Neuroscience Letters 701 (2019) 71–76

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Research article

VNTR polymorphism in the *monoamine oxidase A* promoter region and cerebrospinal fluid catecholamine concentrations in forensic autopsy cases

Aya Matsusue[a,*], Shin-ichi Kubo[a], Tomoya Ikeda[b], Naoto Tani[b], Toshiki Maeda[c], Masayuki Kashiwagi[a], Kenji Hara[a], Brian Waters[a], Mio Takayama[a], Natsuki Ikematsu[a], Takaki Ishikawa[b]

[a] Department of Forensic Medicine, Faculty of Medicine, Fukuoka University, 7-45-1 Nanakuma, Jonan-ku, Fukuoka 814-0180, Japan
[b] Department of Legal Medicine, Osaka City University Medical School, Asahi-machi 1-4-3, Abeno, Osaka 545-8585, Japan
[c] Department of Preventive Medicine and Public Health,Faculty of Medicine, Fukuoka University, 7-45-1 Nanakuma, Jonan-ku, Fukuoka 814-0180, Japan

ARTICLE INFO

Keywords:
Monoamine oxidase A
Variable number tandem repeat
Catecholamine
Autopsy case

ABSTRACT

Monoamine oxidase A (MAOA) plays important roles in the metabolism of catecholamines and modulates adrenergic, noradrenergic, and dopaminergic signaling. A polymorphic promoter variable number tandem repeat (VNTR) locus (MAOA-uVNTR) is located approximately 1.2 kb upstream from *MAOA* exon 1. Functional studies revealed that MAOA-uVNTR affects gene expression. In the present study, we examined the frequencies of MAOA-uVNTR alleles in Japanese autopsy cases, in which amphetamines or psychotropic drugs were not detected. In total, 87 males and 35 females were evaluated and investigated for the possible effect of MAOA-uVNTR polymorphisms on cerebrospinal fluid (CSF) catecholamine concentrations. In males, there was no significant association between MAOA-uVNTR polymorphisms and CSF adrenaline (Adr), noradrenaline (Nad), or dopamine (DA) levels. In contrast, females who were homozygous for the 3-repeat allele (i.e., 3/3 genotype carriers) had higher CSF levels of Adr ($p = 0.024$) and DA ($p = 0.035$) than individuals who were heterozygous or homozygous for the 4-repeat allele (3/4 and 4/4, respectively). We found no significant association between MAOA-uVNTR polymorphisms and CSF Nad levels in females. Thus, the results of the present study indicated that MAOA-uVNTR polymorphism influences CSF Adr and DA levels in females.

1. Introduction

The catecholamines adrenaline (Adr), noradrenaline (Nad), and dopamine (DA) act as neurotransmitters in the central and peripheral nervous systems. Impaired neurotransmission or excess catecholamine levels lead to pathophysiologic effects [1]. Catecholamines are removed from the circulation either by reuptake into nerve terminals or by metabolism [2]. Catecholamine catabolism mainly involves two enzymes, monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT). Specifically, Adr is metabolized to dihydroxymandelic acid by MAO and to metanephrine by COMT; Nad is metabolized to dihydroxymandelic acid by MAO and to normetanephrine by COMT; and DA is metabolized to dihydroxyphenylacetic acid by MAO and to 3-methoxytyramine by COMT. There are two types of MAOs (MAOA and MAOB) in humans. MAOA and MAOB play a key role in the degradation of amine neurotransmitters. MAOA preferentially catabolizes serotonin and Nad, whereas MAOB prefers β-phenylethylamine [3]. In the human brain, MAOA is found in catecholaminergic neurons, whereas MAOB is present in serotonergic neurons and glial cells [4]. Therefore, MAOA is the predominant enzyme responsible for catecholamine deamination [5].

MAOA is expressed in most human tissues [6]. The gene encoding MAOA is located on Xp11.3. Given that one of the X chromosomes is randomly inactivated in female mammals [7], one of the MAOA alleles will be inactivated in a given cell in the female body. Various polymorphisms in the *MAOA* gene have been identified and investigated [8]. A functional polymorphism of a variable number tandem repeat (VNTR) in the promoter region of the *MAOA* gene (MAOA-uVNTR) has been described; this VNTR consists of a 30-bp repeated sequence present in 2, 3, 3.5, 4, 5, or 6 copies [9]. Alleles with 3.5 and 4 repeats are transcribed 2–10 times more efficiently than the 3- and 5-repeat alleles [10]. This polymorphism has been found to be associated with suicide [11], panic disorder among women [12,13], and antisocial behaviors [14].

