Mechanisms for the Interaction of Dopamine and Norepinephrine in the Prefrontal Cortex: Implications for the Treatment of Cognitive Symptoms of Schizophrenia

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Reductions in prefrontal cortical dopamine (DA) levels have been associated with the cognitive symptoms of schizophrenia. When removal of the dopamine innervation to the prefrontal cortex (PFC) was tested in animal models, researchers reported a loss of dendritic spines. Anatomical arrangements in the PFC suggest that dopamine may play a role in the regulation of dendritic architecture. Atypical antipsychotics, but not typical antipsychotics, reverse the loss of dendritic spines seen upon DA denervation. Atypical antipsychotic drugs have also been reported to reduce cognitive symptoms of schizophrenia. Taken together with their ability to reverse spine loss, these data suggest that spine loss may be a pathological correlate to cognitive deficits associated with the prefrontal cortex. The mechanism by which these drugs act to restore DA tone in the PFC remains unclear. Recent data has suggested that norepinephrine (NE) terminals are capable of releasing the NE "precursor" DA. Atypical antipsychotic drugs have a wide target profile, including antagonism of NE autoreceptors. These data suggest that interactions between the DA and NE systems may play a role in treatment for schizophrenia. Although DA and NE have been implicated in disorders involving the prefrontal cortex such as schizophrenia, affective disorders, and attention-deficit hyperactivity disorder (ADHD), the mechanism for interactions between DA and NE has not been widely investigated. Understanding how these systems interact should have a major impact on therapeutic possibilities for disorders arising from disruption of PFC function.

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Dopamine (DA) and norepinephrine (NE) have consistently been shown to play a crucial role in cognitive processes. DA and NE share a common synthetic pathway, and have both been implicated in psychiatric disorders such as attention-deficit hyperactivity disorder (ADHD)[1,2], affective disorders[3], and schizophrenia[4-6]. Both transmitter systems send projections to the prefrontal cortex (PFC), where they have been shown to be involved in processes such as attention, working memory, executive function, and behavioral inhibition[1, 2, 4, 7-14]. Disturbances in PFC function are linked to the cognitive symptoms of schizophrenia, and are thought to be a result of a hypodopaminergic state in the PFC[15]. First generation antipsychotics, such as haloperidol, primarily target the D_2 dopamine receptor[16]. These drugs tend to improve the positive symptoms of the disorder, such as hallucinations and delusions, yet have little effect on cognitive and negative symptoms[17]. Interestingly, second generation antipsychotics, such as clozapine, have a larger target profile and are more effective in treating the cognitive and negative symptoms of schizophrenia, such as deficits in working memory and a flattened affect[18, 19]. Among those receptors targeted by second-generation drugs are NE receptors, including α_{2C}-receptors, increasing interest in the possible interactions of these parallel pathways. Despite commonalities in synthesis, localization, and drug interactions, interactions between DA and NE systems within the prefrontal cortex remain poorly understood. Here we will review evidence for the role of DA and NE in aspects of cognition, then delve into recent studies that investigate possible interactions of these systems at the level of receptors, transporters, and possible co-release, and finally the implications that DA/NE interactions have for our understanding of neuropsychiatric disorders.

DOPAMINE AND NOREPINEPHRINE NEURONS PROJECT TO THE PFC

Early studies of both dopamine and norepinephrine focused on the localization of these transmitters in the brain. Using fluorescent histochemistry, as well as electron microscopy, these studies showed that both DA and NE are present in the prefrontal cortex[20-22].

Prefrontal cortical DA projections originate from neurons in the ventral tegmental area (VTA)[23], while NE projections originate from the locus coeruleous (LC)[24]. Dopamine has an abundance of axon terminals in deep layers of cortex in the rodent[20] and primate[25], primarily in layer V. This coincides well with the distribution of dopamine receptors of which D_1 is the dominant form in the PFC[26]. This selective area of activation implies a selective function for the DA pathway in the PFC, which is further strengthened by the presence of specific synaptic contacts being made onto the shafts and spines of layer V pyramidal cells[25]. Several studies suggest that NE terminals are more evenly distributed than DA terminals throughout the prefrontal cortex[21, 27]. The diffuse nature of NE terminals across both rodent and primate PFC lamina suggests a more general role of this transmitter in the PFC. Norepinephrine terminals lack the synaptic contacts made by DA terminals. However, functional specificity of NE may be determined by NE receptors' laminar distribution. Norepinephrine and DA distribution in the PFC suggests these transmitters' involvement in PFC function.

