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Dopamine Receptors: Neurobiological Hypotheses Involved in Schizophrenia

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Abstract

Specific dopaminergic receptors, distinct from the classic alpha and beta-adrenergic receptors, are found in the central and peripheral nervous system and in some non-neuronal tissues. Two types of dopaminergic receptors have different functions and different second messengers. Dopamine is a potent agonist for both types of receptors; the action of dopamine is antagonized by phenothiazines and thioxanthines. The Dj receptor mediates sodilation in the renal, mesenteric, coronary and cerebral territories. Fenoldopam is an investigational selective agonist of the Dj receptor. The D2 receptor inhibits the transmission of nerve impulses in the sympathetic ganglia, inhibits the release of NE from the sympathetic nerve endings by acting on the presynaptic membrane (ura 70-2), inhibits the release of prolactin from the pituitary gland and causes vomiting. Selective D2 receptor agonists include: bromocriptine, lergotril and apomorphine, while butyrophenones such as haloperidol (active in the central nervous system), domperidone (does not cross the blood-brain barrier easily) and sulpiride (a benzamide) are relatively selective D2 receptor antagonists.

Keywords: Schizophrenia; Neurotransmitter; Dopamine; Serotonin; Glutamate; GABA

Abbreviations: GTP: Guanosine Triphosphate; cAMP: Cyclic Adenosine Monophosphate; PIP2: Phosphatidylinositol-4,5-Bisphosphate, IP3: Inositol-1,4,5-Trisphosphate; DAG: l,2-Diacylglycerol; HVA: Homovanillic acid; VTA : Ventral Tegmental Area; LSD: Lysergic acid diethylamide; GABA: Gamma-aminobutyric acid.

Introduction

Adrenergic receptors belong to a superfamily of related G protein-coupled membrane proteins, which includes the visual protein - rhodopsin and muscarinic cholinergic receptors. These proteins have similar sequences and, as it results from the properties of the constituent amino acids, a similar topography in the structure of the cell membrane.

Structure and Function of Adrenergic Receptors

The postulated structure of this protein-receptor family is schematically illustrated in figure 70-4. The characteristic features include 7 hydrophobic transmembrane sequences containing 20-28 amino acids each. The transmembrane sequences, especially M-7 (ura 70-4), seem to be important for the characteristic binding of the agonist. Coupling receptor occupancy with cellular response The major mediators of adrenergic cellular responses (and many others) belong to a family of regulatory proteins called G proteins, which, when activated, bind the nucleotide guanosine triphosphate (GTP). The best described G proteins are those that stimulate or