In the present study, we investigated the MAOA-uVNTR genotype in autopsy cases and evaluated associations with Adr, Nad, and DA

* Corresponding author at: Department of Forensic Medicine, Faculty of Medicine, Fukuoka University, 7-45-1 Nanakuma, Jonan-ku, Fukuoka 814-0180, Japan.
E-mail address: miyoshi@fukuoka-u.ac.jp (A. Matsusue).

https://doi.org/10.1016/j.neulet.2019.02.029
Received 12 December 2018; Received in revised form 13 February 2019; Accepted 18 February 2019
Available online 19 February 2019
0304-3940/

Table 1
Case profiles.

	Number of cases	Age, years (median)	Postmortem interval (day) (median; h)
Male	87	16–91 (63)	< 0.5–3 (27.3)
Female	35	11–88 (72)	< 0.5–4 (27.9)

concentrations in cerebrospinal fluid (CSF) to clarify the influence of the MAOA-uVNTR genotype on catecholamine metabolism.

2. Materials and methods

2.1. Autopsy materials

Several psychotropic drugs target the major neurotransmitter systems in the brain. Amphetamines induce the release of neurotransmitters such as catecholamine [15], resulting in high postmortem CSF levels of catecholamine in drug intoxication cases [16]. Therefore, we examined autopsy cases in which amphetamines or psychotropic drugs were not detected in blood and urine samples (Table 1). The causes of death of the examined forensic autopsy cases are summarized in Table 2. Although vasopressor administration was not clearly indicated in hospital reports, no significant differences in catecholamine levels in CSF were found between cases with and without critical medical care at the time of death. During autopsy, CSF was collected from openings of the cranial cavities using sterile syringes. Blood samples were collected from right cardiac chambers. Urine samples were drawn using an aseptic syringe after opening of the abdominal cavities. This study was approved by the Fukuoka University Medical Ethics Review Board and the institutional ethics committee of the Osaka City University Graduate School of Medicine. The work described in this article was carried out in accordance with *The Code of Ethics of the World Medical Association (Declaration of Helsinki)* and the *Uniform Requirements* for manuscripts submitted to biomedical journals (http://www.icmje.org).

Table 2
Cause of death of the forensic autopsy cases.

	Cause of death	Number of cases
Male	Blunt head injury	3
	Blunt injury (Others)	10
	Sharp instrument injury (Hemorrhagic shock)	6
	Fire fatality	19
	Asphyxia	8
	Drowning	6
	Hypothermia (Cold exposure)	3
	Hyperthermia (Heat stroke)	2
	Intoxication (Others)	5
	Acute cardiac death	15
	Natural death excluding acute cardiac death	7
	Others*	3
Female	Blunt head injury	1
	Blunt injury (Others)	3
	Sharp instrument injury (Hemorrhagic shock)	4
	Fire fatality	14
	Asphyxia	1
	Drowning	3
	Hypothermia (Cold exposure)	1
	Hyperthermia (Heat stroke)	0
	Intoxication (Others)	3
	Acute cardiac death	2
	Natural death excluding acute cardiac death	3
	Others	0

* Cervical spinal cord and common artery injury (n = 1), Anaphylactic shock (n = 2).

2.2. Analytical procedure

CSF concentrations of the catecholamines Adr, Nad, and DA were determined as described previously [16]. Toxicological analyses were performed on right heart blood and urine samples using gas chromatography/mass spectrometry and liquid chromatography-tandem mass spectrometry.

2.3. Genotyping

Peripheral blood was obtained from 122 autopsy cases, and genomic DNA was isolated from each using a QIAamp DNA Mini Kit (Qiagen, Hilden, Germany) in accordance with the manufacturer's instructions. The specific primers used were designed to amplify the MAOA-uVNTR polymorphic region (forward primer: 5′- AGCGTGCTCCAGAAACATGA -3′ and reverse primer: 5′- CTCAGAACGGACGCTCCATT -3′). MAOA-uVNTR polymorphisms were amplified by PCR in a total reaction volume of 25 µl containing 2.5 units TaKaRa *Ex Taq* Hot Start Version (TaKaRa Bio Inc., Otsu, Shiga, Japan), 10× *Ex Taq* Buffer, 200 µM dNTP mixture, 500 nM each primer, and 100–200 ng genomic DNA. The PCR cycling conditions were as follows: 30 cycles consisting of 94 °C for 20 s, 60 °C for 30 s, and 72 °C for 1 min, followed by a final extension step at 72 °C for 7 min. An aliquot (4 µl) of the resulting PCR products was subjected to electrophoretic separation on a 2% NuSieve™ 3:1 Agarose gel (Lonza, Basel, Switzerland), stained with Gelgreen (Biotium, CA, USA), and visualized using UV illumination. Fragment sizes were determined by comparison with a 50-bp DNA Ladder (TaKaRa Bio Inc.). The lengths of PCR products corresponding to 2, 3, and 4 repeats were 244 bp, 274 bp, and 304 bp, respectively. The identities of the products obtained from several of the samples were confirmed by direct sequencing.

