

Dopamine Hypothesis of Mania

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The discovery of dopamine and its pathways

Dopamine (DA) was first synthesized in 1910 from 3,4-dihydroxy phenyl alanine (DOPA) by Barger and Ewens at Wellcome Laboratories in London. It is a catecholamine and in the 1940s Blaschko in Cambridge proposed that DA was a precursor in synthesis of the catecholamine neurotransmitters noradrenaline (norepinephrine) and adrenaline (epinephrine). In 1957 it was shown to be present in the brain with other catecholamines (1). In 1958, Carlsson discovered the function of dopamine a neurotransmitter (2), while studying the action of reserpine, isolated in 1952 from the root of Rauwolfia, used traditionally in India for the treatment of insanity. Reserpine irreversibly blocks the vesicular monoamine transporter, thus depleting neuronal serotonin, dopamine and norepinephrine. In mammals it produces loss of movement or “akinesia”, a symptom of Parkinson’s disease. The degree of akinesia induced by reserpine correlated most closely with the depletion of dopamine, and could be reversed by L-dopa.

In Vienna, Hornykiewicz who had worked with Blaschko, measured dopamine in Parkinson’s disease brains, and in 1960 reported depletion of dopamine in the corpus striatum in these brains, and later postulated that striatal dopamine deficiency accounts for the motor symptoms of Parkinson’s disease (3).

Carlsson demonstrated dopamine was concentrated in the basal ganglia. Using the technique of monoamine histofluorescence, dopamine pathways were mapped in the brain including the nigrostriatal pathway, from A9 neurons in the substantia nigra to the corpus striatum (4). In 1967, Cotzias in New York developed a technique, raising the dose of DOPA gradually, up to 16 grams per day, to treat Parkinson’s disease (5). Thus the role of dopamine in movement control and Parkinson’s disease was established by 1967.

Catecholamine hypothesis of mania

Schildkraut (1965) proposed a catecholamine hypothesis of affective disorders, in which depression was postulated to result from “deficiency” of “catecholamines particularly norepinephrine” at “functionally important adrenergic receptor

sites in the brain”, and elation (mania) resulted from an excessive activity of catecholamines (6). He emphasised the role of norepinephrine and not dopamine.

One of the supports of this hypothesis was the effect of amphetamines which release catecholamines. Low doses of amphetamines produce a state resembling mild mania but with reduced hunger and appetite and anomalous endocrine effects (7).

Dopamine agonists, such as bromocriptine, used to treat prolactinomas can lead to psychotic states, including mania (8). Likewise, a manic episode may be triggered by amphetamine in predisposed individuals (9), and L-dopa can trigger mania in individuals with a bipolar predisposition (10).

The tranquilising and depressant effect of reserpine in man was another piece of Schildkraut’s evidence. Furthermore alpha-methyl para-tyrosine, which inhibits the rate-limiting step in catecholamine synthesis, reduces the severity of mania (11); and depleting L-dopa and lowering brain catecholamines, by ingesting a drink of branched chain amino acids, improves mania (12).

Antipsychotics in mania and schizophrenia

The antimanic effect of antipsychotics became another foundation of the catecholamine hypothesis of mania, but there was considerable misunderstanding of the role of antipsychotics in mania until the era of newer antipsychotics stimulated research into their effects.

Dopamine hypothesis of schizophrenia

Early antipsychotics such as chlorpromazine and haloperidol have varied pharmacological actions including antagonism of norepinephrine. However the main mechanism common to all antipsychotics was discovered by Carlsson and Lindqvist in 1963, showing that they increase the release of metabolites of dopamine and epinephrine, and speculating the mechanism to be blockade of the receptors for dopamine (13). Van Rossum in 1966 articulated the hypothesis that dopamine pathways may be overactive in schizophrenia (14).

The importance of dopamine receptor blockade for antipsychotics was confirmed in 1974 by Seeman (15), showing

with Creese that clinical doses of antipsychotics for schizophrenia correlated closely with their ability to block D2 receptors (16).

The hypothesis was refined by Davis et al in 1991, proposing that schizophrenia is characterized by frontal hypodopaminergia resulting in striatal hyperdopaminergia (17).

The dopamine hypothesis of schizophrenia in 2012 emphasises excessive presynaptic striatal dopamine release (18).

Dopamine hypothesis of mania

Chlorpromazine was the most widely investigated antipsychotic in early comparative trials in mania and is obviously sedative in its effects. In New York in 1990, haloperidol (38% of prescriptions) was the most widely used antipsychotic in mania, followed by fluphenazine, and chlorpromazine (19).

However, drugs with more specific dopamine-receptor blocking actions have antimanic properties, although these drugs are less sedative, being without blocking actions at histamine or noradrenaline receptors. It was reported in 1976 that the selective dopamine receptor antagonist pimozide possesses antimanic activity (9,20). This suggested a dopaminergic mechanism (9). Cookson and Silverstone hypothesised that mania may result from overactivity of dopamine in certain brain pathways (20).

In a comparative trial, pimozide was no less efficacious than chlorpromazine in improving the severity of mania over two weeks. It was suggested that the dopamine pathways involved in mania may be different from those in schizophrenia and include the nucleus accumbens (21); dopamine agonists applied there stimulated locomotion (22).

Mechanisms of antimanic actions of antipsychotics

Antipsychotics owe their antimanic effects mainly to blockade of dopamine receptors but additionally to some extent to blockade of noradrenaline at alpha-1 receptors (eg haloperidol) (21,23), and blockade of histamine at H-1 receptors (eg chlorpromazine) (24).

