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The neurobiology of relapse in schizophrenia

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ABSTRACT

Dopamine's proposed role in psychosis proved a starting point in our understanding of the neurobiology of relapse, fitting given the central role positive symptoms play. This link is reflected in early work examining neurotransmitter metabolite and drug (e.g. amphetamine, methylphenidate) challenge studies as a means of better understanding relapse and predictors. Since, lines of investigation have expanded (e.g. electrophysiological, immunological, hormonal, stress), an important step forward if relapse per se is the question. Arguably, perturbations in dopamine represent the final common pathway in psychosis but it is evident that, like schizophrenia, relapse is heterogeneous and multidimensional. In understanding the neurobiology of relapse, greater gains are likely to be made if these distinctions are acknowledged; for example, efforts to identify trait markers might better be served by distinguishing primary (i.e. idiopathic) and secondary (e.g. substance abuse, medication nonadherence) forms of relapse. Similarly, it has been suggested that relapse is 'neurotoxic', yet individuals do very well on clozapine after multiple relapses and the designation of treatment resistance. An alternative explanation holds that schizophrenia is characterized by different trajectories, at least to some extent biologically and/or structurally distinguishable from the outset, with differential patterns of response and relapse. Just as with schizophrenia, it seems naïve to conceptualize the neurobiology of relapse as a singular process. We propose that it is shaped by the form of illness and in place from the outset, modified by constitutional factors like resilience, as well as treatment, and confounded by secondary forms of relapse.

1. Introduction

Defining relapse remains a subject of debate (Falloon, 1984; Zubin et al., 1992; Lader, 1995), despite it representing the crux of maintenance treatment in schizophrenia. In individuals diagnosed with first-episode schizophrenia, relapse rates exceed 80% within five years (Robinson et al., 1999a), and relapse itself represents an important predictor of subsequent relapse, tripling costs in the year following (Ascher-Svanum et al., 2010). Further, multiple relapses have been associated with poorer long-term outcome (Lieberman et al., 1993, 1996; Andreasen et al., 2013).

This review first examines clinically related variables that shed light on the biology of relapse, focusing on antipsychotic nonadherence and substance abuse. Relapse itself has been subdivided into interventional and natural (Zubin et al., 1992), what might also be conceptualized as secondary and primary, each important for different reasons. Evidence suggests interventional or secondary relapse is more common, with antipsychotic nonadherence and substance abuse the most significant contributing factors to the "revolving door" patient (Haywood et al., 1995). In contrast, natural or primary relapse may be more intriguing as it represents relapse in the absence of such influences. Following a discussion of these clinically related variables, focus turns to the putative role of specific biological variables. In line with a recently proposed model that positions dopamine as the final common pathway in psychosis (Howes and Kapur, 2009), we posit the same holds true in terms of relapse. As can be seen in the review of evidence, this is where much of the focus has concentrated and, in fact, results have generally supported such a position. Although speculative, we shall propose a model that attempts to integrate the other evidence in order to move the field ahead.

At the outset, several caveats warrant comment. To permit the broadest overview, relapse is not specifically defined here. While a single definition is lacking (Gleeson et al., 2010), most align with a state of clinical worsening after improvement has been observed. Discussions here are couched in the context of worsening in *psychosis* (or positive symptoms); psychotic exacerbation has been used to define relapse elsewhere (Hirsch and Jolley, 1989) and, arguably, still

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represents that facet of the illness central to increased health care demands (e.g., hospital admissions) (Harvey et al., 2013). This said, the more enduring aspects of the illness, such as deficit and cognitive symptoms, do not necessarily factor into relapse per se but may play a greater role in functional recovery (Ventura et al., 2009). The review is not exhaustive but builds upon the last such review of this topic (Muller, 2004), focusing on clinical/biological variables that have been identified as important and garnered a body of evidence over the years.

2. Clinical

2.1. Antipsychotics

Current guidelines position antipsychotics as the mainstay of treatment in illnesses such as schizophrenia, arguing for early and continuous treatment (American Psychiatric Association, 2004; Canadian Psychiatric Association, 2005; National Institute for Health and Clinical Excellence, 2009).

2.1.1. Nonadherence

Maintenance antipsychotic treatment decreases relapses rates by over 50% at one year (Leucht et al., 2012). Furthermore, there is evidence that relapses may be 'toxic', associated with both increased time to recovery and diminished level of response (Lieberman et al., 1993, 1996; Andreasen et al., 2013). Exactly what pharmacological feature(s) of antipsychotic drugs account for their protection remains unclear, although the fact that efficacy seems inextricably linked to dopamine [DA] D_2 antagonism implicates this particular attribute as at least one important feature (Kapur and Remington, 2001).