2.4. Statistical analysis

Allele frequencies were estimated, and Hardy–Weinberg equilibrium was performed using SNPAlyze software ver. 8.0.2 (Dynacom, Chiba, Japan). Catecholamine concentrations and MAOA-uVNTR polymorphisms were compared using nonparametric Wilcoxon rank-sum and Steel–Dwass tests. Statistical analyses were performed using SAS statistical software (SAS Enterprise Guide, Cary, NC, USA). The association between log-*transformed* CSF catecholamine concentrations and MAOA-uVNTR polymorphisms was analyzed using linear regression analysis adjusted for age. Linear regression analysis was performed using STATA statistical software (StataCorp LLC, TX, USA). Differences were considered significant when $p < 0.05$.

3. Results

Table 3 shows the results of the MAOA-uVNTR genotype frequency analyses. We identified only three alleles (2, 3, and 4 repeats). There were no significant deviations from Hardy–Weinberg equilibrium for the genotype distribution in the female autopsy case group. MAOA-uVNTR allele frequencies in this study were similar to those reported

Table 3
Frequency of the variable number tandem repeat (uVNTR) allele in the *monoamine oxidase A* (MAOA) promoter region in forensic autopsy cases.

	MAOA-uVNTR	n	Frequency (%)
Male	2	1	1.15
	3	55	63.22
	4	31	35.63
Female	2/4	1	2.86
	3/3	11	31.43
	3/4	16	45.71
	4/4	7	20.00

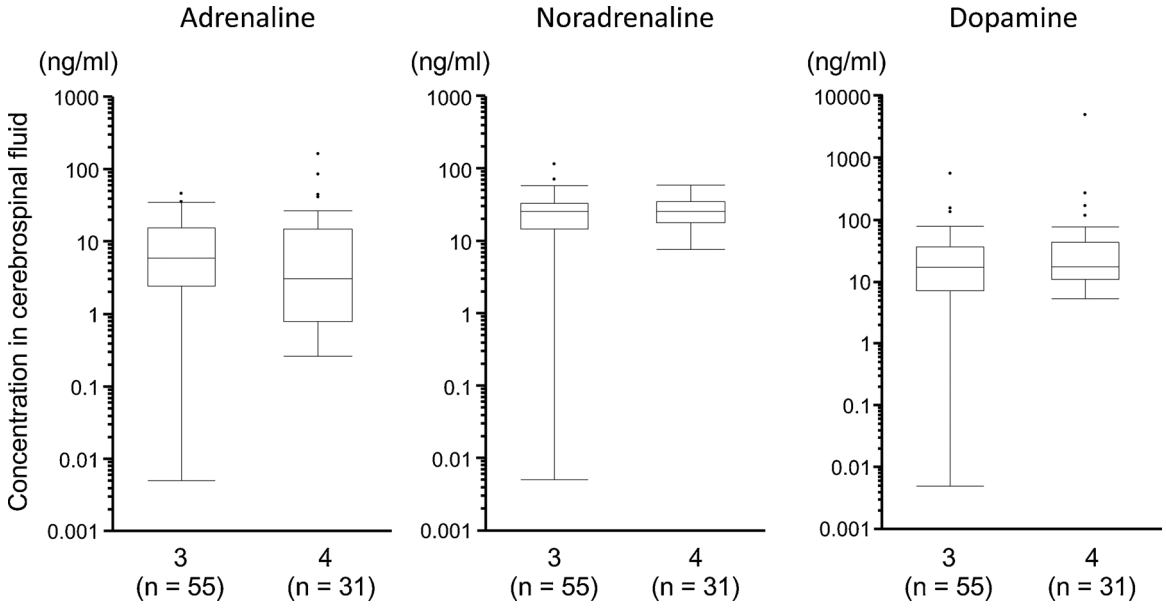

Fig. 1. Cerebrospinal fluid levels of catecholamine (ng/ml) in forensic autopsy cases according to VNTR polymorphism in the *monoamine oxidase A* promoter region in males. Bars, boxes, whiskers, and open circles indicate medians, 25th and 75th percentiles, ranges, and outliers, respectively.

previously for Asian populations [17,18].

