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Quinolinate Accumulation in the Brains of the Quinolinate Phosphoribosyltransferase (QPRT) Knockout Mice

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1. Introduction

The kynurenine pathway (KP) is the main route of L-tryptophan catabolism, thus resulting in the production of the essential pyridine nucleotide, nicotinamide adenine dinucleotide (NAD^+) (Figure 1) (Stone, 1993). Quinolinic acid (QA) is one of the KP metabolites, which are synthesized from the essential amino acid tryptophan (Trp). QA is a potent endogenous excitotoxin of neuronal cells that acts as N-methyl-D-aspartate (NMDA) receptor agonist. Quinolinate phosphoribosyltransferase (QPRT) is the only enzyme that degrades QA in mammalian cells, so the concentration of QA is modulated directly by the QPRT activity. QA is an endogenous excitotoxin acting on N-methyl-D-aspartate receptors (NMDARs) which leads to pathological and neurochemical features similar to those observed in HD. Neurons expressing high levels of NMDARs are lost early from the striatum of individuals affected with Huntington's Disease (HD), and injection of NMDA receptor agonists, such as QA, into the striatum of rodents or non-human primates mimics the pattern of neuronal damage observed in HD. When QA is loaded into rat brains by autodialysis, the striatal region is specifically severely damaged (Schwarcz & Köhler, 1983). An autoradioreceptor assay showed that the number of NMDA glutamate receptors in patients of HD was reduced by 93% (Young et al., 1988), thus supporting the hypothesis that an endogenous agonist of the receptor is primarily responsible for the neural degradation associated with the disease. Unlike kainate or ibotenate, QA is thought to be the only physiological agonist for the NMDARs involved in the disorder (Stone et al., 1981). Thus, a dysfunction of QA metabolism in the human brain has been postulated to be involved in the pathogenesis of

such neurodegenerative disorders as epilepsy, Alzheimer's Disease (AD) and HD (the "quinolinate hypothesis") (Schwarcz et al., 1986).
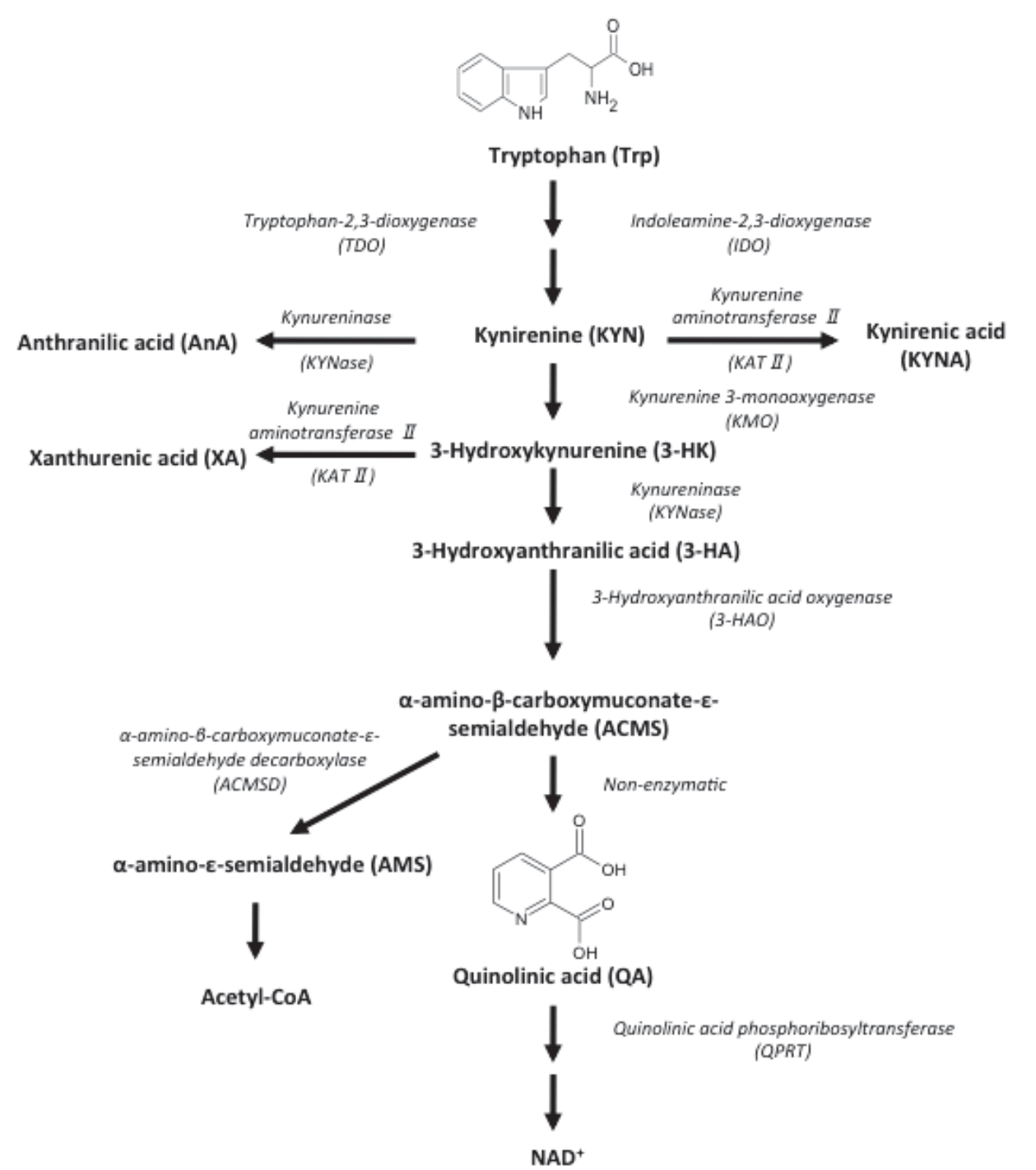

