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Cardiac sympathetic activity in 22q11.2 deletion syndrome

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ABSTRACT

Aim: 22q11.2 deletion syndrome (22q11.2DS) affects catechol-*O*-methyl-transferase (COMT), which involves the degradation of norepinephrine (NE). Clinically, adults with 22q11.2DS are at increased risk for sudden unexpected death. Although the causes are likely multifactorial, increased cardiac sympathetic activity with subsequent fatal arrhythmia, due to increased levels of NE, should be considered as a possible mechanism predisposing to this premature death. The purpose of this study was to determine whether cardiac sympathetic activity is increased in 22q11.2DS, both at baseline and following an acute NE depletion with alpha-methyl-*para*-tyrosine (AMPT).
Methods: Five adults with 22q11.2DS and five age- and sex-matched healthy controls underwent 2 sessions with either AMPT or placebo administration before ^{123}I-*m*IBG scintigraphy. Heart-to-mediastinum ratios (H/M) were determined from the images 15 min (early) and 4 h (late) after administration of ^{123}I-*m*IBG and the washout (WO) was calculated as an indicator of adrenergic drive.
Results: At baseline there were no significant differences in both early and late H/M between 22q11.2DS and controls. However, there was a significant difference in WO between 22q11.2DS and controls (-4.92 ± 2.8 and -10.44 ± 7.2, respectively; $p = 0.027$), but a "negative WO" does not support an increased sympathetic drive. In addition there was a trend towards a higher late H/M after AMPT administration compared to baseline which was more pronounced in 22q11.2DS.
Conclusion: This study for the first time suggests normal cardiac sympathetic activity in adults with 22q11.2DS assessed by ^{123}I-*m*IBG scintigraphy. Although there is a small difference in adrenergic drive compared to healthy subjects, this most likely does not explain the increased unexpected death rate in the 22q11.2 DS population.

1. Introduction

22q11.2 deletion syndrome (22q11.2DS) is caused by a microdeletion on the long arm of chromosome 22 and affects approximately 1:2000 live births [1,2]. This genetic condition has a highly variable clinical phenotype with amongst others congenital heart disease (CHD) and psychiatric disorders [3]. The deleted region in 22q11.2DS spans more than 40 genes, one of which is the gene that encodes for catechol-*O*-methyl-transferase (COMT) [4]. This enzyme involves the degradation of catecholamines, including dopamine (DA) and norepinephrine (NE) (Fig. 1). People with 22q11.2DS have haploinsufficiency of COMT, resulting in lower enzymatic activity [5], which may result in abnormal catecholamine levels. Indeed, we showed that in 22q11.2DS subjects urinary DA concentrations are increased and urine and plasma levels of DA metabolites are decreased compared with healthy subjects [6]. In addition, acute monoamine depletion paradigms using alpha-methyl-*para*-tyrosine (AMPT), a reversible inhibitor of the first and rate-limiting step in the biosynthesis of catecholamines (Fig. 1), has been used successfully to assess endogenous brain DA in vivo [7].

Clinically, individuals with 22q11.2DS who survive childhood have diminished life expectancy and have an increased risk of sudden unexpected death [8]. Although the causes are likely multifactorial, hyperactivity of the cardiac sympathetic system is an important factor for the pathophysiology of fatal arrhythmias including enhance automaticity, triggered automaticity and reentrance [9]. Therefore increased cardiac sympathetic activity, due to increased levels of NE, should be considered as a possible mechanism predisposing to premature death in 22q11.2DS. However, to the best of our knowledge, no data are available whether the cardiac sympathetic system is affected in adults with 22q11.2DS.

NE is a sympathetic neurotransmitter that stimulates the β-adrenoreceptors, which induces positive chronotropic and inotropic effects (Fig. 2). *Meta*-iodobenzylguanidine (*m*IBG), a NE analog, shares

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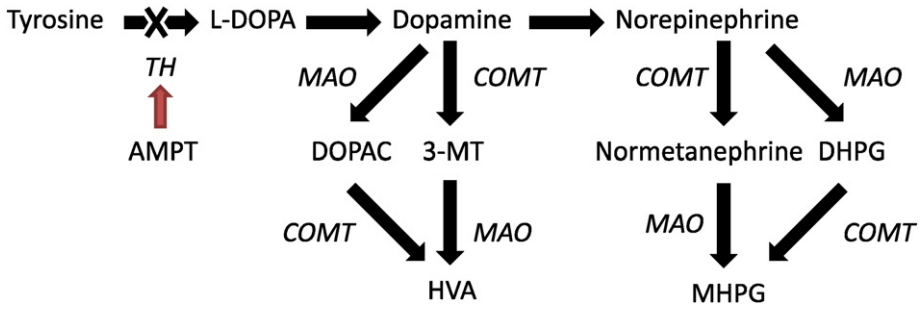

Fig. 1. Catecholamine metabolism and the negative effect of alpha-methyl-*para*-tyrosine (AMPT), a reversible inhibitor of tyrosine hydroxylase (TH), on the biosynthesis of catecholamines. MAO, monoamine oxidase; COMT, catechol-*O*-methyl-transferase; DOPAC,3,4-dihydroxyphenylacetic acid; 3-MT, 3-methoxytyramine; DHPG, dihydroxyphenylglycine; HVA, homovanillic acid; MHPG, 3-methoxy-4-hydroxyphenylglycol.

the same presynaptic uptake, storage and release mechanism as NE. Radiolabeling with ^{123}I allows assessment of presynaptic ^{123}I-*m*IBG uptake through the uptake-1 mechanism (i.e. NE transporter). This non-invasive technique has been extensively validated and shown to be of clinical value in many cardiac diseases [10–12].