The effects of the MAOA-uVNTR genotype on the CSF levels of Adr, Nad, and DA were determined in autopsy cases. In these analyses, the median CSF Adr concentrations in males and females were 5.51 and 3.98 ng/ml, respectively; the median CSF Nad concentrations in males and females were 25.9 and 23.6 ng/ml, respectively; and the median CSF DA concentrations in males and females were 17.1 and 13.7 ng/ml, respectively. There were no significant differences between males and females in terms of CSF Adr, Nad, and DA levels.

CSF levels of Adr, Nad, and DA were not associated with MAOA-uVNTR genotypes in males (Fig. 1). CSF levels of Adr, Nad, and DA were not associated with individual MAOA-uVNTR genotypes in females (Fig. 2A). In contrast, females who were homozygous for 3-repeat alleles (i.e., 3/3 genotype carriers) had higher CSF levels of Adr and DA than females who were heterozygous or homozygous for 4-repeat alleles (3/4 and 4/4, respectively) (Fig. 2B). Specifically, the median CSF concentrations of Adr in 3/3 genotype carriers and 4-repeat-allele (3/4 and 4/4) carriers were 5.76 and 3.19 ng/ml, respectively ($p = 0.024$), for Adr; and 18.8 and 10.3 ng/ml, respectively ($p = 0.035$), for DA. Before adjustment for age, females who were homozygous for 3-repeat alleles had higher CSF levels of Nad than females who were heterozygous or homozygous for 4-repeat alleles. However, after adjustment for age, CSF levels of Nad were not associated with MAOA-uVNTR genotype in females ($p = 0.060$).

4. Discussion

In this study, the MAOA-uVNTR genotype was associated with CSF levels of Adr and DA in females. As assessed in transfected human neuroblastoma and human placental choriocarcinoma cell lines, MAOA-uVNTR constructs containing 3 repeats have lower transcriptional activity than constructs containing 4 repeats [10,12]. MAOA activity in male skin fibroblast cultures with 3 MAOA-uVNTR repeats was significantly lower than that in cultures with 4 repeats [19]. Therefore, MAOA activity in carriers of the 3/3 genotype was expected to be lower than that in carriers of the 4/4 genotype. However, the present study did not detect a significant difference in CSF levels of catecholamines when comparing between 3/3 genotype carriers and 4/4 genotype carriers. This discrepancy may reflect the limited number of cases examined in the present work. In contrast, when we compared 3/3 genotype carriers to individuals harboring 4-repeat alleles (i.e., 3/4 and 4/4 genotype carriers), there was a significant difference in CSF Adr and DA levels. The MAOA gene is located on the X chromosome, and most X-chromosome genes are inactivated on one or the other X chromosome in females. Nonetheless, a number of genes escape X-chromosome inactivation, such that 15% of X-linked genes are expressed from both the active and inactive X chromosome [20]. However, it has been reported that *MAOA* is indeed subjected to X-chromosome inactivation in humans [21,22]. Females heterozygous for X-linked genes have mixtures of two types of cells due to X-chromosome inactivation [23]. Because the inactivation of one X chromosome in each cell is a random event, females have varying X-inactivation ratios, defined as the proportions of the two types of cells [24]. Although the contribution of X chromosome inactivation to the regulation of MAOA levels is unclear, it seems that the MAOA activity of individuals who are heterozygous (3/4) is higher than 3/3 genotype carriers. The observation in the present study of higher Adr and DA concentrations in the CSF of female 3/3 genotype carriers was consistent with the lower activity compared with 4 repeats allele (3/4 and 4/4) carriers in females. After adjustment for age, CSF levels of Nad were not associated with the MAOA-uVNTR genotype in females. Catecholamines apparently decrease in the brain as some species age [25]. CSF Adr and DA levels in females were not associated with age in this study. Although we found no significant association between CSF Nad and age in females ($p = 0.056$), CSF Nad levels may have been influenced by age. The Km of MAOA for Nad is higher than that for Adr and DA in homogenates from human cerebral cortex [26]. For these reasons, it is considered that there was no significant association between CSF Nad and MAOA-uVNTR in females.

In contrast to the observation in females, the MAOA-uVNTR genotype was not associated with the CSF levels of Adr, Nad, and DA among males. Notably, females have two X chromosomes, whereas males have one X chromosome. Therefore, the correlation between genotype and gene activity is expected to be simpler in males. Notably, the activity of MAOA differed 515-fold among male skin fibroblast cultures [19] and varied considerably by individual. In the present study, CSF Adr, Nad, and DA concentrations in males exhibited wide variation compared with the CSF concentrations of the respective catecholamines in females. This wider variance may explain the failure to detect a significant difference in males.