Fig. 1.

However, this hypothesis has not yet been corroborated by the measurement of endogenous QA in neurodegenerative disorders. In this study, we generated QPRT gene deficient mice (QPRT knockout mice) to investigate this hypothesis *in vivo*. We succeeded in detecting the endogenous QA accumulation-induced neurodegenerations in the striatum of middle-aged

QPRT knockout (KO) mice by an immunohistochemical analysis. In KO mice, the expression levels of KP enzymes and NMDA receptor (NMDAR) subunits were altered compared to those of wild type (WT) mice. The expression of the NR2B subunit was also significantly increased in middle-aged KO mice. The results of biochemical analyses indicated that QA tended to exert NMDAR-mediated excitotoxiciy in the brains of these mice. We observed behavioral disorders in QPRT KO mice using two behavioral tests. Many previous studies have demonstrated that disturbances in gait are symptomatic of Parkinson's Disease (PD) and HD. Gait abnormalities in PD include a shortened stride length. HD also shows gait abnormalities include changes in stride length (Koller & Trimble, 1985). We therefore measured the stride length of KO mice based on these studies. We found that the aged QPRT KO mice displayed shortening of their strides compared to the WT group. In contrast, the middle-aged QPRT KO mice did not exhibited any significant gait abnormalities. Fernagut et al. reported that the stride length is a reliable index of motor disorders due to basal ganglia dysfunction in mice (Carter et al., 1999). Our findings suggest that the striatal neuronal lesions in the QPRT KO mice progressed with age, such that the younger mice had not yet developed sufficient basal ganglia dysfunction to result in a change in gait. The shortening of strides may be an event that occurs during the later stage of neurodegeneration.

2. Generation of QPRT gene deficient models

2.1 Construction of the QPRT gene targeting vector

Based on the genomic information obtained previously and using genomic clones of the 129 Svj mouse QPRT gene, a 2.9 kb 50 homologous recombination region including a portion of exon 2, intron 3, exon 3, and a portion of intron 4 was amplified by PCR. A PGK-βgeo selection marker cassette was ligated and subcloned into the targeting vector with the MC1-diphtheria toxin A gene to select against nonhomologous recombination (Figure 2a).

