Abnormalities of Ubiquitin and Ubiquitin-Like Systems in Schizophrenia

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INTRODUCTION

Diverse post-translational modifications, are thought to underlie protein expression and trafficking abnormalities seen in schizophrenia. Ubiquitin is a post translational modifier that is activated by E1s, conjugated by E2s and ligated by E3s to protein substrates. Ubiquitin--like (UBL) modifiers such as SUMO, Ufm and NEDD8 also undergo activation, conjugation and ligation by specific E1, E2 and E3s, however, their substrates are not targeted for degradation but participate in protein stabilization and translational modification. At the mRNA level, several groups have reported abnormalities of the ubiquitin and ubiquitin-like (UBL) systems in different areas of the brain in schizophrenia. These findings, in addition to the differences in the expression level of specific proteins found in schizophrenia, led us to hypothesize that some protein expression abnormalities seen in this illness are a consequence of abnormal processing by the ubiquitin-proteasome and UBL systems.

METHODS

We performed Western blot protein expression analysis in postmortem human brain tissue from patients diagnosed with schizophrenia and a comparison group. We focused our studies in the superior temporal gyrus. Subjects were divided into 13 pairs according to sex, age, pH and postmortem interval.

RESULTS

<table>
<thead>
<tr>
<th>Protein</th>
<th>Function</th>
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<tbody>
<tr>
<td>Ubiquitin</td>
<td>Ub or UBL proteins</td>
</tr>
<tr>
<td>Ub or UBL</td>
<td>E1, Ub protein activating enzyme</td>
</tr>
<tr>
<td>Ub or UBL</td>
<td>E2, Ub protein conjugating enzyme</td>
</tr>
<tr>
<td>Ub or UBL</td>
<td>E3, Ub and/or UBL protein ligating enzyme</td>
</tr>
</tbody>
</table>

Ubiquitination is an enzymatic post translational modification that results in protein degradation, protein-protein interaction, protein trafficking or protein transcription regulation.

SUMOylation changes the molecular interactions of the sumoylated proteins, resulting in changes in localization, altered activity and stability of the modified protein.

CONCLUSIONS

Taken together, our studies show significant disruption of the ubiquitin proteasome and ubiquitin-like systems, suggesting that defects found in schizophrenia are a result of the disruption of canonical mechanisms. The abnormal protein expression and localization previously described in schizophrenia may have their roots in post-translational modifications rather than individual pathway abnormalities. A thorough evaluation of E3s and their specific substrates is needed to determine the extent of the influence of ubiquitin in this illness.

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