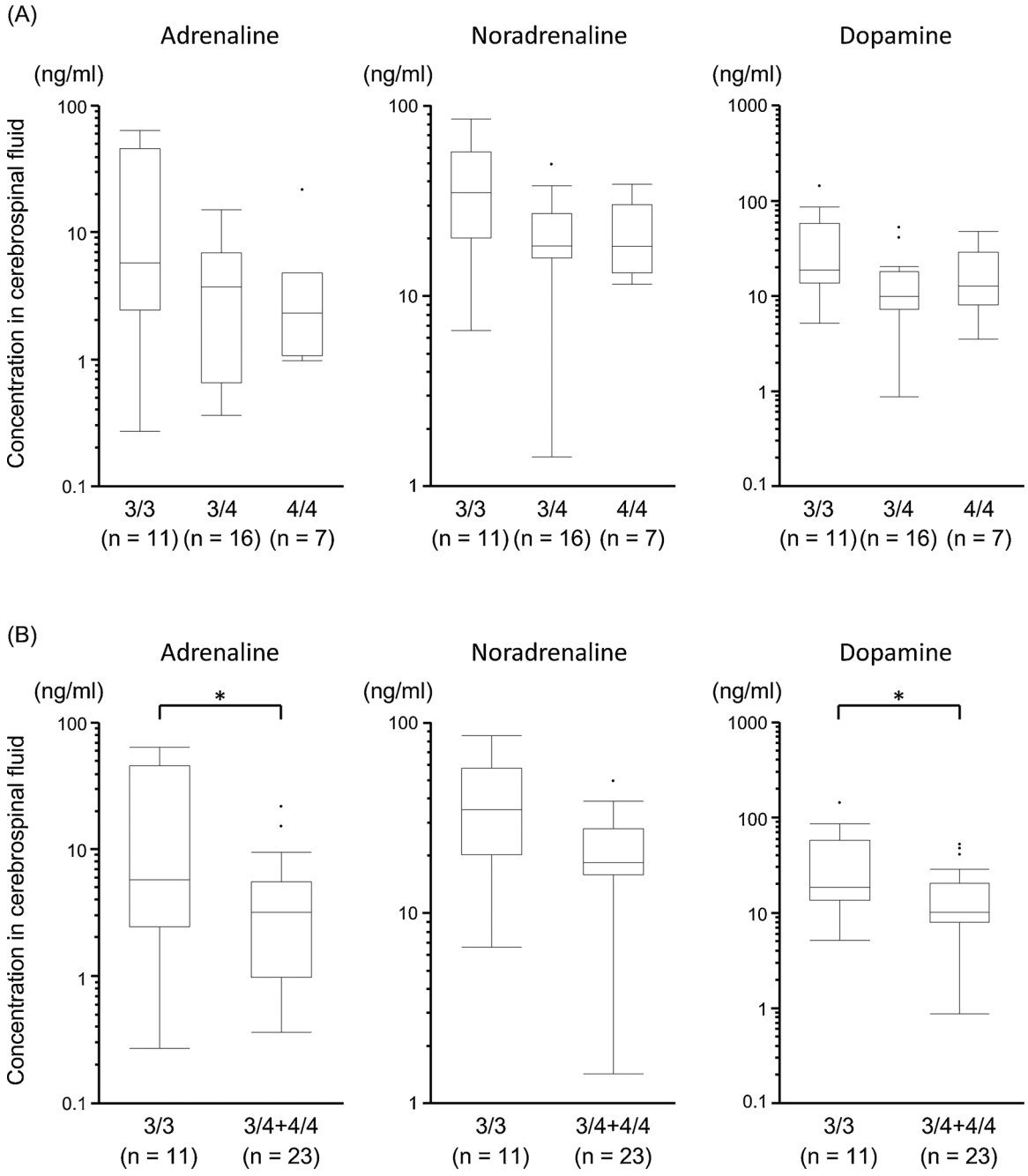

Fig. 2. Cerebrospinal fluid levels of catecholamine (ng/ml) in forensic autopsy cases according to VNTR polymorphism in the *monoamine oxidase A* promoter region in females. (A) Genotype (B) 3/3 versus 3/4 + 4/4. Bars, boxes, whiskers, and open circles indicate medians, 25th and 75th percentiles, ranges, and outliers, respectively. Differences between genotypes are indicated as follows: $*p < 0.05$.