2.2 Generation of the QPRT disrupted mice

The constructed targeting vector was introduced into a 129 Svj mouse ES cell line (Genome Systems) by electroporation. ES cells were selected in media containing G418, and the surviving cells were purified by dilution to obtain single clones. Homologous recombination in the ES cells was confirmed by a Southern blotting analysis using a probe localized 50 methods. The positive clone was injected into C57BL/6N mouse blastocysts to obtain chimeric mice that transmitted the mutation through the germline. Mice were bred and maintained using standard mouse husbandry procedures. The detailed physiological and biochemical analyses of the QPRT gene deficient mice will be published elsewhere.

2.3 Validation studies

Genomic DNA extracted from mice tails was used for genotyping PCR. Figure 2b is an electropherogram of the mouse DNA amplification products. Figure 2b is an electropherogram of the mouse DNA amplification products. WT, heterozygous (HZ) and KO mice showed distinct band patterns.
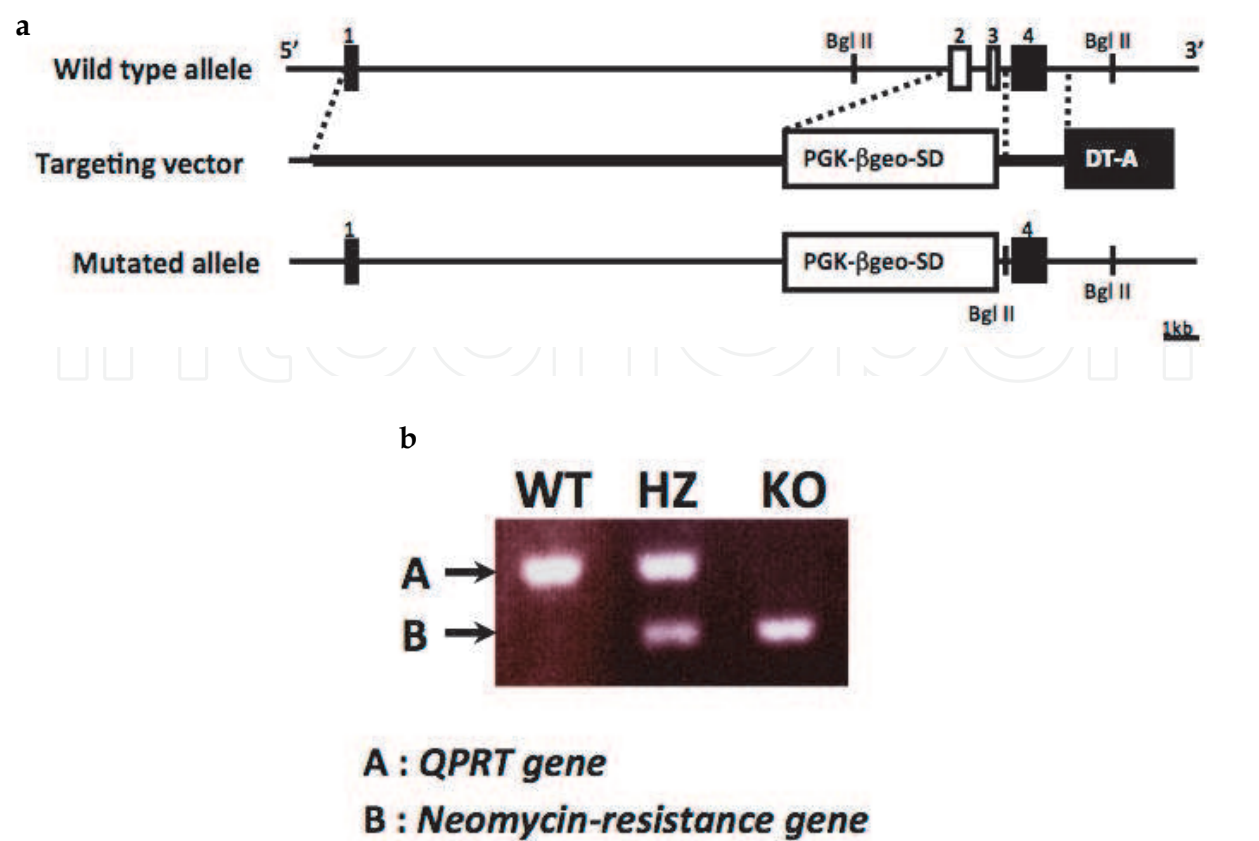
Fig. 2. Generation of QPRT gene deficient mice. WT, wild type mice; KO, QPRT KO mice. (a) The targeting strategy used for QPRT gene disruption. Exons are represented as *numbered boxes*. DT-A, diphtheria toxin-A. (b) An agarose gel showing genotyped PCR amplicons. Genomic DNA extracted from mouse tails were used for PCR with primer pairs for the QPRT and PGK-βgeo genes. The product sizes are 398 and 221 base pairs (bp), respectively.

