRIs: both dopamine and norepinephrine increase in prefrontal cortex. J. Clin. Psychiatry 64 (3), 230–231.
Sulzer, D., Sonders, M.S., Poulsen, N.W., Galli, A., 2005. Mechanisms of neurotransmitter release by amphetamines: a review. Prog. Neurobiol. 75 (6), 406–433.
Varrone, A., Halldin, C., 2014. Human brain imaging of dopamine transporters. In: Imaging of the Human Brain in Health and Disease. Academic Press, pp. 203–240.
Wall, V.Z., Parker, J.G., Fadok, J.P., Darvas, M., Zweifel, L., Palmiter, R.D., 2011. A behavioral genetics approach to understanding D1 receptor involvement in phasic dopamine signaling. Mol. Cell. Neurosci. 46 (1), 21–31.
Wang, J.X., Kurth-Nelson, Z., Kumaran, D., Tirumala, D., Soyer, H., Leibo, J.Z., Botvinick, M., 2018. Prefrontal cortex as a meta-reinforcement learning system. Nat. Neurosci. 21 (6), 860–868.
Wiencke, K., Horstmann, A., Mathar, D., Villringer, A., Neumann, J., 2020. Dopamine release, diffusion and uptake: a computational model for synaptic and volume transmission. PLoS Comput. Biol. 16 (11), e1008410.
Zuber, B., Nikonenko, I., Klauser, P., Muller, D., Dubochet, J., 2005. The mammalian central nervous synaptic cleft contains a high density of periodically organized complexes. Proc. Natl. Acad. Sci. 102 (52), 19192–19197.