DA is metabolized to homovanillic acid (HVA) via either of two pathways by MAO and COMT. The MAOA-uVNTR genotype has been reported to significantly influence the HVA concentration. Specifically, a low-activity MAOA-uVNTR genotype was associated with higher CSF HVA levels in healthy male volunteers [27], in an overall male sample (including individuals with alcoholism and healthy controls) [28], and in female patients with treatment-resistant depression [29]. A high-activity MAOA-uVNTR genotype was associated with higher CSF HVA levels in healthy female volunteers [27] and in male patients with mental health disorders [30]. These results for low- and high-activity genotypes are inconsistent with each other. CSF HVA levels may be altered by the rate of biosynthesis, release, and reuptake of DA [28]. The effect of the MAOA-uVNTR genotype on CSF HVA concentration may change depending on gender or case. Notably, MAOA-uVNTR genotype was not associated with the level of 3-methoxy-4-hydroxyphenylglycol (MHPG), a Nad metabolite, in these subjects [27–30]. Thus, MAOA-uVNTR was not associated with either CSF Nad levels or the MHPG concentration.

High or low concentrations of catecholamines are related to a wide variety of health conditions. MAOA-uVNTR polymorphism has been reported to be associated with reactive impulsive experimental aggressiveness in healthy men and women [31], psychopathological disorders such as anxiety depending on gender [32], and enhanced vulnerability to suicide in males with depression [33]. The MAOA-uVNTR polymorphism also has been reported to be associated with diverse mental health conditions, an effect that may reflect differences in catecholamine concentrations caused by differences in MAOA activity.

Many factors influencing catecholamine concentrations were not

considered in this study. Notably, catecholamines are released during the stress response; catecholamine levels fluctuate with the circadian rhythm; and Adr and Nad concentrations increase markedly during exercise [34]. In forensic autopsy cases, there is often little or no antemortem information available. The precedent conditions can vary markedly among subjects, resulting in ambiguity as to the cause of death, estimated time of death, nature of the last meal, and elapsed time between that meal and death. Subjects also are highly likely to be under great stress before death or at the time of death. Thus, many factors other than MAOA-uVNTR may influence CSF catecholamine concentrations in autopsy cases. The ratio of the concentration of catecholamines to the resulting metabolite of the reaction regulated by MAOA-uVNTR should be investigated in further studies. Additionally, our data were limited by the small sample size. A larger sample size would be required to verify the relationship between CSF catecholamine concentration and MAOA-uVNTR by analyzing cases where conditions are matched as much as possible.

5. Conclusions

In this study, we examined the relationships between catecholamine levels in CSF and MAOA-uVNTR genotype in autopsy cases in which amphetamines or psychotropic drugs were not detected. These analyses showed significantly higher CSF Adr and DA concentrations in female cases with the 3/3 genotype than in cases harboring a 4-repeat allele (3/4 and 4/4 genotypes). The MAOA-uVNTR genotype was not associated with CSF levels of Nad in females. Among males, no significant associations were identified between MAOA-uVNTR genotype and the CSF levels of Adr, Nad, or DA. These data suggest that the MAOA-uVNTR genotype affects CSF Adr and DA levels in females. High CSF levels of catecholamine may affect diverse health conditions.

Funding sources

The authors declare that they have no proprietary, financial, professional, or other personal interest of any kind in any product, service, and/or company that could be construed as influencing this current manuscript entitled “VNTR polymorphism in the *monoamine oxidase A* promoter region and cerebrospinal fluid catecholamine concentrations in forensic autopsy cases”.

Declarations of interest

None.

Acknowledgements

None.