DOPAMINE AND NOREPINEPHRINE RECEPTOR LOCALIZATION

Following these careful characterizations of dopamine and norepinephrine distribution, investigation began to shift from neurotransmitters to their receptors. Autoradiography was used in early studies, using tridiated ligands that showed specificity for the various dopamine and norepinephrine receptors[28-30].

Currently, five dopamine receptors have been identified, which are classified as adenylate cyclase activating "D_1-like", or inhibiting "D_2-like" receptors, with D1 and D_5 being grouped together and $D_{2\text{-}4}$ grouped together[31]. Dopamine receptor identification in early studies made no distinction between the various subtypes, and suggested that DA receptor localization in the PFC was focused in the deep layers V and VI[29]. D_2 receptors are localized to the PFC, yet the relative amount of this receptor is significantly lower than its counterpart[26]. Early studies indicated that D_1 was most abundant in superficial layers I, II, and III, with slightly lower levels in layers V and VI in primates, while showing specificity to deeper layers in a rat model[28, 30]. D_2 receptors show laminar localization primarily to layer V. Findings by Richfield et al. suggest a uniform distribution of D_1 receptors across all lamina in cats and monkeys, but rats had increased D_1 receptor binding in deep layers V and VI[26]. An mRNA expression study of all five receptor subtypes in the PFC of primates found that expression for all five subtypes was highest in layer V[32]. This was in agreement with studies of mRNA levels performed in the human PFC[33], suggesting that layer V has a particularly important role in catecholamine activity in the prefrontal cortex.

Norepinephrine acts on two classes of receptors, both α- and β-adrenergic receptors. These two classes are further broken into α_1 and α_2 as well as β_1, β_2, and β_3 subtypes. The α subtypes are each further divided into three subclasses, A, B and C[31]. The β-receptors activate adenylate cyclase[34], while α_2-receptors act to inhibit this enzyme[35, 36]. The α_1-receptors are linked to PKC and the release of intracellular calcium through G_q coupling[35, 37]. The β receptors appear less abundant in the PFC than the α receptors and show an inverse laminar distribution[28]. The α_1-receptors are more abundant than β-receptors, yet remain less prominent in the PFC than α_2-receptors. Prazosin, a selective ligand for α_1-receptors, exhibits strong binding in deep layers V and VI. The most abundant NE receptor in the PFC is the α_2-receptor. Clonidine binding (α_2) shows a decreasing gradient from superficial to deep layers[28]. Both α_{2A} and α_{2C}-receptors are found both presynaptically and postsynaptically in the PFC[38]. Presynaptic autoreceptors provide feedback inhibition to the NE terminal[38, 39].

It is at the level of receptor binding that it first becomes apparent that interactions between DA and NE systems are likely to occur. It has been shown that DA is capable of acting as an agonist at adrenergic receptors[40, 41]. Likewise, D_1 and D_2 radioligands have been shown to be displaced by both DA and NE, implying NE binding to DA receptors[42]. Cornil et al showed that DA has affinity for the α_{2c}-adrenoceptor in rat brain[43]. It is widely recognized that NE transporters have a higher affinity for DA than for NE, allowing possible interactions through transmitter reuptake. Finally, 2nd generation antipsychotics such as clozapine and olanzapine have affinities for both DA and NE receptors[44-46]. Due to the possibilities for interactions between these systems, an investigation of the mechanisms of these interactions appears critical to our understanding of the effects of either pathway in PFC function.

DOPAMINE AND NOREPINEPHRINE IN THE PREFRONTAL CORTEX

The importance of interactions between NE and DA is underlined by the roles of these transmitters during PFC function. The prefrontal cortex is thought to control such executive cognitive functions as working memory and attention. Given the innervation patterns of both dopamine and norepinephrine, it is not surprising that both have individually been shown to have links to these functions. Through the use of lesion studies within the prefrontal cortex, as well as studies of structures projecting to the PFC, transmitter loss-of-function has been explored.

Lesion of DA in the PFC can be performed directly by injection of 6-hydroxydopamine (6-OHDA) into the PFC[47], or indirectly by injection of 6-OHDA into the VTA which supplies DA to the PFC[48] along with a NET blocker such as desipramine to spare NE terminals. Studies using both methods have suggested the importance of DA in working memory, and attention[49]. Interestingly, further research has shown that excess DA in the PFC can have detrimental effects on cognitive tasks as well[5].

