[S1-1] [4/17/2003(Thur) 14:00-14:30/Grand Hall]

Therapeutic Intervention of Aggregate Formation in Huntington's Disease: A Potential Role of Tissue Transglutaminase (tTG)

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The cause of Huntington's disease (HD) is a pathological expansion of the polyglutamine domain within the N-terminal region of huntingtin. Neuronal aggregates composed of mutant huntingtin within certain neuronal populations are a characteristic hallmark of HD. Because tissue transglutaminase (tTG) cross-links proteins into aggregates and polypeptide-bound glutamines are primary determining factors for tTG-catalyzed reactions, it has been hypothesized that tTG may contribute to the formation of aggregates. Therefore, it is of fundamental importance to establish whether tTG plays a role in the formation of aggregates.

The preliminary study demonstrated that tTG expression and transglutaminase activity are elevated in specific brain areas affected in HD in a grade-dependent manner. In the striatum, transglutaminase activity was significantly higher in grade 2 and 3 HD cases as compared with controls. In the superior frontal cortex, transglutaminase activity was significantly higher in all HD cases as compared with controls. These data clearly indicate that tTG is elevated in HD brain and may play a role in the disease process.

To determine a possible role of increased tissue transglutaminase in the brain of HD patients in terms of the aggregate formation of mutant huntingtin, the frequency of aggregates in the presence or absence of tissue transglutaminase was examined. These data demonstrated that tTG did not coprecipitate with mutant huntingtin. Furthermore, tTG was totally excluded from the aggregates, and significantly increasing tTG expression had no effect on the number of aggregates or their intracellular localization. These findings clearly demonstrate that tTG is not required for aggregate formation and does not facilitate the process of aggregate formation.

It is clear that tTG levels and activity increase in HD brain. However, the exact role(s) of

tTG in the etiology of HD remain unclear. At present it seems unlikely that tTG plays a role in the aggregate formation of mutant huntingtin in HD brain. Accordingly, to develop agents that modulate aggregate formation of mutant huntingtin, chemicals that facilitate or inhibit beta-sheet formation, which is considered as a responsible mechanism for aggregate formation of mutant huntingtin, should be examined.