inhibit adenylate cyclase, proteins designated Gs, respectively Gj (ura 70-5). Betaj, beta2 and Dj receptors are coupled to Gs; the action of the receptors is therefore associated with the stimulation of adenylate cyclase and determines the intracellular increase of cyclic adenosine monophosphate (cAMP), which leads, in turn, to the activation of protein-kinase A and other cAMP-dependent protein-kinases. Consecutive phosphorylation of some proteins changes the activity of some enzymes and the function of other proteins, culminating in the cellular response characteristic of the stimulated tissue. The alpha2 receptor, the M2 subtype of the muscarinic cholinergic receptor and the D2 receptor are coupled to Gj, causing a decrease in adenylate cyclase activity and a decrease in cAMP concentration. The consecutive changes in the enzyme activity and the function of other proteins determine a series of alternative cellular responses, often opposite. Although many alphaj responses can be explained by inhibition of adenylate cyclase, other mechanisms may also be involved. The alpha adrenergic receptor (like the Mj subtype of the acetylcholine receptor) appears to be coupled to a different G protein, which activates phospholipase C; this G protein has not been so well characterized and is sometimes designated Gq. The action of the receptor stimulates phospholipase C, which catalyses the breakdown of some phospholipids attached to the membrane, especially phosphatidylinositol-4,5-bisphosphate (PIP2) with the production of inositol-1,4,5-trisphosphate (IP3) and l,2-diacylglycerol (DAG), both acting as second messengers (ura 70-5). IP3 rapidly mobilizes calcium from the intracellular stores of the endoplasmic reticulum, producing an increase in free cytoplasmic calcium, which, itself and via the calcium-calmodulin-dependent protein-kinase pathway, influences cellular processes appropriate to the stimulated cell. The transient increase in calcium, produced by IP3 by release from intracellular stores, is reinforced in the presence of continuous agonist stimulation by changes in membrane calcium flow, possibly resulting in the capture of calcium from the extracellular environment through mechanisms that are incompletely characterized. DAG, the second secondary messenger produced under the action of phospholipase C on PIP2 (as on other membrane phospholipids), remains associated with the cell membrane and activates protein kinase C, which has different substrates than those of IP3-stimulated calcium-calmodulin-dependent kinases. Phosphorylation of proteins, stimulated by protein kinase C, contributes to specific tissue responses in ways that are little known. The increase in intracellular calcium also potentiates the action of protein kinase C (ura 70-5). There can be many possible anomalies associated with schizophrenia, but among them, neurotransmitter disorders are the most studied and best understood. It is accepted by most researchers that neurotransmitter disorders are only part of the biological pathology of schizophrenia. The most accepted hypotheses of the neurotransmitter disorder in schizophrenia are the dopaminergic and the serotoninergic hypothesis. The new information provided by the PET studies once again highlighted the central role of the dopaminergic system in the treatment of psychoses. The plasma level of homovanillic acid (HVA), the metabolite of dopamine, has been shown to be often correlated with the severity of psychotic symptoms and with the consistent response to antipsychotic treatment. Glutamate, the major excitatory neurotransmitter in the central nervous system, is at least as important as dopamine (DA) in the pathophysiology of schizophrenia. GABA is the major inhibitory neurotransmitter in the brain and the loss of this inhibitory effect can produce an overactivity observed in other neurotransmitter systems (dopaminergic, serotoninergic, and possibly adrenergic). Dopamine is the most investigated neurotransmitter system in schizophrenia. It was proposed in 1973 that schizophrenia is linked to dopamine hyperactivity. This theory became the basic pathophysiological hypothesis for the next 15 years, being strongly supported by the fact that all available antipsychotics have an antagonistic effect on dopaminergic D2 receptors in relation to their clinical potency [1]. In addition, dopamine agonists, such as amphetamines and methylphenidate, exacerbate psychotic symptoms in the subgroup of patients with schizophrenia. Moreover, as noted later, the most important postmortem reports on schizophrenia found in the literature were those related to the increase of D2 receptors in the striatum. An important role belongs to dopamine in the physiopathology of schizophrenia, a fact that emerges from studies that measure the plasma level of the major metabolite of dopamine, homovanillic acid. Some studies have indicated that the level of plasma concentration of homovanillic acid can reflect the concentration of homovanillic acid in the central system. The plasma level of homovanillic acid (HVA), the metabolite of dopamine, has been shown to be correlated with the severity of psychotic symptoms and with the response to antipsychotic treatment. The new information provided by the PET studies showed once again the central role of the dopaminergic system in the treatment of psychoses. When measuring the synthesis of dopamine in the brain by using a PET scan, using the administration of radiolabeled fluoro-L-DOPA (dopamine precursor), an increase in dopamine was observed in schizophrenic patients who had never taken medication compared to the control group of the same age [2]. SPECT studies using alpha-methyltyrosine showed that there are no significant changes in dopamine in schizophrenic patients compared to the control group. They appreciated the importance of this study but suggested that this may reflect the heterogeneity of dopaminergic dysfunction. Dopaminergic receptors in schizophrenia. Currently, 5 subtypes of dopamine receptors have been discovered D1, D2, D3, D4 and D5 (Table 1).

Dopaminergic Receptor Subtypes	
The D1 receptor family	The D2 receptor family
D1	D2
D5	D3
	D4

Table 1: Subtypes of Dopamine Receptors.