Through injection of the NE terminal specific toxin DBH-saporin, similar PFC specific lesions of NE can be performed[50]. Before the development of this toxin, DNAB lesions using 6-OHDA were used[1]. Studies using both of these methods have shown cognitive deficits similar to those seen in the DA system[1, 14, 50]. Once again, excess levels of NE can have detrimental effects[37, 51]. These studies suggest that there is an optimal range for DA and NE within the PFC necessary for higher order functioning. Given the involvement of the prefrontal cortex in cognitive functions such as working memory, and attention, as well as the role of DA and NE in these processes, understanding the interactions between these transmitters within the PFC could lead to major changes in the treatment of neurological disorders, such as attention-deficit hyperactivity disorder (ADHD) and schizophrenia.

PREVIOUS HYPOTHESES

Past research often cites potential DA/NE interactions as having an effect on their studies' results[3, 52, 53]. Previous work in this area has focused on drugs that interact with both systems, rather than these systems' interactions with each other, and the body of literature working directly to determine the mechanisms of these interactions is small. It has been well documented that changes in dopamine and norepinephrine in the prefrontal cortex are well-correlated, changing together in disorders such as schizophrenia[53], and as a response to physiological changes, such as stress[51]. (The link to stress may prove to be of further interest, as stress often induces schizophrenia symptoms. However, this link will not be discussed in this review). The correlation between DA and NE levels in the PFC is particularly evident in response to antipsychotic drugs[54, 55]. However, the mechanism of this DA/NE interaction is still being debated. Hypotheses that have been put forth include: a direct effect of NE on DA release[56, 57], an effect of NE on DA reuptake[58, 59], and co-release of DA and NE from NE terminals[60]. Few researchers have actively attempted to validate these hypotheses by studying the mechanisms by which these two transmitters are interacting.

STUDIES ADDRESSING THE DIRECT EFFECT OF NE ON DA RELEASE

Pozzi et al. used lesion studies, along with selective DA and NE reuptake inhibitors, to further the hypothesis that increases in NE directly increase DA levels[57]. This study showed that increasing extracellular NE was correlated to increases in extracellular DA. Similarly, Gresch et al. suggested two possible explanations for their findings, 1) NE regulation of DA through receptors regulating DA release, or 2) transport of DA into noradrenergic terminals[56].

STUDIES ADDRESSING DA REUPTAKE THROUGH NE TERMINALS

The idea of NE affecting the uptake of DA has been suggested given the relatively low abundance of DA transporter (DAT)[61] in the PFC, and the broad coverage of NE transporter (NET) in this area[62]. Moron et al. were able to show that DAT knockout mice had normal rates of DA uptake in the frontal cortex, while NET knockout mice exhibited greater than 50% loss of DA uptake[59]. This indicates that DA uptake in the PFC occurs largely through NET activity. If NE release increases, the probability of DA being taken up by these transporters decreases, thereby increasing the extracellular levels of DA in the region. In this indirect way, NE may increase extracellular DA. Studies using the α_2-receptor antagonist mainserin, along with two NET inhibitors, reboxetine and desipramine, suggest that NET uptake of DA is significantly higher in the PFC than in the parietal cortex or occipital cortex[58] due to a lower NE/DA ratio than in the latter two areas. It is important to note that mainserin was administered via i.p. injection, so effects were global and not PFC specific. Treatment caused an increase in DA levels in all three regions, and the authors attributed this to the effect of the drug in the VTA causing DA neuron firing, rather than action in the PFC. NET's high affinity for DA could cause more rapid clearance of DA than NE, and could cause the increases in DA when extracellular NE is increased. Later research in which mainserin was administered locally suggests that α_2-receptors have a significant effect locally on DA release in the PFC[63].

STUDIES ADDRESSING DOPAMINE AND NOREPINEPHRINE CO-RELEASE

Ahn and Klinman reported on the rate limiting steps of norepinephrine synthesis over 20 years ago[64]. They report that dopamine beta monooxygenase (dopamine beta hydroxylase, DBH), and not tyrosine hydroxylase, may be the rate-limiting step in NE synthesis. DBH is the final enzyme that converts DA into NE within the vesicles of NE terminals. If DBH

