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Review article

Is elevated norepinephrine an etiological factor in some cases of schizophrenia?

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ABSTRACT

A number of hypotheses have been put forth regarding the etiology of schizophrenia, including the dopamine hypothesis, NMDA receptor hypofunction hypothesis, and others. A lesser known theory is that elevated noradrenergic signaling plays a causative role in the disease. This paper briefly re-examines the merits of this hypothesis, including as it relates to some recently published studies. Several lines of evidence are investigated, including: endogenous level studies of norepinephrine (NE); modulation of the disease by noradrenergic drugs; association of the disease with bipolar disorder and hypertension, since these latter two conditions may involve elevated NE transmission; and effects of psychological stress on the disease, since stress can produce elevated release of NE. For many of these lines of evidence, their relationship with prepulse inhibition of startle is examined. A number of these studies support the hypothesis, and several suggest that elevated NE signaling plays a particularly prominent role in the paranoid subtype of schizophrenia. If the hypothesis is correct for some persons, conventional pharmaceutical treatment options, such as use of atypical antipsychotics (which may themselves modulate noradrenergic signaling), may be improved if selective NE transmission modulating agents are added to or even substituted for these conventional drugs.

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1. Introduction

Identification of the precise etiological factors responsible for schizophrenia remains a widely debated topic. Dating back a number of decades, a variety of biological theories have been put forth to explain this severe neuropsychiatric disorder. These theories include the widely known and intensely debated "dopamine hypothesis of schizophrenia", where both elevated and decreased dopamine transmission have been posited (Carlsson, 1977; Grace, 1991; Carlsson et al., 1997; Carlsson and Carlsson, 2006). A more recent, widely studied theory suggests that hypofunction of the glutamatergic NMDA receptor is a prominent causative factor in the disease

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(Jentsch and Roth, 1999; Olney et al., 1999; Coyle et al., 2003). Yet another theory, which may also relate to neurochemical causes of schizophrenia, is that prenatal exposure to pronounced maternal stress can have deleterious effects on neurodevelopment, predisposing offspring to the disease later in life (Brixey et al., 1993; Kinney et al., 2010).

There is a large body of data supporting these hypotheses (and others), where they may interact with one another or with other neurotransmitter systems in particular cases of schizophrenia (Carlsson, 1977; Carlsson and Carlsson, 1989; Carlsson et al., 1997). The dopamine hypothesis may be valid given the widespread use and, to some degree, success of treatment with antipsychotic drugs that partly achieve their effects by blocking dopaminergic transmission (Attard and Taylor, 2012). However, successful treatment by a particular biological mechanism of action does not necessarily indicate etiology for that mechanism. It is possible that other etiological factors exist, at least in a subset of cases, where the identification of potential additional factors may result in improvement in treatment, through use of pharmaceuticals and other methods.

This paper puts forth the hypothesis that elevated noradrenergic signaling is an etiological factor in some cases of schizophrenia. Earlier studies have also suggested that elevated NE signaling plays a pathophysiological role in schizophrenia (Yamamoto et al., 1994; Yamamoto and Hornykiewicz, 2004; Lechin and van der Dijs, 2005). The current hypothesis suggests that an elevated synaptic concentration of NE, present in particular brain circuits involved in schizophrenia, is an etiological factor in the disease. The hypothesis does not contradict the theories mentioned above, such as the dopamine hypothesis or the NMDA receptor hypofunction hypothesis, but rather suggests that elevated NE is an additional factor to consider in understanding and treating the disease, at least in a subset of persons (van Kammen and Kelley, 1991). A more general variant of the elevated NE hypothesis is that elevated synaptic transmission of NE, whether mediated by an increased synaptic concentration of NE or by increased sensitivity of NE′s postsynaptic receptor populations, is an etiological factor in some cases of schizophrenia.