Based on pharmacological similarities, dopamine receptors have been classified into the D1-like family (D1 and D5 receptors) and the D2-like family (D2, D3 and D4 receptors). DA receptors vary differently in human brain regions. D1 receptors have an extensive neocortical distribution, including in the prefrontal cortex, and are present in increased density in the striatum. D5 receptors are concentrated in the hippocampus and entorhinal cortex. D2 receptors are concentrated in the striatum with a reduced density in the medial temporal structures (hippocampus, entorhinal cortex, amygdala) and at the level of the thalamus. The density of D2 receptors in the prefrontal cortex is extremely low. D3 receptors are present in the striatum, where their density is increased especially in the ventral part. D4 receptors are present in the prefrontal cortex and hippocampus, but have not been detected in the striatum [1]. D1 receptors play an important role in negative symptoms. D1 receptors are predominantly expressed in the dendrites of pyramidal neurons. The reduction of D1 receptors observed in the prefrontal cortex of schizophrenic patients is thought to lead to cognitive dysfunction and the severity of negative symptoms [3]. It was noted in 1991 that clozapine has a different affinity for D4 receptors and they hoped that D4 receptors might be a possible candidate pathophysiological cause for schizophrenia. Contrary to initial expectations, D4 receptors are not the only ones that differentiate atypical from typical antipsychotics [4].

There are 4 dopaminergic pathways in the brain:

- The nigrostriatal pathway - the projection from the *substantia nigra* to the basal ganglia, is part of the extrapyramidal nervous system and controls movements.
- The mesolimbic pathway, the projection from the ventral tegmental area (VTA) to the nucleus accumbens (part of the limbic system of the brain) which is believed to be involved in the feeling of pleasure, delirium and hallucinations in psychosis, in the production of a strong euphoria in drug abuse.
- The mesocortical pathway also starts from the VTA but sends its axon extensions to the limbic cortex, having a role in mediating the negative and cognitive symptoms of schizophrenia.
- The tuberoinfundibular pathway, which has a role in controlling prolactin secretion, originates from the hypothalamus to the anterior pituitary gland.

The studies carried out have highlighted that there is an over activity at the level of the mesolimbic dopaminergic pathway from the ventral tegmental area (VTA) to the limbic region.

This is believed to be associated with the induction of positive psychotic symptoms (hallucinations, delirium, bizarre behavior, thought disorders). The decrease in dopaminergic transmission at the level of the mesocortical pathway (from the VTA to the prefrontal cortex) would represent the main cause that modulates the negative symptoms of schizophrenia (anhedonia, avolition, alogia, affective flattening, lack of socialization). At the same time, dopaminergic transmission in the nigrostriatal pathway (from the *substantia nigra* to the basal ganglia) is believed to be intact in untreated schizophrenia. The extrapyramidal adverse effects are a consequence of the dopaminergic inhibition transmitted in this region [5]. It is known that dopamine works closely with serotonin, glutamate, and other systems, therefore changes in one of the systems affect the balance of the other systems.

It is clear that dopamine is involved in the response to stress, and we know that schizophrenic patients tend to relapse after stress.

Serotonin

Interest in serotonin and its implication in the physiopathology of schizophrenia began in 1950 with the discovery that the hallucinogen Lysergic acid diethylamide (LSD) has a primary action on the serotonergic neurotransmitter, producing several aspects similar to schizophrenia including a severe psychotic episode with especially visual and very rarely auditory hallucinations.

The central serotonergic neuronal areas from the raphe nucleus in the midbrain and the extensive ramifications, innervating the essential parts of the brain, have large postsynaptic contact with various neurons. It is estimated that there are over 1 million serotonin vesicles per mm^3 in the hippocampus. The new atypical antipsychotics (clozapine, risperidone, olanzapine, quetiapine and ziprasidone) have an increased affinity rate for 5HT2A and D2. This led to the hypothesis that the balance between serotonin and dopamine would be altered [6].