3. Morphological analysis

3.1 The presence of QA in the brains

The QA in the brain of middle-aged (18-week-old) WT and QPRT KO mice was stained using an anti-QA antibody (Figure 3). The histochemical analyses were performed with frozen-section tissues prepared from brains fixed with 4% paraformaldehyde in phosphate-buffered saline (PBS). The frozen sections were excised and embedded in O. C. T. compound for cryosectioning, then dried and treated with 5% BSA for 30 min at room temperature. The tissues were incubated with 5 μg/ml rabbit anti-QA antibody (Ab) (Sigma, MO) for 12 hours at 4°C, followed by 0.5 μg/ml secondary biotinylated donkey anti-rabbit IgG Ab (Molecular Probes, OR) for 2 hours at room temperature. The immunostaining was visualized with a VECTASTAIN ABC kit (Vector Laboratories, CA) using DAB as the chromagen. The images were captured with a fluorescence microscope (Axioplan2; Carl Zeiss Inc., Jena, Germany) equipped with a CCD camera. The staining intensities were determined by using the Image-J software program to measure the stained areas in each striatum of sections after the experiment. Stained cells existed in both groups, especially in their striatum. There was no consistent pattern of labeling with regard to specific cell types. Quantification of QA

staining intensities suggested that there were high QA levels in the middle-aged KO mouse striatum. In the striatum, KO mice showed approximately two times the amount of QA staining intensity compared to WT mice (Data not shown).
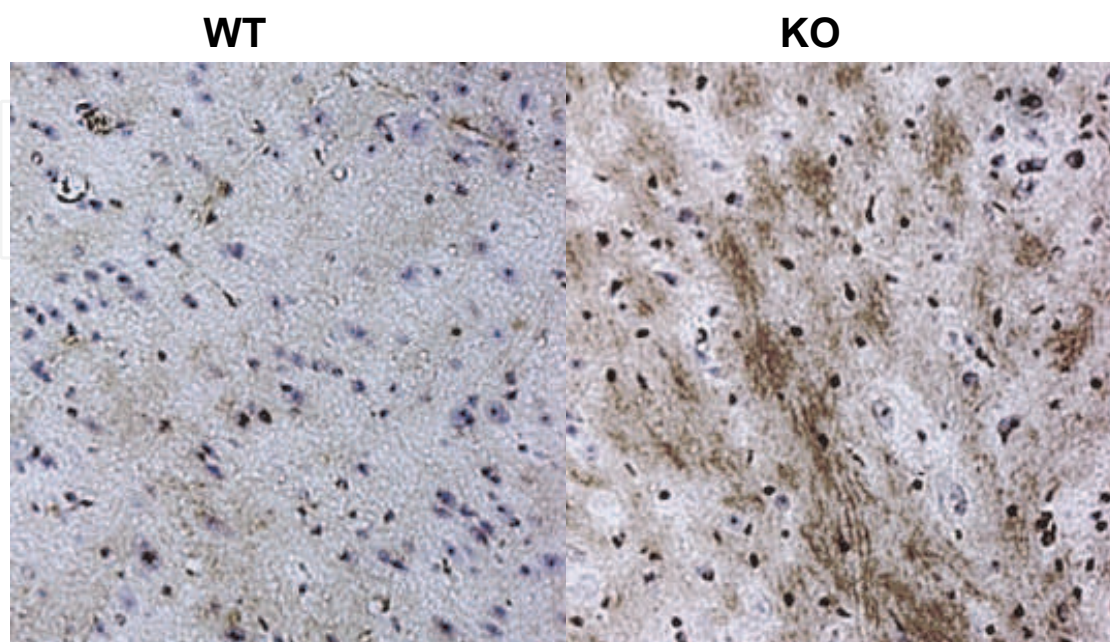