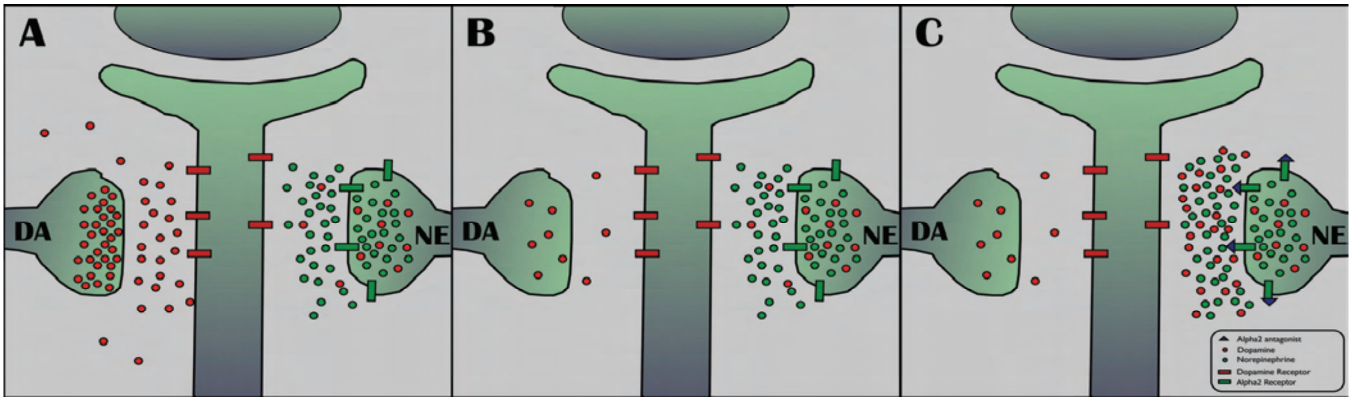

Figure 1 | **A possible mechanism for the effects of olanzapine and clozapine on DA tone** A) Proper DA and NE signaling. B) DA tone disturbance while NE signaling remains intact. C) The effects of a α_2-receptor antagonist as it re-establishes DA tone through the NE terminal. DA (red circles) and receptors (red boxes), NE (green circles) and α_2-receptors (green boxes), α_2-receptor antagonist (blue triangle).

is rate limiting, at times the firing rate of NE neurons could be intensified, causing release of DA from these terminals along with NE. This interaction, coined the "co-release" hypothesis, proposes that DA and NE are released together from the NE terminal[60]. Microdialysis allowed investigation of the possible co-release of DA and NE in the PFC[60]. Looking at DA innervated regions (PFC) and non-, or minutely DA innervated regions (occipital cortex, primary motor cortex) using dialysis, Devoto et al. showed that the extracellular levels of DA were similar in both DA innervated and non-innervated regions. This implies another source of DA in these areas. Using selective α_2-receptor antagonist infused through the probe, investigators saw increases in DA in all three areas, suggesting that DA was being released through NE terminals, and furthermore that this release was, in part, regulated by α_2-receptors[65]. The α_2-receptor agonist, clonidine, reduced extracellular DA levels along with NE levels, while the antagonist, idazoxan, increased DA and NE levels. A further study in 2003 by the same group performed a similar study looking at the dopamine metabolite 3,4-dihydroxyphenylacetic acid (DOPAC)[66]. This study further verified that DA is likely being released from both DA and NE terminals in the PFC, but only by DA terminals in subcortical regions. Using clozapine, the first atypical antipsychotic, Devoto et al. showed the effects of this drug on PFC DA and NE levels. In this study, treatment with clozapine elevated both NE and DA levels in the PFC and occipital cortex, as did treatment with a α_2 antagonist. Interestingly, treatment with clonidine, an α_2-receptor agonist, reversed these effects, while treatment with a D_2 agonist, which has been shown to decrease DA release in the striatum, had no effect[66]. This evidence again suggests that DA is being released through the NE terminal, and that the atypical antipsychotic drug clozapine is acting through a α_2-receptor mechanism to restore PFC DA levels. In later experiments, Devoto et al showed that activation of the LC was sufficient to increase extracellular dopamine in the PFC[67]. Considered with the results discussed above, it is likely that this increase is not solely due to the LC acting on the VTA but also through NE terminal firing in the PFC. Finally, Devoto et al. demonstrated that lesioning the VTA and removing DA innervation to the PFC has no affect on extracellular DA levels[68]. Tissue content of DA was significantly reduced, however extracellular levels remained unchanged. These data provide very strong evidence suggesting that NE terminals do, in fact, release DA, providing an alternative explanation to the hypotheses that NE is affecting DA levels through direct interaction with DA terminals or through DA reuptake.