If elevated NE is an etiological factor in some cases of schizophrenia, when and where in the brain does pathologically increased signaling by this molecule take place? This paper is suggesting that such elevation is largely genetic (Hui et al., 2013) and present throughout the individual′s life, although psychological stress may exacerbate this effect (Myin-Germeys et al., 2002). While the precise circuitry underlying the putative effect of elevated NE on schizophrenia remains to be identified, one possibility is that it involves dysregulated signaling in prefrontal cortex (Robbins, 2005; Arnsten, 2011). Executive functional alterations, such as impaired working memory, have been shown to occur in schizophrenia (Barch and Ceaser, 2012). A number of studies in macaque monkeys suggest that pharmacological modulation of alpha1 and alpha2 adrenergic receptors can alter working memory capability (Arnsten and Cai, 1993; Arnsten and Jentsch, 1997; Arnsten et al., 1988). The noradrenergic neurons of the locus coeruleus have been linked with cognition, including through prefrontal mechanisms (Aston-Jones et al., 2000; Chamberlain and Robbins, 2013). One possibility is that impaired cognitive function in schizophrenia is partly mediated by altered NE release in prefrontal cortex, acting at a molecular level through the protein kinase C signaling pathway (Arnsten, 2004).

To assess the hypothesis, several lines of evidence are briefly presented below: endogenous level studies of NE and its metabolite MHPG; modulation of the disease by drugs that increase or decrease noradrenergic signaling; association of the disease with bipolar disorder and hypertension, since these latter two conditions may involve elevated noradrenergic transmission (Schildkraut, 1965; Solt et al., 1990; Masuo et al., 2005); and effects of psychological stress on the disease, since stress can produce elevated release of NE (Hajos-Korcsok et al., 2003). For many of these lines of evidence, their relationship with prepulse inhibition of startle (PPI) is also examined, since this is a widely used assay in both animal models and human studies of schizophrenia. The Pubmed database was searched as recently as May 5, 2013. Keyword searches included the following terms (typically combined with "schizophrenia" and "prepulse inhibition"): (1) plasma/cerebrospinal fluid + concentration, (2) desipramine/"tricyclic antidepressant(s)"/clonidine/guanfacine/yohimbine/prazosin/"beta blocker(s)"/propranolol, (3) pheochromocytoma, (4) "bipolar disorder" + proband(s), (5) hypertension + comorbidity, and (6) "psychological stress" + comorbidity. This is certainly not meant to be an exhaustive review of the literature on these topics, but rather to present some representative studies, many of which support the hypothesis.

2. Norepinephrine and metabolite level studies

Blood and cerebrospinal fluid (CSF) studies of persons with schizophrenia (PWS) suggest that NE or its metabolites may be elevated in the disease. In PWS compared with healthy controls, where the PWS were unmedicated, serum levels of NE and dopamine ranged from normal to more than three times that level for those with the disease (Bondy et al., 1984). However, a comparison of PWS with healthy controls found no difference in the CSF level of the NE metabolite, MHPG (Gattaz et al., 1982). Plasma MHPG levels, measured before and during 6 weeks of treatment with the antipsychotic drug, haloperidol, showed a decrease in MHPG during treatment in good responders to this drug (Chang et al., 1990).

A comparison of PWS and healthy controls found a higher level of plasma NE in the disease, which correlated with global psychopathology, positive symptomatology, and paranoia (Dajas et al., 1983). Other investigators found higher levels of plasma MHPG during high psychosis phases of the disease in comparison with times of lower psychosis, and also found higher MHPG in persons with paranoid schizophrenia relative to healthy controls (Ko et al., 1988). Elevated levels of plasma MHPG declined with neuroleptic treatment in acute schizophrenia, and this decrease correlated with a reduction in positive symptomatology (Kaneko et al., 1992). CSF NE levels were elevated in PWS relative to non-psychiatric controls, and PWS who had high NE levels scored higher in a measure of positive symptomatology (Kemali et al., 1990). A comparison of PWS and healthy matched controls found plasma and CSF NE were significantly higher in the disease, particularly in paranoid schizophrenia (Kemali et al., 1982). In drug-free PWS, CSF NE and MHPG levels correlated both with the severity of negative symptoms and with psychosis ratings (van Kammen et al., 1990).

In summary, many of the NE level studies described above found elevations in NE or its metabolite MHPG in schizophrenia, particularly during states of paranoia or positive symptomatology. However, one possible confounding factor is that the disease may produce psychological stress that feeds back on these measures in PWS.

3. Desipramine and other tricyclic antidepressant studies

NE boosting antidepressants such as desipramine may alter schizophrenia-related symptomatology, including PPI measures. PWS who received 4 weeks of adjunctive treatment with the NE boosting tricyclic antidepressants, amitriptyline or desipramine, exhibited greater hallucinatory behavior and thought disturbance than patients receiving placebo (Kramer et al., 1989). In contrast, adjunctive desipramine treatment had beneficial effects on both