Fig. 3. Detection of QA by immunostaining of the striatum of WT and QPRT KO mice. WT, wild type mice; KO, QPRT KO mice. The frozen sections of middle-aged WT and KO brains were labeled by anti-QA polyclonal antibodies. The QA-positive cells were stained in the striatum of WT (a, left) and KO (a, right).

3.2 Detection of neurodegeneration

According to the results of the morphological analysis using the QA antibody, we prepared sections from middle-aged WT mice and QPRT KO mice to detect neuronal degeneration by Fluoro Jade C staining (Figure 4).

To detect neurodegeneration, the tissues were treated with fluoro-jade C (Histo-Chem Inc.; Jefferson, AR) according to the previously described method. The slides bearing frozen cut tissue sections were first immersed in a basic alcohol solution consisting of 1% sodium hydroxide in 80% ethanol for 5 min. They were then rinsed for 2 min in 70% ethanol, for 2 min in distilled water, and then incubated in 0.06% potassium permanganate solution for 10 min. Slides were subsequently transferred for 10 min to a 0.0001% solution of Fluoro-Jade C dissolved in 0.1% acetic acid vehicle. The slides were then rinsed through three changes of distilled water for 1 min per change. Excess water was drained onto a paper towel, and the slides were air dried on a slide warmer at 50°C for at least 5 min. The air dried slides were then cleared in xylene for at least 1 min and then coverslipped with entellan new (Merck Inc., Japan) non-fluorescent mounting media.

The neurons in the striatum of the KO mouse brains were labeled in their cell bodies. In contrast, there were few stained neurons in the WT mouse brain sections. These results indicate that neurodegeneration occurred remarkably in the middle-aged QPRT KO mouse striatum, but not in those of WT mice.
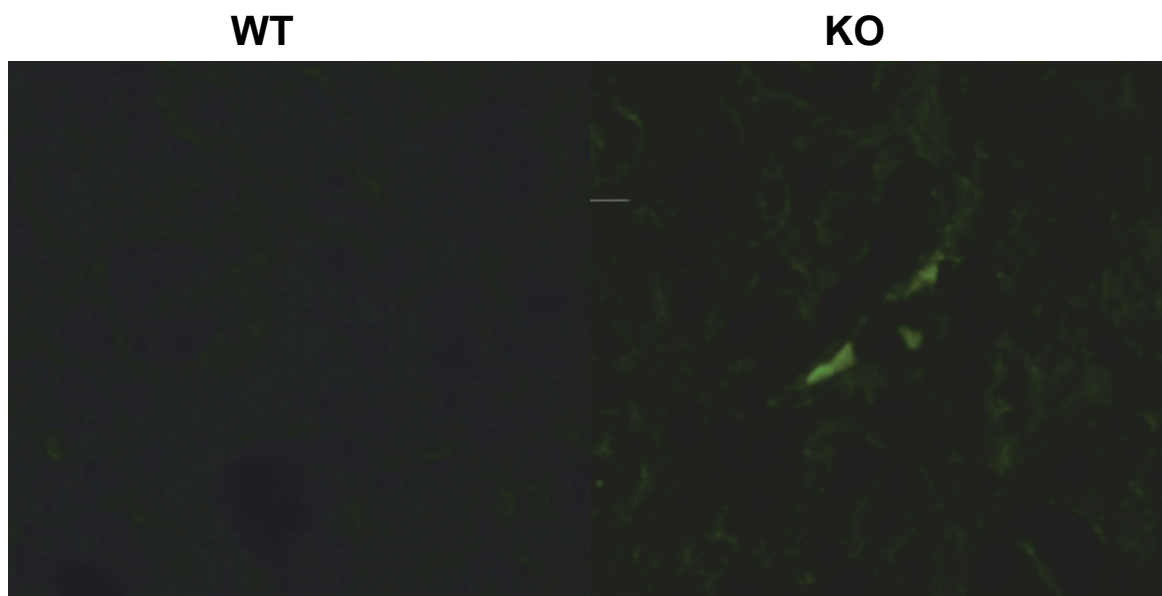
WT   **KO**