The release of DA from NE terminals may help to explain data derived in our own lab. We have shown that a loss of DA innervation from the VTA causes a loss of dendritic spines on PFC layer V pyramidal cells[48]. This loss of dendritic spines could be related to the loss of cortical volume seen in schizophrenia patients[69], providing a possible pathological correlate to behavioral data suggesting impaired cognitive function in animals with a loss of PFC DA signaling. Interestingly, the loss of spines in these cells could be reversed through treatment with olanzapine, but not haloperidol. Given the ability of atypical, but not typical antipsychotic drugs to help in the relief of cognitive symptoms of schizophrenia, this lends credibility to the importance of dendritic spines in PFC function. Dendritic structure is maintained through DA tone in the striatum[70]. If the same is true for the PFC, it can be hypothesized that following DA depletion of the PFC, atypical drug treatment acts to restore DA tone through an alternative DA source. Under normal conditions, it appears that extracellular DA comes both from the DA and NE terminals, with DA terminals shouldering the majority of this load (**Figure 1a**). However, in certain states such as schizophrenia, these DA levels are reduced, possibly through reduced transmission through the DA terminals (**Figure 1b**). Through treatments capable of antagonizing the α_{2c}-receptor, DA tone can be restored through release of DA through the NE terminal (**Figure 1c**). Clozapine, the original atypical antipsychotic, as well as olanzapine, has a high affinity for α_2-receptors[44] making these drugs candidates to act at the NE terminal.

CONCLUSIONS

Atypical antipsychotic drugs appear to have effects on cognitive deficits not seen with typical antipsychotic treatments[18]. These drugs also have a restorative effect on DA denervated pyramidal cell morphology in the PFC[48]. Linking these two functions of atypical antipsychotics could provide strong evidence that the ability of atypical antipsychotic drugs to treat the cognitive deficits and negative symptoms of schizophrenia is a result of their ability to affect non-DA receptors, including the α_2-receptor. Data from Devoto et al. have suggested that atypical antipsychotic drugs are capable of causing release of DA from NE terminals[66]. Our own work suggests that this may be a factor in restoring dendritic spines in the PFC. Further research is critical to linking the interactions of the DA and NE systems to the restorative effects of atypical antipsychotic treatment. In the future, understanding the mechanism of interaction of DA and NE should lead to improved treatments of disorders of the prefrontal cortex, ranging from affective disorders to schizophrenia.

REFERENCES

1. Tait DS, Brown VJ, Farovik A, Theobald DE, Dalley JW and Robbins TW (2007). Lesions of the dorsal noradrenergic bundle impair attentional set-shifting in the rat. *Eur J Neurosci*. **25** (12): 3719-3724.
2. Arnsten AF, Scahill L and Findling RL (2007). alpha2-Adrenergic receptor agonists for the treatment of attention-deficit/hyperactivity disorder: emerging concepts from new data. *J Child Adolesc Psychopharmacol*. **17** (4): 393-406.
3. Antelman SM and Caggiula AR (1977). Norepinephrine-dopamine interactions and behavior. *Science*. **195** (4279): 646-653.
4. Bubser M and Koch M (1994). Prepulse inhibition of the acoustic startle response of rats is reduced by 6-hydroxydopamine lesions of the medial prefrontal cortex. *Psychopharmacology (Berl)*. **113** (3-4): 487-492.
