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How antipsychotics become anti-'psychotic' – from dopamine to salience to psychosis

Shitij Kapur

Centre for Addiction and Mental Health, and the University of Toronto, 33 Russell Street Toronto, Ontario M5S 2S1, Canada

The relationship between dopamine, psychosis and antipsychotics has been challenged by the suggestion that there is a delay, of weeks, between the onset of dopamine receptor blockade and improvement in psychosis. However, recent data show that there is no significant delay. In light of these new findings, it is proposed that dopamine, through its role in reward prediction and motivational salience, provides a link to psychosis. Psychosis results from aberrant reward prediction and aberrant attribution of salience that is caused by disordered dopamine transmission. Antipsychotics become anti-'psychotic' by blocking dopamine transmission and attenuating the motivational salience of the symptoms, leading to the common statement from patients that symptoms 'don't bother me as much anymore'. This attenuation of salience also impacts on normal motivational drives, providing an explanation for why antipsychotics might induce iatrogenic negative symptoms and dysphoria, often leading to non-compliance by patients. The implications of this framework for relapse and other clinical phenomena, animal models and future studies are discussed.

The introduction of chlorpromazine as a treatment for psychosis, half a century ago, launched the era of modern antipsychotic agents, and subsequently dozens of antipsychotics have been developed and tested clinically. Despite extensive research, blockade of dopamine D2 receptors remains necessary and sufficient for antipsychotic activity, even in this era of atypical antipsychotics [1]. Given that an abnormally active dopamine system is implicated in psychosis [2], the relationship between dopamine, psychosis and antipsychotics ought to be straightforward. However, the Achille's heel of this argument has been the paradox that dopamine receptor blockade occurs within hours of starting medication whereas the antipsychotic response is delayed by weeks.

This idea of a 'delayed onset' of antipsychotic action gained favour during the 1970s and is now firmly embedded in standard psychiatric textbooks [3]. According to this hypothesis, there is a delay of 2–3 weeks between the start of medication and the onset of a specific antipsychotic effect. Because dopamine receptor blockade can be achieved within the first day of treatment [4,5], this hiatus was a major stumbling block in the establishment of a direct relationship between dopamine, dopamine receptor blockade, psychosis and antipsychotics. But, is the onset of antipsychotic action really delayed?

Onset of antipsychotic action – not delayed anymore

Agid *et al.* [3] recently reported the results of a meta-analysis of 42 double-blind, comparator-controlled studies that examined the onset of response to antipsychotics. The meta-analysis examined data on 7450 patients with schizophrenia or schizoaffective disorder who were treated with common typical (haloperidol and chlorpromazine) and atypical (risperidone and olanzapine) antipsychotics. Psychosis improved in all patients within the first week of treatment [3]. This early improvement in psychosis was not just due to a change in aggression and excitement but was a specific and distinct improvement in core psychotic symptoms (i.e. conceptual disorganization, hallucinatory behaviour, grandiosity and unusual thought content). In fact, the improvement in psychosis during the first two weeks of treatment was much greater than the improvement observed during any subsequent two-week period during treatment (Figure 1).

If antipsychotic action starts within the first week of treatment, how early does it start? Antipsychotics have been used in emergency rooms for their immediate effect; however, it has been assumed that these immediate effects are merely sedation and behavioural control (because it was known that a specific antipsychotic response is 'delayed'). To address the question of how early the antipsychotic action begins, we evaluated data [35] from a large ($n = 311$) double-blind, placebo-controlled study that compared the effects of haloperidol, olanzapine and placebo within the first 24 h after injection in patients experiencing a psychotic exacerbation (i.e. those patients experiencing a worsening of their psychotic symptoms). An anti-'psychotic' effect was evident within the first 24 h of treatment for both olanzapine and haloperidol. This change in psychosis was an independent factor that was distinct from changes in agitation and excitement. The concept of a delayed onset is further rejected by a recent study by Abi-Dargham *et al.* [6] who showed that α-methyl-para-tyrosine, an agent that depletes synaptic