It was found in 1999 that the degree of occupation of 5HT2A serotonin receptors (but also of other serotonin receptors) by antipsychotic drugs depends on the brain area involved, and can be associated with improvements in cognition and depression, D2 receptors being responsible for mediating extrapyramidal effects (EPS).

Serotonergic Receptors in Schizophrenia

15 receptor subtypes have been identified. Two types of receptors, 5HT6 and 5HT7, have been proposed as candidates for the action of atypical drugs, becoming study targets for physiopathology. The results of animal research suggest that the simultaneous blocking of 5HT2A and D2 receptors would cause a relative stimulation of the mesocortical dopaminergic pathway while respecting the nigrostriatal and mesolimbic pathways. The hypothesis of simultaneous blocking of 5HT2A/D2 receptors would satisfactorily explain why antagonists of only 5HT2A receptors but not D2 receptors (such as ritanserin) do not have a predominant antipsychotic activity when administered alone.

There is evidence that shows that antipsychotic drugs with action on 5HT2A receptors lead to the improvement of affective disorders. As research in affective disorders has suggested, serotonin activity disorders are involved in suicide and impulsive behaviour that can be observed in schizophrenic patients. 5-HT 2C receptors have not received much attention in studies related to antipsychotic medication, but they could have an important role in explaining some differences observed between antipsychotics, and would represent a starting point in the discovery of other new antipsychotics. 5HT1A receptors are probably the most characteristic subtype of 5HT receptors and play an important role in controlling the activity of monoaminergic neurons.

This subtype of receptors could be considered as having an antagonistic functionality with that of 5HT2A receptors, both at the presynaptic and postsynaptic level. In the brain, both subtypes of 5HT1A and 5HT2A receptors are located in pyramidal neurons.

The activity of 5HT1A receptors can contribute to the effectiveness of the antipsychotic agent aripiprazole, which is a partial agonist of this subtype of receptors, this drug also showing some antagonistic properties of postsynaptic D2 receptors [7].

Parallel to the decrease in dopaminergic transmission in the mesocortical pathway, an excessive serotoninergic transmission from the raphe nuclei to this pathway is possible. There is probably a serotonergic overactivity in different regions of the brain. Atypical antipsychotics (second generation) block this excess of serotonin, with an important reduction of negative symptoms. The increase in serotonergic transmission would lead to the inhibition of the mesocortical dopaminergic pathway. Postmortem studies in schizophrenic patients found an increase in serotonin and its metabolites in the nucleus of the striatum. Probably the previous exposure to neuroleptics contributed to this change. Another discovery is the decrease in the density of 5HT2A receptors in the prefrontal cortex. Several postmortem studies and recent in vivo studies have shown increased 5HT1A receptor density in the cortex of patients with schizophrenia [8].

Glutamate and the N-Methyl-D-Aspartate (NMDA) Receptor

Glutamate, the major excitatory neurotransmitter in the central nervous system, is at least as important as DA in the pathophysiology of schizophrenia. It is involved in learning, memorization, and brain development, synaptic plasticity, and may be involved in the neurodevelopment of aspects of schizophrenia, as well as in the modulation of motor functions. There are 5 excitatory amino acid receptors in the brain: NMDA, AMPA, kainate, metabotropic, and L-AP-4.

Phencyclidine (PCP), which is a non-competitive antagonist of NMDA receptors, has been observed to produce a psychotic episode similar to that of schizophrenia. There are data from some postmortem studies suggesting the alteration of pre- and postsynaptic markers for glutamatergic neurons in schizophrenic patients. It was shown that there is an alteration of the NMDA receptors expressed in the brain areas of schizophrenic patients.

Other findings that suggested a glutamatergic hypofunction in schizophrenia are the decrease in the level of glutamate in the cerebrospinal fluid, the increase in the number of NMDA receptors as well as the decrease in glutamate binding in the neocortex in postmortem studies. The glutamate hypothesis in schizophrenia is one of the most active areas of current research. Substances that block NMDA receptors cause both positive and negative symptoms in healthy volunteers and schizophrenic patients, while dopaminergic agonists cause only positive symptoms. Postmortem studies showed an increase in the number of glutamatergic receptors in several prefrontal regions where evidence of glutamatergic hypofunctioning was discovered in the prefrontal cortex and the temporal region [9].