5. Murphy BL, Arnsten AF, Goldman-Rakic PS and Roth RH (1996). Increased dopamine turnover in the prefrontal cortex impairs spatial working memory performance in rats and monkeys. *Proc Natl Acad Sci U S A*. **93** (3): 1325-1329.
6. van Kammen DP, Agren H, Yao JK, O'Connor DT, Gurklis J and Peters JL (1994). Noradrenergic activity and prediction of psychotic relapse following haloperidol withdrawal in schizophrenia. *Am J Psychiatry*. **151** (3): 379-384.
7. Yamamuro Y, Hori K, Iwano H and Nomura M (1994). The relationship between learning performance and dopamine in the prefrontal cortex of the rat. *Neurosci Lett*. **177** (1-2): 83-86.
8. Clinton SM, Sucharski IL and Finlay JM (2006). Desipramine attenuates working memory impairments induced by partial loss of catecholamines in the rat medial prefrontal cortex. *Psychopharmacology (Berl)*. **183** (4): 404-412.
9. Brozoski TJ, Brown RM, Rosvold HE and Goldman PS (1979). Cognitive deficit caused by regional depletion of dopamine in prefrontal cortex of rhesus monkey. *Science*. **205** (4409): 929-932.
10. Carter CJ and Pycock CJ (1980). Behavioural and biochemical effects of dopamine and noradrenaline depletion within the medial prefrontal cortex of the rat. *Brain Res*. **192** (1): 163-176.
11. Cooper BR, Howard JL, Grant LD, Smith RD and Breese GR (1974). Alteration of avoidance and ingestive behavior after destruction of central catecholamine pathways with 6-hydroxydopamine. *Pharmacol Biochem Behav*. **2** (5): 639-649.
12. Granon S, Passetti F, Thomas KL, Dalley JW, Everitt BJ and Robbins TW (2000). Enhanced and impaired attentional performance after infusion of D1 dopaminergic receptor agents into rat prefrontal cortex. *J Neurosci*. **20** (3): 1208-1215.
13. Kalsbeek A, de Bruin JP, Matthijssen MA and Uylings HB (1989). Ontogeny of open field activity in rats after neonatal lesioning of the mesocortical dopaminergic projection. *Behav Brain Res*. **32** (2): 115-127.
14. Milstein JA, Lehmann O, Theobald DE, Dalley JW and Robbins TW (2007). Selective depletion of cortical noradrenaline by anti-dopamine beta-hydroxylase-saporin impairs attentional function and enhances the effects of guanfacine in the rat. *Psychopharmacology (Berl)*. **190** (1): 51-63.
15. Abi-Dargham A (2004). Do we still believe in the dopamine hypothesis? New data bring new evidence. *Int J Neuropsychopharmacol*. **7 Suppl 1**: S1-5.
16. Howes OD and Kapur S (2009). The dopamine hypothesis of schizophrenia: version III--the final common pathway. *Schizophr Bull*. **35** (3): 549-562.
17. Kasper S and Resinger E (2003). Cognitive effects and antipsychotic treatment. *Psychoneuroendocrinology*. **28 Suppl 1**: 27-38.
18. Meltzer HY and McGurk SR (1999). The effects of clozapine, risperidone, and olanzapine on cognitive function in schizophrenia. *Schizophr Bull*. **25** (2): 233-255.
19. Kane J, Honigfeld G, Singer J and Meltzer H (1988). Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. *Arch Gen Psychiatry*. **45** (9): 789-796.
20. Van Eden CG, Hoorneman EM, Buijs RM, Matthijssen MA, Geffard M and Uylings HB (1987). Immunocytochemical localization of dopamine in the prefrontal cortex of the rat at the light and electron microscopical level. *Neuroscience*. **22** (3): 849-862.
21. Seguela P, Watkins KC, Geffard M and Descarries L (1990). Noradrenaline axon terminals in adult rat neocortex: an immunocytochemical analysis in serial thin sections. *Neuroscience*. **35** (2): 249-264.
22. Levitt P and Moore RY (1978). Noradrenaline neuron innervation of the neocortex in the rat. *Brain Res*. **139** (2): 219-231.
23. Emson PC and Koob GF (1978). The origin and distribution of dopamine-containing afferents to the rat frontal cortex. *Brain Res*. **142** (2): 249-267.