Some newer antipsychotics (e.g. olanzapine, quetiapine) share these actions, and are also potent blockers of serotonin 5HT-2 receptors, but are selective for sub-types of dopamine receptors; others (amisulpride) block only sub-types of dopamine receptors. It cannot be assumed that drugs effective in schizophrenia will be effective in mania or vice versa.

Antipsychotics in mania: Patterns of symptom improvement: sedative, antipsychotic or antimanic?

It had been suggested that antipsychotics owe their effects in mania either to non-specific sedation, or to combating psychotic symptoms. However, this view fails to recognise that non-sedative dopamine-blocking drugs can improve mania; these would now include aripiprazole and ziprasidone. In studies of olanzapine, risperidone, quetiapine, and aripiprazole, the improvement in

mania occurred in patients with or without psychotic symptoms (25). When individual symptoms of mania were analysed, drug treatment (with olanzapine, quetiapine and presumably the other antipsychotics) improved the whole range of symptoms (including elation, flight of ideas, grandiosity, sexual interest, irritability, aggression, general appearance and insight, as well as the items most sensitive to sedation: insomnia, overactivity and pressure of speech). These findings lead to the inevitable conclusion that the drugs are not just antipsychotic, but also antimanic (25).

The speed of action and size of effect of antipsychotics makes them especially useful for control of emergent (hypomanic) symptoms (25) and in the case of haloperidol for acute tranquillisation in severe mania (24).

Antipsychotics in schizophrenia and mania

The so-called "atypical" antipsychotics were screened in animal models to have fewer extrapyramidal or Parkinsonian side effects than the older drugs. The "atypicals" share no other quality than this. Meta-analyses show small but real superiority in efficacy (26), and effectiveness (27) for some new drugs (particularly clozapine) over older ones in schizophrenia.

The differences are more striking when the treatment of mania is analysed. In our own experience the benzamide drug, remoxipride, did not bring about sustained improvement in mania in doses shown to be effective in schizophrenia (24). A multitreatment meta-analysis (28) confirms the impression from individual randomised controlled trials (25) that no atypical antipsychotic is superior in efficacy to haloperidol in mania and some, such as quetiapine, aripiprazole, asenapine and ziprasidone, are distinctly inferior. All produce fewer extrapyramidal side effects than haloperidol and are therefore more acceptable to patients. In addition, some atypicals are associated with less post-manic depression, which can be another manifestation of extrapyramidal effects (akinetic depression) (25).

Thus it is likely that the DA pathways and receptor subtypes involved in mania are different from those involved in schizophrenia.

The function of dopamine

The midbrain dopamine neurones have three component pathways: a dorsal nigro-striatal pathway from the A9 area (substantia nigra) to the corpus striatum, the meso-limbic pathway from the A10 area to limbic areas including the nucleus accumbens and the frontal cortex (also called the meso-frontal pathway), and a ventral pathway from area A8, behind the red nucleus, to the "extended amygdala" (amygdala, ventral striatum, hippocampus) (29). Loop circuitry from the nucleus accumbens influences ascending dopamine projections to the other areas of the striatum (30).

The DA projections areas of the three main dopamine pathways are also the site of termination of glutamate fibres from areas of the cerebral cortex that complete neuronal "loops" from the DA rich areas through thalamic nuclei.

DA systems have roles in motivational salience and reward prediction. Activity in DA cells recorded electrophysiologically by Schultz showed no clear covariations with movements, but revealed activation after reward-related events and attention-inducing sensory stimuli. When a conditioned stimulus is established, cell firing occurs in response to the conditioned stimulus rather than to the reward. Moreover, failure of the reward to follow the CS, is associated with reduction in DA cell firing (31). Berridge and Robinson concluded that “dopamine neurones mediate motivational salience, whereby neutral events become attention-grabbing and capture thought and behaviour” (32).

These responses occur in similar manner in A8, A9, and A10 in a range of behavioral situations but as the pattern of responding shifts from immediate reward to anticipation and cues, so the localisation of DA cell activation shifts dorsally from the ventral area to more dorsal striatum. Thus enjoyment of music involves DA release in the caudate during the anticipation and in the nucleus accumbens during the peak emotional response (33). A similar dorsal shift in DA release occurs during repeated doses of amphetamine (34).

Everitt and Robbins reviewed the development of addictive behaviours. Whereas the initiation of addiction involves voluntary or impulsive drug use and an initial hedonic response, mediated

through prefrontal cortex and ventral areas of the dopamine system, with repetition the behaviour becomes habitual with loss of control, and more dorsal parts of the dopamine system become recruited. Eventually the habit becomes a compulsive behaviour in which the goal becomes relief of withdrawal symptoms with striatal rather than cortical control over drug taking (35).

Dopamine pathways in schizophrenia and mania

Whereas the dopamine hypothesis of schizophrenia proposes abnormal activity in the striatum and the prefrontal cortex, the hypothesis for mania implies a different anatomy. It is speculated that whereas the initial hypomanic stage is mediated by ventral dopamine paths such as the A10 projection to the nucleus accumbens and a loop to the prefrontal cortex, during severe mania hyperactivity shifts to more dorsal nigrostriatal paths. This shift may correspond to the development of psychotic features or catatonic symptoms. Hence mild mania may respond to an atypical antipsychotic with low propensity to impair extrapyramidal function, but severe or psychotic mania requires more potent antipsychotics that are associated with extrapyramidal side effects.

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