Glutamatergic Pathways Involved in Schizophrenia

Glutamate mediates the transmission of information from the hippocampus to the anterior cingulate cortex, then to the frontal neocortex. Moreover, glutamate mediates the local and regional feed-back system, which modulates the restoration of the activity of the system in general and probably also of the learning system. Abnormalities in glutamatergic transmission are reported in many areas of the brain such as the frontal cortex, hippocampus, limbic cortex, striatum and thalamus, with changes in gene expression being reported in these areas. Hypoglutamatergy in schizophrenia can have very important modulatory effects on catecholaminergic

neurotransmission and plays an important role in neurodevelopment as well as in neurocognition [10].

The Model of Glutamatergic Deficiency in Schizophrenia

The inhibitory GABA-ergic projections of neurons from the striatum to the thalamus constitute a highly selective filter mechanism that protects the cerebral cortex from overload. A reduction in thalamic inhibition can lead to an information overload that would lead to confusion and psychosis. Since GABA-ergic activity is under dopaminergic and glutamatergic control, both the increase in dopaminergic activity in the striatum and a decrease in glutamate function would lead to the opening of the striatal inhibition filter of the thalamus [11].

GABA

GABA is the major inhibitory neurotransmitter in the brain. Evidence for the involvement of GABA in schizophrenia has come from 2 lines of investigation. First of all, clinical studies have shown that benzodiazepines (GABA A receptor agonists) administered together with antipsychotic medication are effective in reducing symptoms in patients with schizophrenia. In postmortem studies, a GABA interneuron deficit was found in the anterior cingulum, the prefrontal cortex and at the level of the hippocampus. GABAergic neurons are particularly vulnerable to glucocorticoid hormones and glutamatergic excitotoxicity. GABA-ergic neurons are inhibitory, and the loss of this inhibitory effect can produce an overactivity observed in other neurotransmitter systems (dopaminergic, serotoninergic, and possibly adrenergic) [12].

Peptides

Neurotensin is colocalized in several dopaminergic neurons and acts as a neuromodulator of them and other neurotransmitters. It was discovered that the level of neurotensin in the CSF is low in schizophrenic patients compared to the control group made up of healthy subjects, but also compared to other patients with other mental illnesses. It was found that antipsychotic drugs increase the level of neurotensin in the brain [13]. Other peptides that must be considered for a role in the physiopathology of schizophrenia are cholecystokinin, somatostatin, substance P, neuropeptide Y.

Norepinephrine

They have described the existence of an important relationship between the increase in plasma norepinephrine and positive symptoms. Studies have shown that prolonged administration of antipsychotics decreases the activity of noradrenergic neurons in the locus ceruleus. Clozapine produces increases in the noradrenergic index of functioning [14].

The Role of Dopaminergic (D2) and Serotoninergic Receptors in the Action of Antipsychotic Drugs

Most antipsychotics, except clozapine, have been observed to have high D2 receptor occupancy (70% or more) at the clinical doses used. Subsequent studies have demonstrated that there is a "therapeutic window" for most antipsychotics with 60-65% receptor blockade required to achieve optimal antipsychotic response, and occupancy greater than 80% is associated with EPS. Blockade of D2 receptors may adequately explain the beneficial effects of typical antipsychotics on positive symptoms in acute psychotic episodes. Blockade of D2 receptors contributes to the antipsychotic effect of serotonergic-dopaminergic receptor antagonists. EPS and prolactin elevations produced by antipsychotics can be satisfactorily explained by antagonism of dopaminergic neurotransmission mediated by D2 receptors in the striatum (which is part of the extrapyramidal nervous system) for extrapyramidal symptoms and at the level of the hypothalamic tuberoinfundibular system. For adverse neuroendocrine effects [15]. The difference between typical and atypical antipsychotics is given by their affinity for D2 receptors (Table 2).