24. Ungerstedt U (1971). Stereotaxic mapping of the monoamine pathways in the rat brain. *Acta Physiol Scand Suppl*. **367**: 1-48.
25. Goldman-Rakic PS, Leranth C, Williams SM, Mons N and Geffard M (1989). Dopamine synaptic complex with pyramidal neurons in primate cerebral cortex. *Proc Natl Acad Sci U S A*. **86** (22): 9015-9019.
Description of synaptic triad arrangement in the prefrontal cortex suggesting an DA plays an important role in regulating excitatory inputs to PFC neurons.
26. Richfield EK, Young AB and Penney JB (1989). Comparative distributions of dopamine D-1 and D-2 receptors in the cerebral cortex of rats, cats, and monkeys. *J Comp Neurol*. **286** (4): 409-426.
27. Geffard M, Patel S, Dulluc J and Rock AM (1986). Specific detection of noradrenaline in the rat brain by using antibodies. *Brain Res*. **363** (2): 395-400.
28. Goldman-Rakic PS, Lidow MS and Gallager DW (1990). Overlap of dopaminergic, adrenergic, and serotoninergic receptors and complementarity of their subtypes in primate prefrontal cortex. *J Neurosci*. **10** (7): 2125-2138.
29. Murrin LC and Kuhar MJ (1979). Dompamine receptors in the rat frontal cortex: an autoradiographic study. *Brain Res*. **177** (2): 279-285.
30. Savasta M, Dubois A and Scatton B (1986). Autoradiographic localization of D1 dopamine receptors in the rat brain with [3H]SCH 23390. *Brain Res*. **375** (2): 291-301.
31. Squire LR (2003). Fundamental neuroscience, 2nd Edition. San Diego, CA: Academic.
32. Lidow MS, Wang F, Cao Y and Goldman-Rakic PS (1998). Layer V neurons bear the majority of mRNAs encoding the five distinct dopamine receptor subtypes in the primate prefrontal cortex. *Synapse*. **28** (1): 10-20.
33. Meador-Woodruff JH, Damask SP, Wang J, Haroutunian V, Davis KL and Watson SJ (1996). Dopamine receptor mRNA expression in human striatum and neocortex. *Neuropsychopharmacology*. **15** (1): 17-29.
34. Ordway GA, O'Donnell JM and Frazer A (1987). Effects of clenbuterol on central beta-1 and beta-2 adrenergic receptors of the rat. *J Pharmacol Exp Ther*. **241** (1): 187-195.
35. Ramos BP and Arnsten AF (2007). Adrenergic pharmacology and cognition: focus on the prefrontal cortex. *Pharmacol Ther*. **113** (3): 523-536.
36. Ramos BP, Stark D, Verduzco L, van Dyck CH and Arnsten AF (2006). Alpha2A-adrenoceptor stimulation improves prefrontal cortical regulation of behavior through inhibition of cAMP signaling in aging animals. *Learn Mem*. **13** (6): 770-776.
37. Birnbaum SG, Yuan PX, Wang M, Vijayraghavan S, Bloom AK, Davis DJ, Gobeske KT, Sweatt JD, Manji HK and Arnsten AF (2004). Protein kinase C overactivity impairs prefrontal cortical regulation of working memory. *Science*. **306** (5697): 882-884.
38. MacDonald E, Kobilka BK and Scheinin M (1997). Gene targeting--homing in on alpha 2-adrenoceptor-subtype function. *Trends Pharmacol Sci*. **18** (6): 211-219.
39. Ihalainen JA and Tanila H (2002). In vivo regulation of dopamine and noradrenaline release by alpha2A-adrenoceptors in the mouse prefrontal cortex. *Eur J Neurosci*. **15** (11): 1789-1794.
40. Nimit Y, Cantacuzene D, Kirk KL, Creveling CR and Daly JW (1980). The binding of fluorocatecholamines to adrenergic and dopaminergic receptors in rat brain membranes. *Life Sci*. **27** (17): 1577-1585.
41. Weitl N and Seifert R (2008). Distinct interactions of human beta1- and beta2-adrenoceptors with isoproterenol, epinephrine, norepinephrine, and dopamine. *J Pharmacol Exp Ther*. **327** (3): 760-769.
42. Titeler M, Weinreich P, Sinclair D and Seeman P (1978). Multiple receptors for brain dopamine. *Proc Natl Acad Sci U S A*. **75** (3): 1153-1156.
43. Cornil CA and Ball GF (2008). Interplay among catecholamine systems: dopamine binds to alpha2-adrenergic receptors in birds and mammals. *J Comp Neurol*. **511** (5): 610-627.
44. Bymaster FP, Calligaro DO, Falcone JF, Marsh RD, Moore NA, Tye NC, Seeman P and Wong DT (1996). Radioreceptor binding profile of the atypical antipsychotic olanzapine. *Neuropsychopharmacology*. **14** (2): 87-96.
45. Gioanni Y, Thierry AM, Glowinski J and Tassin JP (1998). Alpha1-adrenergic, D1, and D2 receptors interactions in the prefrontal cortex: implications for the modality of action of different types of neuroleptics. *Synapse*. **30** (4): 362-370.
46. Briand LA, Gritton H, Howe WM, Young DA and Sarter M (2007). Modulators in concert for cognition: modulator interactions in the prefrontal cortex. *Prog Neurobiol*. **83** (2): 69-91.
47. Venator DK, Lewis DA and Finlay JM (1999). Effects of partial dopamine loss in the medial prefrontal cortex on local baseline and stress-evoked extracellular dopamine concentrations. *Neuroscience*. **93** (2): 497-505.
48. Wang HD and Deutch AY (2008). Dopamine depletion of the prefrontal cortex induces dendritic spine loss: reversal by atypical antipsychotic drug treatment. *Neuropsychopharmacology*. **33** (6): 1276-1286.
First description of spine changes in the PFC and alterations through antipsychotic treatment.
49. Sokolowski JD, McCullough LD and Salamone JD (1994). Effects of dopamine depletions in the medial prefrontal cortex on active avoidance and escape in the rat. *Brain Res*. **651** (1-2): 293-299.
50. Newman LA, Darling J and McGaughy J (2008). Atomoxetine reverses attentional deficits produced by noradrenergic deafferentation of medial prefrontal cortex. *Psychopharmacology (Berl)*. **200** (1): 39-50.
51. Arnsten AF (2009). Stress signalling pathways that impair prefrontal cortex structure and function. *Nat Rev Neurosci*. **10** (6): 410-422.
52. Tassin JP (1992). NE/DA interactions in prefrontal cortex and their possible roles as neuromodulators in schizophrenia. *J Neural Transm Suppl*. **36**: 135-162.
53. Lieberman JA and Koreen AR (1993). Neurochemistry and neuroendocrinology of schizophrenia: a selective review. *Schizophr Bull*. **19** (2): 371-429.
54. Westerink BH, de Boer P, de Vries JB, Kruse CG and Long SK (1998). Antipsychotic drugs induce similar effects on the release of dopamine and noradrenaline in the medial prefrontal cortex of the rat brain. *Eur J Pharmacol*. **361** (1): 27-33.
55. Li XM, Perry KW, Wong DT and Bymaster FP (1998). Olanzapine increases in vivo dopamine and norepinephrine release in rat prefrontal cortex, nucleus accumbens and striatum. *Psychopharmacology (Berl)*. **136** (2): 153-161.