2.1.2. Treatment response and schizophrenia subtypes

A closer examination of antipsychotic response, however, argues against ongoing D_2 antagonism as the singular requirement. Rates of relapse have been reported to be lower with second generation antipsychotics, although most comparisons have been with haloperidol and potential influences such as side effects and nonadherence are not adequately addressed (Dossenbach et al., 2005; Kishimoto et al., 2013). More compelling is the finding that a subgroup of individuals, even early in treatment, show poor symptom control despite treatment with D_2 blocking agents (Robinson et al., 1999b; Agid et al., 2011; Emsley et al., 2013). Clozapine is uniquely different in this 'treatment resistant' population (Kane et al., 1988; Meltzer et al., 1989; Lieberman et al., 1994; Agid et al., 2011), suggesting that for at least a subgroup of individuals D_2 blockade in and of itself is insufficient for either symptom control or maintenance of response. Third, there is a subgroup of individuals who also fail to respond adequately to clozapine, the so called "ultraresistant" subpopulation (Mouaffak et al., 2006). We neither understand what aspects of clozapine account for its efficacy in treatment resistant schizophrenia, or the underlying pathophysiology that mediates ultraresistance. Taken together, these findings indicate that psychosis must be viewed as multidimensional, mediated by distinctly different mechanisms impacting response and risk of relapse.

More recently it has been established that for the subpopulation responsive to treatment with non-clozapine D_2 blocking agents, high and sustained D_2 blockade may not be necessary to maintain antipsychotic efficacy (Remington and Kapur, 2010). This appears to hold true both at a molecular level, given the established efficacy of antipsychotic compounds with transient receptor binding (Seeman and Tallerico, 1998; Kapur and Seeman, 2001), as well as at the systemic level where intermittent, but regular, antipsychotic treatment has been shown to be as effective as continuous treatment (Remington et al., 2005, 2011).

We raise this topic to highlight the more current conceptualization of schizophrenia as a heterogeneous group of disorders (Molina and Blanco, 2013). Just as there may be different groups based on response and treatment needs, it is possible that relapse rates vary between groups that may, as of yet, not be fully articulated.

2.1.3. Chronic antipsychotic exposure: tolerance, supersensitivity psychosis, and morphology

Various lines of investigation speak to the issue of risk and magnitude of relapse fluctuating over the illness' course. For example, there is preclinical evidence of physiological adaptation in response to continued antipsychotic exposure (Kurachi et al., 1995; Vernon et al., 2011), as well as behavioral evidence that suggests antipsychotic tolerance can occur (Samaha et al., 2008); clinically, there are reports of attenuated antipsychotic response and the need for increased doses in at least a subpopulation of individuals over time (Margolese et al., 2002). Somewhat related is the notion of supersensitivity psychosis (SSP), thought to occur in the context of abrupt antipsychotic discontinuation following ongoing treatment (Chouinard and Jones, 1980). It has been argued that biological changes in response to ongoing antipsychotic exposure, in particular the involvement of DA, can produce sensitization that leaves individuals more prone to psychotic exacerbation/relapse in the face of abrupt antipsychotic discontinuation (Muller and Seeman, 1978; Kostrzewa et al., 2008; Seeman, 2011). However, clinical evidence is conflicting on this point (Moncrieff, 2006). A comparatively large study examining abrupt vs. gradual antipsychotic discontinuation did indicate higher relapse rates in those exposed to abrupt, compared to gradual, antipsychotic discontinuation (Viguera et al., 1997). Using upregulated dopamine receptors in the face of ongoing antipsychotic exposure as the common pathway, a link has also been made between SSP and antipsychotic-induced tardive dyskinesia (TD) (Chouinard and Chouinard, 2008; Fallon and Dursun, 2011).

At present, there is insufficient evidence to confirm that either tolerance or SSP exist as true clinical entities. The strongest support for tolerance relates to preclinical work, and the clinical data, as well as being limited, do not adequately control for the confound of higher dosing frequently used as a strategy in treatment resistance (Sernyak and Rosenheck, 2007). In terms of SSP, changes at the level of dopamine receptors with ongoing antipsychotic exposure have certainly been documented, including increased number of receptors as well as increased receptors in the upregulated state (Seeman, 2011). However, evidence linking such changes to SSP is conflicting at best, and struggles with distinguishing SSP from symptom exacerbation in the absence of treatment. For example, in one such study reporting higher rates of "survival" with gradual versus abrupt antipsychotic discontinuation (Viguera et al., 1997), a closer examination of the data indicates these differences were not evident within the first weeks, arguing against SSP. From the standpoint of TD, the evidence is even less convincing and has fallen short in distinguishing 'withdrawal dyskinesias' (van Harten and Tenback, 2011), which would be more in line with SSP, from TD per se.

In addition to biochemical alterations, there is a growing number of studies documenting changes in CNS morphology across time. The notion that schizophrenia is neuroprogressive has recently been challenged (Zipursky et al., 2012), and less clear is whether these changes are illness or medication-related (Navari and Dazzan, 2009; Moncrieff and Leo, 2010; Olabi et al., 2011) and the precise association(s) between structural changes and symptoms (Andreasen et al., 2011, 2013). For example, a recent study suggests that extended periods of relapse are associated with significant decreases in both global (e.g., total cerebral volume) and regional (e.g., frontal) brain measures, although it does not shed light on the effects of these changes clinically (Andreasen et al., 2013).

Work examining patterns of response suggests outcome is heterogeneous, reflecting different trajectories (Levine and Rabinowitz, 2010; Levine et al., 2011; Marques et al., 2011) that may, at least to some extent, be predetermined. This aligns with first episode studies indicating morphological differences in the earliest stages of the illness (Andreasen