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Aging rather than aneuploidy affects monoamine neurotransmitters in brain regions of Down syndrome mouse models

Alain D. Dekker [a,b,c], Yannick Vermeiren [a,b], Christelle Albac [c], Eva Lana-Elola [d], Sheona Watson-Scales [d], Dorota Gibbins [d], Tony Aerts [b], Debby Van Dam [a,b], Elizabeth M.C. Fisher [e], Victor L.J. Tybulewicz [d,f], Marie-Claude Potier [c], Peter P. De Deyn [a,b,*]

[a] Department of Neurology and Alzheimer Research Center, University of Groningen, University Medical Center Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands
[b] Laboratory of Neurochemistry and Behaviour, Institute Born-Bunge, University of Antwerp, Universiteitsplein 1, 2610 Wilrijk, Antwerp, Belgium
[c] Sorbonne Universités, UPMC Université Paris 06, INSERM, CNRS (U75, U1127, U7225) and Institut du Cerveau et de la Moelle Epinière (ICM), Boulevard de l'Hôpital, 75013 Paris, France
[d] The Francis Crick Institute, Midland Road, London NW1 1AT, United Kingdom
[e] Department of Neurodegenerative Disease, Institute of Neurology, University College London, Queen Square, London WC1N 3BG, United Kingdom
[f] Department of Medicine, Imperial College London, Du Cane Road, London W12 0NN, United Kingdom

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ABSTRACT

Altered concentrations of monoamine neurotransmitters and metabolites have been repeatedly found in people with Down syndrome (DS, trisomy 21). Because of the limited availability of human post-mortem tissue, DS mouse models are of great interest to study these changes and the underlying neurobiological mechanisms. Although previous studies have shown the potential of Ts65Dn mice – the most widely used mouse model of DS – to model noradrenergic changes, a comprehensive monoaminergic characterization in multiple brain regions has not been performed so far. Here, we used RP-HPLC with electrochemical detection to quantify (nor)adrenergic (NA, adrenaline and MHPG), dopaminergic (DA, HVA and DOPAC), and serotonergic compounds (tryptophan, 5-HT and 5-HIAA) in ten regionally dissected brain regions of Ts65Dn mice, as well as in Dp1Tyb mice – a novel DS mouse model. Comparing young adult aneuploid mice (2.5–5.5 months) with their euploid WT littermates did not reveal generalized monoaminergic dysregulation, indicating that the genetic overload in these mice barely affected the absolute concentrations at this age. Moreover, we studied the effect of aging in Ts65Dn mice: comparing aged animals (12–13 months) with their younger counterparts revealed a large number of significant changes. In general, the (nor)adrenergic system appeared to be reduced, while serotonergic compounds were increased with aging. Dopaminergic alterations were less consistent. These overall patterns appeared to be relatively similar for Ts65Dn and WT mice, though more observed changes were regarded significant for WT mice. Similar human post-mortem studies are necessary to validate the monoaminergic construct validity of the Ts65Dn and Dp1Typ mouse models.

1. Introduction

Down syndrome (DS), caused by an additional copy of chromosome 21 (HSA21), is the most common intellectual disability with a genetic origin affecting nearly six million people worldwide (Ballard et al., 2016). DS is generally characterized by behavioral alterations (Dekker et al., 2015b) and reduced cognitive capacities, in particular impaired verbal short-term memory, explicit long-term memory, morphosyntax and an average IQ of 45 (Lott and Dierssen, 2010; Vicari et al., 2004). Moreover, people with DS are at an extremely high risk to develop dementia: 68–80% develop Alzheimer's disease (AD) by the age of 65 years (Wiseman et al., 2015), compared to 11% in the general (non-intellectually disabled) population of 65 years and older (Alzheimer's Assocation, 2016).

