Letter to Editor

The 'Holy Grail' and 'Poisoned Chalice' Effects of Antipsychotics on Oxidative Stress in Schizophrenia: Can 'Hormesis' Explain this Paradox?

Sir,

Oxidative stress-mediated pathogenesis has been proposed as an overarching model to understand schizophrenia.[1] This letter summarizes the 'holy grail' as well as 'poisoned chalice' effects of antipsychotics on oxidative stress in schizophrenia and hypothesizes the novel utility of 'hormesis' in understanding this curious paradox.

Antipsychotics have been demonstrated to influence oxidative stress in numerous studies ranging from animal models to patient population.[1] While this impact is unequivocal, the differential nature of the influence is puzzling. For instance, it has been shown that short-term antipsychotic treatment can reduce the oxidative stress in schizophrenia.[2] This supports the beneficial 'holy grail' effects of antipsychotics on oxidative stress. On the contrary, antipsychotics have also been shown to increase the 'oxidative stress' in schizophrenia. For instance, haloperidol and clozapine have been shown to induce oxidative stress.[3] Also, extrapyramidal side effects caused by antipsychotics are associated with increased oxidative stress.[4] Moreover, obesity and related metabolic derangements induced by newer antipsychotics are associated with excessive oxidative stress.[5] Intriguingly, the efficacy of antipsychotics has been shown to correlate with the propensity for both extrapyramidal[6] and metabolic[7] side effects. Thus, the long-term 'poisoned chalice' impact of these side effects might frequently co-occur with clinical improvement in psychosis.

I hypothesize that this curious paradox can be understood by the application of the principles of hormesis (defined as an adaptive response characterized by biphasic dose responses of generally similar quantitative features with respect to amplitude and range of the stimulatory response that are either directly induced or the result of compensatory biological processes following an initial disruption in homeostasis[8]). It is possible that the lower doses of oxidative stress induced by antipsychotics in various pathways (i.e., extrapyramidal as well as metabolic) might result in compensatory adaptive, neutralizing responses by biological systems that eventually ameliorate the psychosis. However, if the oxidative stress through these pathways increases beyond desirable limits, the side effects predominate. Rigorous application of this paradigm of hormesis in animal models as well as clinical research promises the potential to ascertain the minimum effective dose of antipsychotics, resulting in optimal clinical benefit with reduced burden of side effects.

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