References

[1] S. Paravati, S.J. Warrington, Physiology, Catecholamines, StatPearls, Treasure Island (FL), 2018.
[2] W.F. Young, Endocrine Hypertension, Williams Textbook of Endocrinology, 13th edition, ELSEVIER, Amsterdam, 2016, pp. 556–588.
[3] J.C. Shih, K. Chen, M.J. Ridd, Role of MAO A and B in neurotransmitter metabolism and behavior, Pol. J. Pharmacol. 51 (1) (1999) 25–29.
[4] T. Nagatsu, Progress in monoamine oxidase (MAO) research in relation to genetic engineering, Neurotoxicology 25 (1-2) (2004) 11–20, https://doi.org/10.1016/S0161-813X(03)00085-8.
[5] C. Schulz, G. Eisenhofer, H. Lehnert, Principles of catecholamine biosynthesis, metabolism and release, Front. Horm. Res. 31 (2004) 1–25, https://doi.org/10.1159/000074656.
[6] K. Chen, J.C. Shih, Monoamine oxidase A and B: structure, function, and behavior, Adv. Pharmacol. 42 (1998) 292–296, https://doi.org/10.1016/S1054-3589(08)60747-4.
[7] C.M. Disteche, J.B. Berletch, X-chromosome inactivation and escape, J. Genet. 94 (4) (2015) 591–599, https://doi.org/10.1007/s12041-015-0574-1.
[8] J. Dorszewska, M. Prendecki, A. Oczkowska, A. Rozycka, M. Lianeri, W. Kozubski, Polymorphism of the COMT, MAO, DAT, NET and 5-HTT genes, and biogenic amines in parkinson’s disease, Curr. Genomics 14 (8) (2013) 518–533, https://doi.org/10.2174/1389202914666131210210241.
[9] C.P. Jacob, J. Muller, M. Schmidt, K. Hohenberger, L. Gutknecht, A. Reif, A. Schmidtke, R. Mossner, K.P. Lesch, Cluster B personality disorders are associated with allelic variation of monoamine oxidase A activity, Neuropsychopharmacology 30 (9) (2005) 1711–1718, https://doi.org/10.1038/sj.npp.1300737.
[10] S.Z. Sabol, S. Hu, D. Hamer, A functional polymorphism in the monoamine oxidase A gene promoter, Hum. Genet. 103 (3) (1998) 273–279, https://doi.org/10.1007/s004390050816.
[11] K. Ursic, T. Zupanc, A.V. Paska, Analysis of promoter polymorphism in monoamine oxidase A (MAOA) gene in completed suicide on Slovenian population, Neurosci. Lett. 673 (2018) 111–115, https://doi.org/10.1016/j.neulet.2018.02.063.
[12] J. Deckert, M. Catalano, Y.V. Syagailo, M. Bosi, O. Okladnova, D. Di Bella, M.M. Nothen, P. Maffei, P. Franke, J. Fritze, W. Maier, P. Propping, H. Beckmann, L. Bellodi, K.P. Lesch, Excess of high activity monoamine oxidase A gene promoter alleles in female patients with panic disorder, Hum. Mol. Genet. 8 (4) (1999) 621–624, https://doi.org/10.1093/hmg/8.4.621.
[13] A. Reif, H. Weber, K. Domschke, B. Klauke, C. Baumann, C.P. Jacob, A. Strohle, A.L. Gerlach, G.W. Alpers, P. Pauli, A. Hamm, T. Kircher, V. Arolt, H.U. Wittchen, E.B. Binder, A. Erhardt, J. Deckert, Meta-analysis argues for a female-specific role of MAOA-uVNTR in panic disorder in four European populations, Am. J. Med. Genet. B Neuropsychiatr. Genet. 159B (7) (2012) 786–793, https://doi.org/10.1002/ajmg.b.32085.
[14] C.A. Ficks, I.D. Waldman, Candidate genes for aggression and antisocial behavior: a meta-analysis of association studies of the 5HTTLPR and MAOA-uVNTR, Behav. Genet. 44 (5) (2014) 427–444, https://doi.org/10.1007/s10519-014-9661-y.
[15] D. Sulzer, M.S. Sonders, N.W. Poulsen, A. Galli, Mechanisms of neurotransmitter release by amphetamines: a review, Prog. Neurobiol. 75 (6) (2005) 406–433, https://doi.org/10.1016/j.pneurobio.2005.04.003.
[16] T. Ishikawa, L. Quan, T. Michiue, O. Kawamoto, Q. Wang, J.H. Chen, B.L. Zhu, H. Maeda, Postmortem catecholamine levels in pericardial and cerebrospinal fluids with regard to the cause of death in medicolegal autopsy, Forensic Sci. Int. 228 (1-3) (2013) 52–60, https://doi.org/10.1016/j.forsciint.2013.02.008.
[17] H. Kunugi, S. Ishida, T. Kato, M. Tatsumi, T. Sakai, M. Hattori, T. Hirose, S. Nanko, A functional polymorphism in the promoter region of monoamine oxidase-A gene and mood disorders, Mol. Psychiatry 4 (4) (1999) 393–395, https://doi.org/10.1038/sj.mp.4000558.
[18] R.B. Lu, J.F. Lee, H.C. Ko, W.W. Lin, K. Chen, J.C. Shih, No association of the MAOA gene with alcoholism among Han Chinese males in Taiwan, Prog. Neuropsychopharmacol. Biol. Psychiatry 26 (3) (2002) 457–461, https://doi.org/10.1016/S0278-5846(01)00288-3.