We hypothesized that, due to COMT haploinsufficiency, people with 22q11.2DS are exposed to increased cardiac levels of NE and thereby have an increased cardiac sympathetic activity. In addition, the effect of acute monoamine depletion by AMPT could give additional information about the cardiac NE metabolism. Therefore, the purpose of this study was to determine whether cardiac sympathetic activity assessed with ^{123}I-*m*IBG scintigraphy, both at baseline and following an acute depletion challenge with AMPT, is different in adults with 22q11.2DS (without CHD) compared with healthy controls.

2. Material and methods

2.1. Subjects

Adults with 22q11.2DS were recruited through the Dutch 22q11.2DS Family Association. For each 22q11.2DS subject, an age- and sex-matched healthy control was included. Inclusion criteria for all

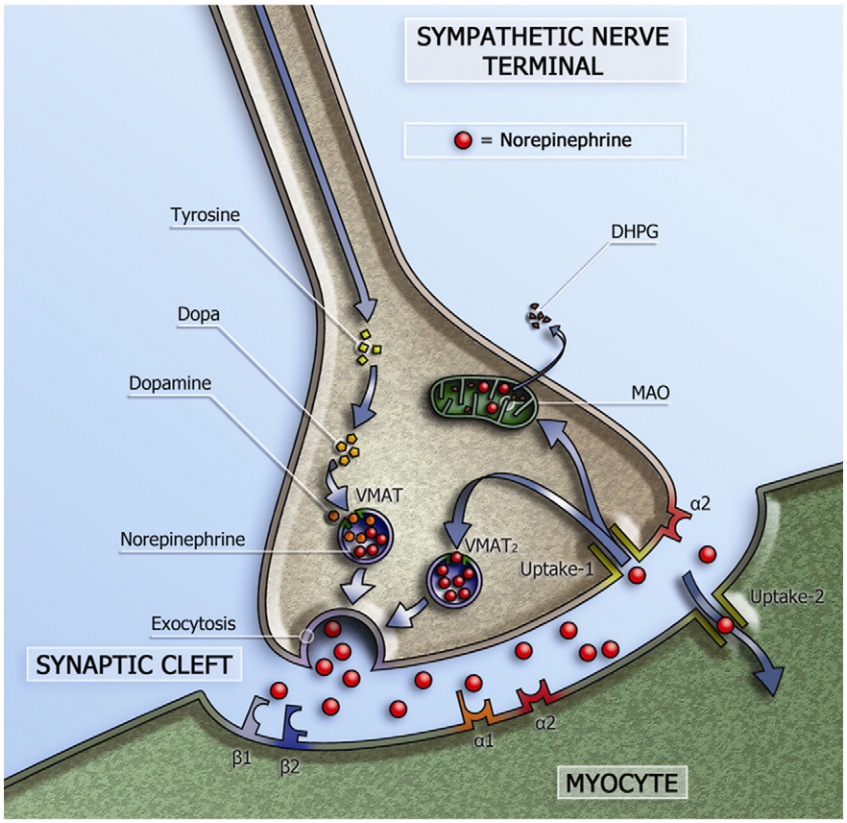

Fig. 2. Schematic representation of the sympathetic synapse. Norepinephrine is synthesized within neurons by an enzymatic cascade. Dihydroxyphenylalanine (DOPA) is generated from tyrosine and subsequently converted to dopamine by DOPA decarboxylase. Dopamine is transported into storage vesicles by the energy-requiring vesicular monoamine transporter (VMAT). Norepinephrine is synthesized by dopamine β-hydroxylase within these vesicles. Neuronal stimulation leads to norepinephrine release through fusion of vesicles with the neuronal membrane (exocytosis). Apart from neuronal stimulation, release is also regulated by a number of presynaptic receptor systems, including α2-adrenergic receptors, which provide negative feedback for exocytosis. Most norepinephrine undergoes reuptake into nerve terminals by the presynaptic norepinephrine transporter (uptake-1 mechanism) and is re-stored in vesicles (following uptake by vesicular monoamine transporter 2 (VMAT2)) or is metabolized in cytosol dihydroxyphenylglycol (DHPG) by monoamine oxidase (MAO). ^{123}I-*m*IBG neuronal uptake is predominantly through the presynaptic uptake-1 mechanism.