Describes the correlation of DA and NE levels in response to antipsychotic treatment.

56. Gresch PJ, Sved AF, Zigmond MJ and Finlay JM (1995). Local influence of endogenous norepinephrine on extracellular dopamine in rat medial prefrontal cortex. *J Neurochem*. **65** (1): 111-116.
57. Pozzi L, Invernizzi R, Cervo L, Vallebuona F and Samanin R (1994). Evidence that extracellular concentrations of dopamine are regulated by noradrenergic neurons in the frontal cortex of rats. *J Neurochem*. **63** (1): 195-200.
58. Valentini V, Frau R and Di Chiara G (2004). Noradrenaline transporter blockers raise extracellular dopamine in medial prefrontal but not parietal and occipital cortex: differences with mianserin and clozapine. *J Neurochem*. **88** (4): 917-927.
59. Moron JA, Brockington A, Wise RA, Rocha BA and Hope BT (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.
60. Devoto P, Flore G, Pani L and Gessa GL (2001). Evidence for co-release of noradrenaline and dopamine from noradrenergic neurons in the cerebral cortex. *Mol Psychiatry*. **6** (6): 657-664.
61. Freed C, Revay R, Vaughan RA, Kriek E, Grant S, Uhl GR and Kuhar MJ (1995). Dopamine transporter immunoreactivity in rat brain. *J Comp Neurol*. **359** (2): 340-349.
62. Miner LH, Jedema HP, Moore FW, Blakely RD, Grace AA and Sesack SR (2006). Chronic stress increases the plasmalemmal distribution of the norepinephrine transporter and the coexpression of tyrosine hydroxylase in norepinephrine axons in the prefrontal cortex. *J Neurosci*. **26** (5): 1571-1578.
63. Devoto P, Flore G, Pira L, Longu G and Gessa GL (2004). Alpha2-adrenoceptor mediated co-release of dopamine and noradrenaline from noradrenergic neurons in the cerebral cortex. *J Neurochem*. **88** (4): 1003-1009.
64. Ahn NG and Klinman JP (1989). Nature of rate-limiting steps in a compartmentalized enzyme system. Quantitation of dopamine transport and hydroxylation rates in resealed chromaffin granule ghosts. *J Biol Chem*. **264** (21): 12259-12265.
65. Devoto P, Flore G, Longu G, Pira L and Gessa GL (2003). Origin of extracellular dopamine from dopamine and noradrenaline neurons in the medial prefrontal and occipital cortex. *Synapse*. **50** (3): 200-205.
66. Devoto P, Flore G, Vacca G, Pira L, Arca A, Casu MA, Pani L and Gessa GL (2003). Co-release of noradrenaline and dopamine from noradrenergic neurons in the cerebral cortex induced by clozapine, the prototype atypical antipsychotic. *Psychopharmacology (Berl)*. **167** (1): 79-84.
67. Devoto P, Flore G, Saba P, Fa M and Gessa GL (2005). Co-release of noradrenaline and dopamine in the cerebral cortex elicited by single train and repeated train stimulation of the locus coeruleus. *BMC Neurosci*. **6**: 31.
68. Devoto P, Flore G, Saba P, Castelli MP, Piras AP, Luesu W, Viaggi MC, Ennas MG and Gessa GL (2008). 6-Hydroxydopamine lesion in the ventral tegmental area fails to reduce extracellular dopamine in the cerebral cortex. *J Neurosci Res*. **86** (7): 1647-1658.

Shows through lesion studies that co-release of DA is occurring through NE terminals.

69. Broadbelt K, Byne W and Jones LB (2002). Evidence for a decrease in basilar dendrites of pyramidal cells in schizophrenic medial prefrontal cortex. *Schizophr Res*. **58** (1): 75-81.
70. Ingham CA, Hood SH, van Maldegem B, Weenink A and Arbuthnott GW (1993). Morphological changes in the rat neostriatum after unilateral 6-hydroxydopamine injections into the nigrostriatal pathway. *Exp Brain Res*. **93** (1): 17-27.

FURTHER INFORMATION

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