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UNDERSTANDING BRAIN DYSFUNCTIONING IN TRISOMY 21 THROUGH ALTERATIONS OF MONAMINE PATHWAYS IN TRANSGENIC MICE FOR CHROMOSOME 21 GENES

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Trisomy 21 (T21/ Down syndrome: DS) is characterized by reduced cognitive capacities, behavioural alterations and early ageing with a high risk to develop dementia earlier than in the general population. In order to understand neurobiological mechanisms which contribute to this large pathophysiology, murine models have been raised overexpressing one, two or several chromosome 21 genes. Some of these models have already provided a lot of information leading even to some therapeutic approaches. Although alterations in some monoamines neurotransmitters have been shown in various brain areas or in serum/plasma from individuals with trisomy 21, very few information have been obtained in the animal models. We will present recent data obtained by HPLC-EC, showing how overexpression of APP, CBS, Dyrk1A genes induce different modifications in the serotoninergic, dopaminergic and adrenergic pathways in the four brain areas studied (hypothalamus, thalamus, hippocampus and striatum). Indeed DYRK1A or/and APP overexpression induce mainly alterations in the serotoninergic and the noradrenergic pathways while CBS overexpression induces mainly modifications in the dopaminergic pathway. Moreover we will show that there is not only a genotype effect depending on the brain areas studied but also a dramatic gender effect. As these genes are involved in neurogenesis, early neurodegeneration and some physiological aspects present in persons with T21, the clear evidence of alterations in monoamines neurotransmitters related to overexpression of one of these genes might facilitate the development of novel disease-modifying strategies.

Biography

J London (Emeritus Professor at University Paris-Diderot) has completed her PhD in the Pasteur Institute under the direction of Professor Jacques Monod (Nobel Prize winner) and Professor Michel Goldberg in the field of Protein Folding and Bacteriology (3 papers). She moved to immunology in Necker's hospital under the direction of Professor Jean François Bach and then was a visiting scientist at NIH (9 papers). After coming back to Paris she settled a laboratory in Molecular Biology at the Blood Centre and cloned glycophorins A and B (13 papers). She then moved again to Necker's Hospital where she joined the group working on Trisomy 21 and settled a laboratory to obtain transgenic mice for the *SOD1* gene and cloned the murine CBS. She published some 35 papers on different aspects of Trisomy 21 using transgenic mice for some chromosome 21 genes: *APP CBS, DYRK1A and SOD1*.

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