Elucidating the underlying neurobiological mechanisms affecting behavior and cognition in DS would greatly contribute to understanding the pathophysiology, as well as facilitate development of novel disease-modifying strategies. Of particular interest in this population are monoamine neurotransmitters: noradrenaline (NA), adrenaline, dopamine (DA) and serotonin (5-HT) and their metabolites (summarized in Fig. 1). A series of neurochemical studies has shown significant alterations in one or more monoamines in various brain regions (Godridge et al., 1987; Reynolds and Godridge, 1985; Risser et al., 1997; Whittle et al., 2007; Yates et al., 1981), cerebrospinal fluid (CSF) (Kay et al.,

* Corresponding author at: Department of Neurology and Alzheimer Research Center, University Medical Center Groningen (UMCG), Hanzeplein 1, 9713 GZ Groningen, The Netherlands.
E-mail address: p.p.de.deyn@umcg.nl (P.P. De Deyn).
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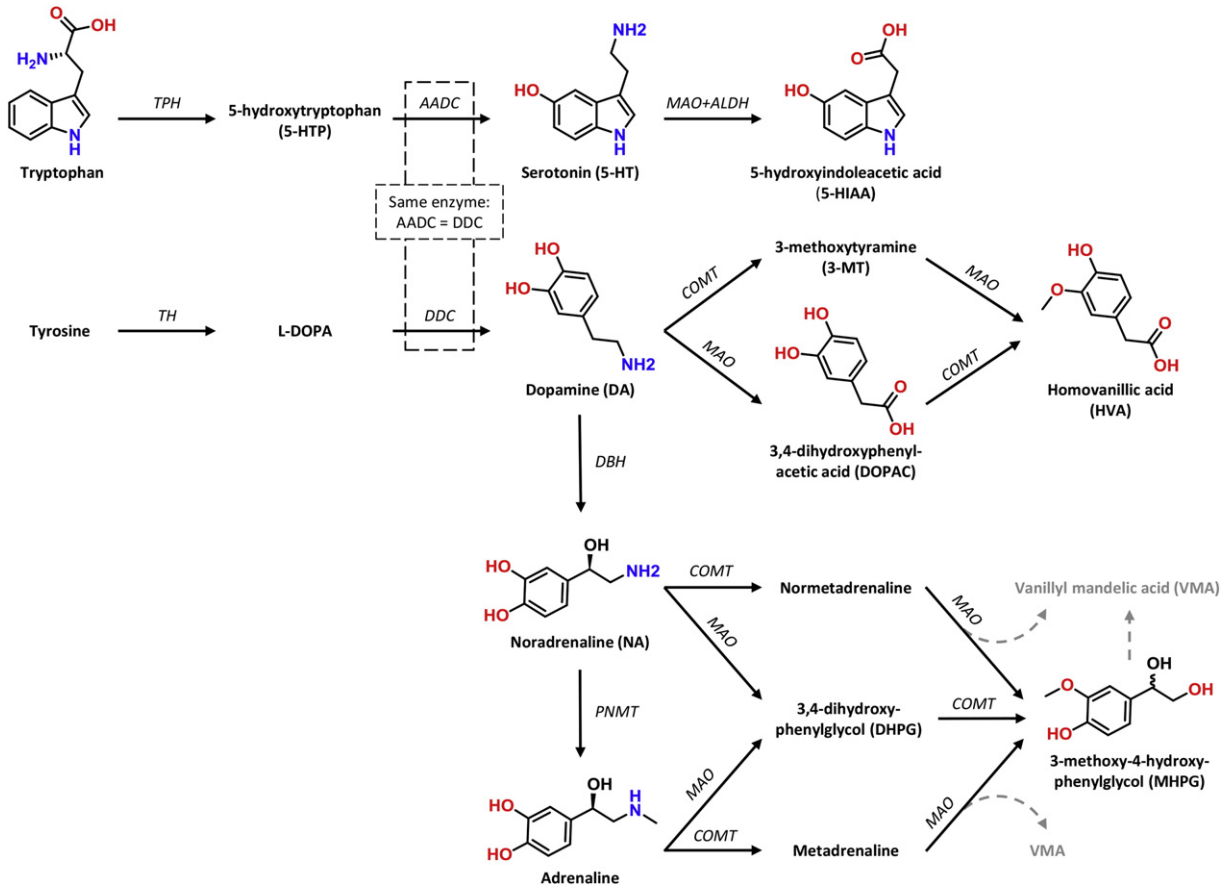

Fig. 1. Schematic biosynthesis routes of monoamine neurotransmitters and their main metabolites. 5-HT is derived from the amino acid tryptophan, whereas DA (and thus NA and adrenaline) are derived from the amino acid tyrosine. The molecular structures are provided for the compounds that are quantified in this study through reversed-phase high-performance liquid chromatography (RP-HPLC) analyses. Abbreviations: AADC, aromatic amino acid decarboxylase; ALDH, aldehyde dehydrogenase; COMT, catechol-*O*-methyltransferase; DBH, dopamine β-hydroxylase; DDC, DOPA decarboxylase; L-DOPA, L-3,4-dihydroxyphenylalanine (levodopa); MAO, monoamine oxidase; PNMT, phenylethanolamine *N*-methyltransferase; TH, tyrosine hydroxylase; TPH, tryptophan hydroxylase.