Corresponding author: Shitij Kapur (shitij_kapur@camh.net).
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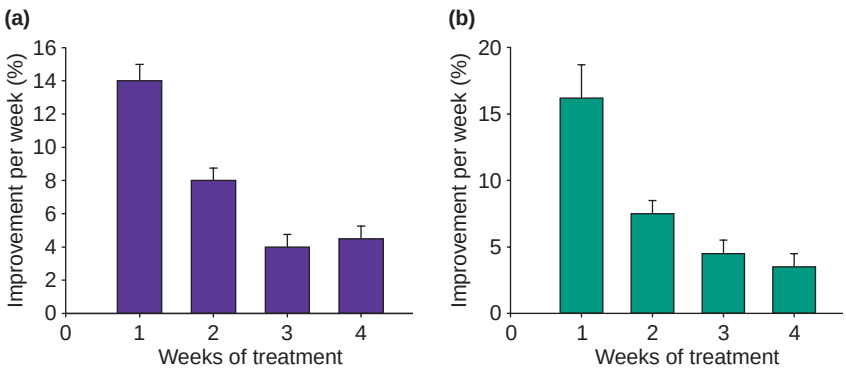

Figure 1. Data show the mean response (percentage) to antipsychotic treatment [compared with baseline (i.e. symptoms before treatment)]. Data are averages from 42 published studies of four antipsychotics (haloperidol, chlorpromazine, risperidone and olanzapine). **(a)** Mean ± SE percentage improvement in the total Brief Psychiatric Rating Scale (BPRS) [36] score per week, for the first four weeks of treatment. **(b)** Mean ± SE percentage improvement in core psychotic symptoms (i.e. conceptual disorganization, hallucinatory behavior, grandiosity and unusual thought content) over time. Reproduced, with permission, from [3]. ©2003 American Medical Association.

levels of dopamine, induces a robust antipsychotic response within the first 72 h of its administration.

Thus, it seems that blocking dopamine transmission at D2 receptors (be it through blockade of receptors or depletion of dopamine stores) leads to an immediate onset of antipsychotic response. By removing the paradox of a 'delayed onset' these new findings emphasize a closer relationship between dopamine, psychosis and the antipsychotic response. This leads to the question: Why does aberrant dopamine transmission lead to psychosis and how does blocking such transmission lead to the observed pattern of antipsychotic response? Because dopamine is pivotal to the question, we begin to address this question by looking at the different roles of dopamine in normal mental function, and use this to explain the positive psychotic symptoms of schizophrenia.

Roles of dopamine in 'reward'

There is near universal agreement for a central role of dopamine in 'reward' and 'reinforcement'. However, precisely what these terms mean and what dopamine contributes to their realization is the subject of competing hypotheses. Original hypotheses suggested that dopamine mediates hedonic pleasure [7]. However, subsequent studies suggested that dopamine is involved not only in appetitive events but also in aversive events [8], and the release of dopamine often precedes the hedonic experience [9,10]. To accommodate these and other findings, two complimentary hypotheses have developed over time. According to one hypothesis, the firing of midbrain dopamine-containing neurons is linked to 'reward prediction'. In this role, the dopamine system is involved when the animal encounters novel rewards in the environment, and changes in neuronal firing relate to how the animal habituates to these rewards and makes associations between the rewards and other neutral stimuli [11]. This action occurs on a sub-second timescale [11]. On a longer timescale, the released dopamine is thought to mediate the 'motivational salience', rather than the hedonic experience, of these rewards [12,13]. Motivational salience refers to the process whereby reward-associated stimuli come to be 'attention grabbing' to the animal and become the focus of goal-directed behaviour. Thus, the dopamine system seems to be involved in detecting new rewards in the environment, learning about them and their associations, and using this information to drive goal-directed behaviour. Under normal physiological conditions, the above functions are combined with the role of dopamine in modulating movement to allow for a seamless conversion of learning and motivation into action [12–14].

Psychosis as a dopamine-mediated state of aberrant salience

Under normal circumstances, it is the context-driven activity of the dopamine system that mediates the experience of novelty and the acquisition of appropriate motivational salience [12,13,15,16]. We hypothesize that in schizophrenia a series of genetic and environmental predispositions [17] results in a dysregulated dopamine system that fires and releases dopamine independently of cue and context (Figure 2). The normal process of context-driven novelty and salience attribution is usurped by an endogenously driven assignment of novelty and salience to stimuli (Figure 2). Thus, the dopamine system, which under normal conditions is a mediator of context-driven novelty and salience, in the psychotic state becomes a creator of aberrant novelty and salience [18].

The hallmarks of established psychosis are delusions (i.e. fixed, false beliefs) and hallucinations (i.e. aberrant perceptions); however, patients usually experience months of a 'prodromal' period that predates the expression of frank psychosis [19]. It is postulated that during the prodrome there is a context-independent or context-inappropriate firing of dopamine-containing neurons and subsequent dopamine release. This produces a perplexing sense of novelty in patients, as captured in these words: 'I developed a greater awareness of […] my senses were sharpened. I became fascinated by the little insignificant things around me' or 'sights and sounds possessed a keenness that he had never experience before' or 'noticed things I had never noticed before' [18]. Patients continue to accumulate several experiences of altered novelty and salience without a clear explanation for them. There is a gradually increasing sense of perplexity and confusion, and alterations in mood and behaviour until this crystallizes into a delusion – and then it all 'makes sense' to the patient [20,21].