Typical Antipsychotic	Profile of Receivers	PET(SPECT)[1]	
		D2(%)[1]	5-HT2 (%)
Haloperidol	Antagonist in particular of rec. D2 like	70-90	0
Amisulpride	Selective D2/3 Antagonist	38-76	0
Clozapine	Multiple antagonist	20-68	84-100
Olanzapine	Multiple antagonist	43-39	90-100
Quetiapine	Multiple antagonist	22-68	48-70
Risperidone	Antagonistic 5-HT2/ D2/α1	59-89	78-100
Sertindole	Antagonist 5-HT2/ D2/α1	50-74	(90+)
Ziprasidone	Antagonist 5-HT2/ D2/α1+Agonist 5HT1A+recaptare NA/5HT	77	95
Zotepine	Antagonist multiplu + recaptare NA	(57-61)	?
[1]The degree of occupancy of D2 receptors of the basal ganglia and cortical 5HT2 receptors			
*Adapted from Buckley et al. 2001			

Table 2: Comparison of the Pharmacological Profile between Typical and Second-Generation Antipsychotics*.

Medication such as clozapine binds slowly and has a rapid dissociation for D_2 receptors compared to typical antipsychotics (such as haloperidol) which have a strong affinity for these receptors. It has been proposed that this rapid dissociation for D_2 receptors and the reduced affinity for these receptors could explain the atypicality of clozapine. Results from a low affinity for dopaminergic D2 receptors. Atypia is given by the fast dissociation rate (Koff) for dopaminergic D_2 receptors [16].

Clozapine is the prototype atypical antipsychotic. As is known, clozapine proved to be the most effective treatment for chronic schizophrenia, having the lowest level of occupation of D2 receptors among all antipsychotic drugs. At very low doses (50mg/day), lower than the usual doses used to obtain the antipsychotic effect, a complete occupation of the 5HT2 system was observed. The effectiveness of clozapine in refractory patients was observed to be at doses between 300 - 400 ng/ml, where the degree of occupation of D2 receptors is between 50-60%. This reduced level of occupancy of rec. D2 explains why clozapine does not give EPS or significant increases in prolactin. Quetiapine's binding profile is similar to that of clozapine, a fact supported by PET studies.

Risperidone becomes therapeutically effective at levels of D_2 occupancy typically seen for typical antipsychotics (at 2 mg doses it develops D_2 occupancy of 60% or greater). Increased levels of 5HT2 occupancy have been observed even at low doses but these do not lead to antipsychotic effects. Olanzapine showed a preferential blockade of 5HT2 receptors comparable to dopaminergic D_2 receptors. The antipsychotic effect is usually observed at doses between 10-20 mg/day, when the degree of D_2 occupancy reaches 65-80%. At doses of 30 mg/day or higher when increases in prolactin and EPS levels were reported, the occupancy threshold exceeded 80%. Amisulpride, unlike other antipsychotics, has no affinity for serotonin $5HT_2$ receptors. Doses of amisulpride between 600-900 mg/day give a D_2 occupancy of 70-80%, while doses >1100mg/day give a D_2 occupancy of >85%, and at these increased doses EPS can be observed [17].

The blocking of $5HT_2A$ receptors and the preferential blocking of certain subtypes of dopaminergic receptors was a relevant hypothesis in defining the mechanism of the effectiveness of atypical or second-generation antipsychotics in treating negative symptoms. PET studies of atypical antipsychotics have shown an extensive occupation of 5HT2A receptors in the cerebral cortex with clozapine, olanzapine, risperidone, and quetiapine, but not with amisulpride. The observed difference between the degree of receptor occupancy and the active clinical doses leads to the question whether the effect on $5HT_2A$ receptors is the only neurochemical determinant of atypia.

Conclusion

Numerous researches with more and more laborious techniques found the answers to some questions but raised new ones, developing new research directions. Once again, the human brain proves to be a universe that needs to be further explored, schizophrenia still remaining an enigma only partially resolved.

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