1987; Schapiro et al., 1987) and serum/plasma (Coppus et al., 2007; Dekker et al., 2015a) of DS individuals as compared to non-DS controls.

Although monoaminergic alterations in CSF and serum/plasma likely reflect changes in the brain, direct analysis of brain tissue is warranted to understand central neurotransmission alterations. Indeed, we previously studied monoamines and metabolites in post-mortem brain regions of behaviorally characterized patients in the general population with (early-onset) AD (Vermeiren et al., 2014a, 2014b, 2015, 2016), frontotemporal dementia (Vermeiren et al., 2016) and dementia with Lewy bodies (Vermeiren et al., 2015). Surprisingly, despite the high risk for dementia in DS, only a few post-mortem studies dating back to the 1980s have investigated monoamines in DS. Unfortunately, post-mortem brain samples from clinically and pathologically well-documented DS individuals have been rarely included in biobanks around the world, severely limiting the possibilities for such research.

Thus, valid mouse models of DS are of great interest to study the potential monoaminergic alterations related to trisomy 21. In addition to the differences between DS and non-DS controls, monoaminergic changes have been reported in DS mouse models, in particular noradrenergic alterations (Dierssen et al., 1997; Lockrow et al., 2011; Salehi et al., 2009). These findings have been primarily observed in Ts(17^{16})65Dn mice (Ts65Dn in short), the most widely used and best characterized DS model. HSA21 contains 233 protein-encoding genes: among those genes with a homologue in mice, the majority (~58%) is found on a large segment of mouse chromosome 16 (Mmu16), and to a lesser extent on shorter segments of Mmu10 and Mmu17 (Lana-Elola et al., 2016). Ts65Dn mice carry an additional mini-chromosome that is formed by the translocation of a duplicated segment of Mmu16 to a small part of Mmu17 (Davisson et al., 1990), making them trisomic for approximately 50% of the genes homologous to HSA21, but also for 60 non-homologous genes on Mmu17 (Duchon et al., 2011).

Of profound interest is the significant loss of neurons in the locus coeruleus (LC), the key production site of NA in the pons, in Ts65Dn mice of 12 months of age but not in Ts65Dn mice at 4 months of age as compared to age-matched euploid wildtype (WT_{Ts65Dn}) littermates (Fortress et al., 2015; Lockrow et al., 2011). Neurodegeneration with progressive aging was further demonstrated by the significant loss of axonal processes and shrinkage of the noradrenergic neurons between 4 and 12 months in Ts65Dn, but not in WT_{Ts65Dn} (Lockrow et al., 2011). Similarly, Salehi and colleagues found a reduced number of LC neurons in Ts65Dn mice at 6 months and 18 months of age, but not in those of 3 months of age, as compared to age-matched WT_{Ts65Dn} mice. Moreover, NA levels in the hippocampus were significantly lower in Ts65Dn than in WT_{Ts65Dn} at 18 months. Despite the pronounced LC degeneration, impaired NA-modulated contextual learning could be rescued in these mice after treatment with the noradrenergic prodrug L-threo-3,4-dihydroxyphenylserine (L-DOPS) or the β1-adrenergic receptor partial agonist xamoterol (Salehi et al., 2009). Restoration of impaired noradrenergic neurotransmission may thus serve as potential disease-modifying therapy in DS (Phillips et al., 2016).

Despite a large number of studies using Ts65Dn mice, a comprehensive monoaminergic characterization of the brain of this mouse model has not been conducted so far. Therefore, this study aimed to investigate the potential of DS mouse models (construct validity) in modelling the monoaminergic changes in DS by (1) establishing the monoaminergic profile in ten regionally dissected brain regions of aneuploid Ts65Dn