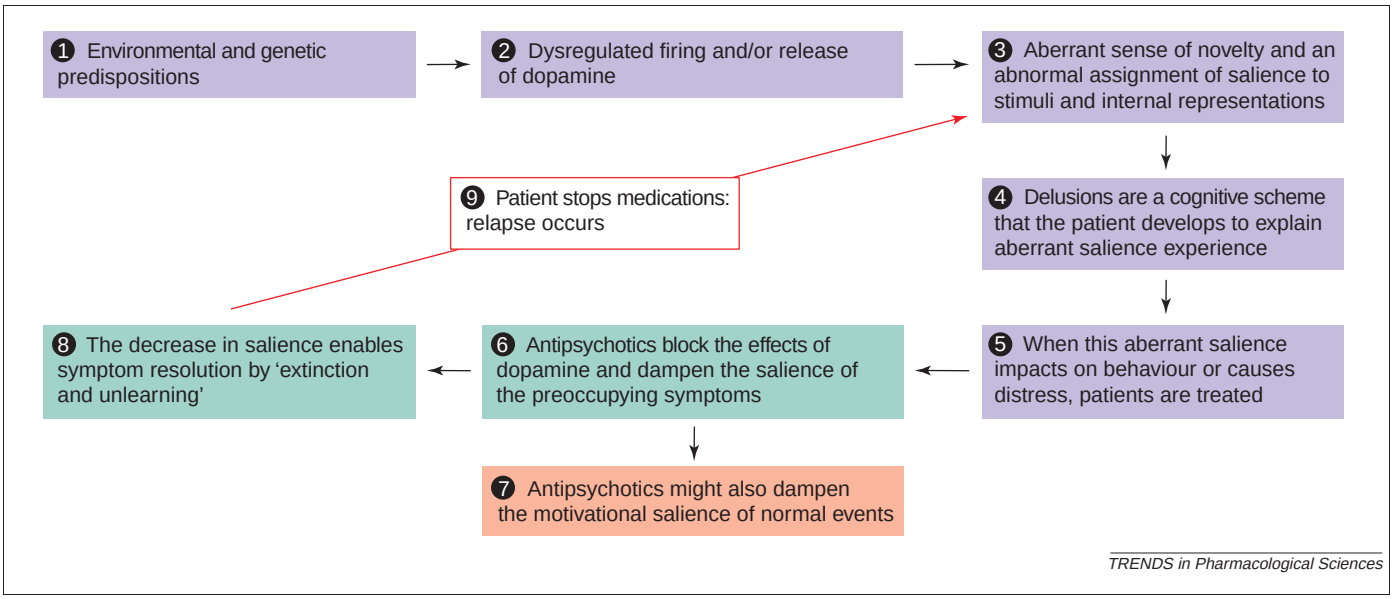

Figure 2. The hypothesis linking dopamine to psychosis and antipsychotics. The diagram shows a scheme for the chronological evolution of symptoms as a consequence of alterations in dopamine transmission and the effects of antipsychotics on these symptoms via blocking the effects of dopamine. A detailed explanation is provided in the main text. The number in each box provides the relative order of the event in the sequence. Boxes 1–5 show aetiology and pathophysiology of symptoms and how aberrant dopamine transmission, via aberrant salience, leads to psychosis; boxes 6–8 show the therapeutic effects and side-effects of antipsychotic treatment, as related to their actions on the dopamine system; and box 9 depicts the common consequence of stopping antipsychotics, and how the resulting relapse leads to a re-entry into the cycle of events.

A delusion in this framework represents a 'top-down' cognitive explanation that the individual imposes on these aberrant novelty and salience experiences in an effort to make sense of them (Figure 2). Because the individual constructs the delusions, the delusions are imbued with the psychodynamic themes and cultural context of the individual. This might explain why the same neurochemical dysregulation convinces a person living in an African village that he is the subject of black magic by an evil Shaman whereas a student living in Toronto is convinced that the Royal Canadian Mounted Police is using the internet to monitor her. Thus, dysregulation of the dopamine system provides the fuel for the creation of the delusion, whereas the patient's personal and cultural history gives it the precise form. This delusional framework then serves as a guiding cognitive scheme for further thoughts and actions. Hallucinations in this framework arise from a conceptually similar and a more direct process – the abnormal salience of the internal representations of percepts, language and memories [18]. Sooner or later these delusions or hallucinations impact on the patient's behaviour, and this is typically when patients are brought to care and antipsychotics are administered (Figure 2).