[19] R.M. Denney, H. Koch, I.W. Craig, Association between monoamine oxidase A activity in human male skin fibroblasts and genotype of the MAOA promoter-associated variable number tandem repeat, Hum. Genet. 105 (6) (1999) 542–551, https://doi.org/10.1007/s004399900183.
[20] J.B. Berletch, F. Yang, J. Xu, L. Carrel, C.M. Disteche, Genes that escape from X inactivation, Hum. Genet. 130 (2) (2011) 237–245, https://doi.org/10.1007/s00439-011-1011-z.
[21] R.W. Hendriks, Z.Y. Chen, H. Hinds, R.K. Schuurman, I.W. Craig, An X chromosome inactivation assay based on differential methylation of a CpG island coupled to a VNTR polymorphism at the 5’ end of the monoamine oxidase A gene, Hum. Mol. Genet. 1 (8) (1992) 662, https://doi.org/10.1093/hmg/1.8.662.
[22] R. Stabellini, L.R. Vasques, J.C. de Mello, L.M. Hernandes, L.V. Pereira, MAOA and GYG2 are submitted to X chromosome inactivation in human fibroblasts, Epigenetics 4 (6) (2009) 388–393, https://doi.org/10.4161/epi.4.6.9492.
[23] M.F. Lyon, X-chromosome inactivation and human genetic disease, Acta Paediatr, Suppl. 91 (439) (2002) 107–112, https://doi.org/10.1111/j.1651-2227.2002.tb03120.x.
[24] J.M. Amos-Landgraf, A. Cottle, R.M. Plenge, M. Friez, C.E. Schwartz, J. Longshore, H.F. Willard, X chromosome-inactivation patterns of 1,005 phenotypically unaffected females, Am. J. Hum. Genet. 79 (3) (2006) 493–499, https://doi.org/10.1086/507565.
[25] A. Amano, M. Tsunoda, T. Aigaki, N. Maruyama, A. Ishigami, Age-related changes of dopamine, noradrenaline and adrenaline in adrenal glands of mice, Geriatr. Gerontol. Int. 13 (2) (2013) 490–496, https://doi.org/10.1111/j.1447-0594.2012.00929.x.
[26] M. Gerlach, P. Riederer, Human Brain MAO, Monoamine Oxidase: Basic and Clinical Aspects, VSP, Utrecht, 1993, pp. 147–158.
[27] E.G. Jonsson, N. Norton, J.P. Gustavsson, L. Oreland, M.J. Owen, G.C. Sedvall, A promoter polymorphism in the monoamine oxidase A gene and its relationships to monoamine metabolite concentrations in CSF of healthy volunteers, J. Psychiatr. Res. 34 (3) (2000) 239–244, https://doi.org/10.1016/S0022-3956(00)00013-3.
[28] F. Ducci, T.K. Newman, S. Funt, G.L. Brown, M. Virkkunen, D. Goldman, A functional polymorphism in the MAOA gene promoter (MAOA-LPR) predicts central dopamine function and body mass index, Mol. Psychiatry 11 (9) (2006) 858–866, https://doi.org/10.1038/sj.mp.4001856.
[29] E. Aklillu, S. Karlsson, O.O. Zachrisson, V. Ozdemir, H. Agren, Association of MAOA gene functional promoter polymorphism with CSF dopamine turnover and atypical depression, Pharmacogenet. Genomics 19 (4) (2009) 267–275, https://doi.org/10.1097/FPC.0b013e328328d4d3.
[30] G. Zalsman, Y.Y. Huang, J.M. Harkavy-Friedman, M.A. Oquendo, S.P. Ellis, J.J. Mann, Relationship of MAO-A promoter (u-VNTR) and COMT (V158M) gene polymorphisms to CSF monoamine metabolites levels in a psychiatric sample of caucasians: a preliminary report, Am. J. Med. Genet. B Neuropsychiatr. Genet. 132B (1) (2005) 100–103, https://doi.org/10.1002/ajmg.b.30094.
[31] Y. Kuepper, P. Grant, C. Wielpuetz, J. Hennig, MAOA-uVNTR genotype predicts

interindividual differences in experimental aggressiveness as a function of the degree of provocation, Behav. Brain Res. 247 (2013) 73–78, https://doi.org/10.1016/j.bbr.2013.03.002.

[32] N. Voltas, E. Aparicio, V. Arija, J. Canals, Association study of monoamine oxidase-A gene promoter polymorphism (MAOA-uVNTR) with self-reported anxiety and other psychopathological symptoms in a community sample of early adolescents, J. Anxiety Disord. 31 (2015) 65–72, https://doi.org/10.1016/j.janxdis.2015.02.004.

[33] F.W. Lung, D.S. Tzeng, M.F. Huang, M.B. Lee, Association of the MAOA promoter uVNTR polymorphism with suicide attempts in patients with major depressive disorder, BMC Med. Genet. 12 (2011) 74, https://doi.org/10.1186/1471-2350-12-74.

[34] H. Zouhal, C. Jacob, P. Delamarche, A. Gratas-Delamarche, Catecholamines and the effects of exercise, training and gender, Sports Med. 38 (5) (2008) 401–423, https://doi.org/10.2165/00007256-200838050-00004.