Antipsychotics attenuate motivational salience

In 1951 Laborit, the first user of antipsychotics, reported that patients given these drugs showed 'desintressement' in their surroundings [22] and in 1952 Delay, the first psychiatrist to systematically use antipsychotics, observed a 'état d'indifférence' [23]. This idea has been echoed during succeeding decades using different words: for example, antipsychotics decrease the 'efficacy of stimuli in controlling and directing behavior', antipsychotics 'decreased stimulus significance' or antipsychotics produced a state of 'psychic indifference' and 'emotional restriction' [18]. In keeping with this tradition and in light of the modern reward framework presented above, we propose that antipsychotics, by blocking dopamine transmission, dampen or attenuate motivational salience.

According to this hypothesis, antipsychotics do not directly erase delusions but provide a neurochemical milieu in which the effects of dopamine are blocked, new aberrant salience is less likely to form and established aberrant saliences are more likely to be diminished [24–26]. This is consistent with how patients experience early improvement: they do not immediately abandon the delusion or hallucination but instead report that it 'doesn't bother me as much anymore' [27,28]. In fact, for most patients this is as good a resolution as antipsychotics can provide. The symptoms are not eradicated but are pushed into a state of dormancy, or as patients often say 'are put on the back burner'. The resolution of symptoms is a dynamic, interactive process: antipsychotics block the effects of dopamine and thereby lessen the salience of the concerns, and the patient 'works through' their symptoms towards a psychological resolution (Figure 2) [26,29]. However, antipsychotics are blunt instruments: they block dopamine systems all over the brain and have no intrinsic mechanism to choose between the aberrant salience accorded to psychotic symptoms and that accorded to normal motivational drives. Antipsychotics attenuate salience across the board, which might explain why patients find antipsychotics 'dysphoric', and as a result non-compliance with these medications continues to be high (Figure 2) [18,30].

When antipsychotic treatment is stopped (or sometimes even in the presence of continuing treatment) dysregulation of the endogenous dopamine system is reinstated (Figure 2). The resurgence of an abnormally heightened dopaminergic state, whether by drugs, stress or endogenous dysregulation, reinvests the dormant symptoms with salience. The same ideas, schemes and percepts that

were previously part of the patient's symptoms become reinvested with salience once again and direct thought and behaviour. This explains why a patient whose paranoid delusions involved 'police from the 52nd division' in one episode is likely to become paranoid about police, and most likely from that very division, in the next episode.

Caveats and Implications

The explanation described here accounts for the 'positive' symptoms of schizophrenia, and not the negative or cognitive symptoms of this disorder. Although dopamine is central to this explanation, dopamine pathology itself might be secondary to a type of neurodevelopmental or glutamate-driven pathology [17]. As is well known, many patients do not respond to treatment despite complete D2 receptor blockade, which emphasizes the fact that dopamine transmission via D2 receptors does not fully explain psychosis. Patients with schizophrenia exhibit abnormalities in cognitive, interpersonal and psychosocial functioning that predate psychosis, and these antecedents also contribute to the development of psychosis [31]. Although we have treated antipsychotics as a single entity, it is well recognized that 'atypical' antipsychotics induce lesser motor and presumably lesser drug-induced negative symptoms than 'typical' antipsychotics. Thus, either by virtue of a differential action on the dopamine systems [32] or by virtue of an action on other neurotransmitter systems [33], the atypical antipsychotics might attenuate the aberrant salience of symptoms while still preserving some of the dopamine-mediated tone required for the motivational salience for life's normal goals.

Despite the above limitations the model has some interesting preclinical and clinical implications. Animal models based on reward and salience should be valid predictors of future antipsychotics. Even drugs that do not directly act on the dopamine system but alter reward and/or salience should have an impact on psychosis. Because the resolution of psychosis is an interaction between the drug-induced attenuation of salience and psychological extinction, one would predict that combining drugs with appropriate psychological therapies might enhance outcome. Indeed, early evidence supports this idea [34].

The model presented here is based on incomplete knowledge related to dopamine, schizophrenia and antipsychotics, and thus will need to evolve as knowledge of these factors increases. Rather than making a single pivotal prediction, the model provides a heuristic framework that can bridge biological data with clinical observations and phenomenological reports. Time will tell whether this is a useful enterprise or just an aberrantly salient idea harboured by the author.

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