Fig. 4. Neuronal degeneration in the WT and QPRT KO mouse striatum stained with Fluoro-Jade C. WT, wild type mice; KO, QPRT knockout mice. 25μm frozen brain sections of middle-aged WT (right) and KO (right) mice were used for immunofluoresence studies with Fluoro-Jade C staining. The degenerated neurons were labeled in their cell bodies.

4. Detection of gene expressions

4.1 The gene expression of kynurenine pathway enzymes in the striatum of WT and QPRT KO mice

We detected the mRNA expression levels of metabolic enzymes in the KP (Figure 1) to clarify the role of metabolism in the QPRT KO mice. To determine the mechanism of KP metabolism in the middle-aged (14 ~ 22-week-old) and aged (68-week-old) mouse striatum, we analyzed the gene expression levels of KP enzymes by real-time PCR using primers for IDO, TDO, KATII, KYNase, KMO, 3-HAO and ACMSD. The total RNA was extracted from the mouse striatum using TRIZOL (Invitrogen, CA). The purity of RNA was confirmed by spectrophotometer readings at 260/280 nm. Total RNA was reverse-transcribed with the PrimeScript RT reagent kit (TaKaRa) and amplified by PCR. For KP enzyme genes (Figure 1), the following primers were used; IDO, 5'-TTCTTCTTAGAGTCAGCTCCCC (sense) and TCACAGAGACCAGACCATTCAC-3' (antisense); TDO, 5'-AAGAGGAACAGATGGCAGAG (sense) and TCGTCGTTCACCTTTACTCA-3' (antisense); KAT II, 5'–CGGTTTGAAGA CGACTTGA (sense) and TTGGGTGGGTAGTTGACAGT-3' (antisense); KYNase, 5'-AGCCCATGAGAAAGAAATAG (sense) and TGCCGCTTTGGAGTAG-3' (antisense); KMO, 5'-CGCGATCATGCCCTCTA (sense) and GGACCCAAGGACAAAGAGTC-3' (antisense); 3-HAO, 5'-TTGAGTGGTTGAGAGCTGTCAC (sense) and GGCTATGGCTG TTAGAAGATCG-3' (antisense); ACMSD, 5'-GGTACATGCCTCTTACATCAGC (sense) and GCTATCCTAGAGCTTGCTATGC-3' (antisense); QPRT, 5'-GCTCCTGTTACCCCCTACAACC (sense) and GGATGCAAAATTGAGGCCCGGG-3' (antisense). GAPDH was used in each reaction as an internal standard. For quantitative analysis, the SYBR Premix Ex Taq™ (TaKaRa) was used according to the manufacturer's instructions in a LightCycler® 480 Real-Time PCR System (Roche, Basel, Schweiz). The conditions for the reaction were as follows: 5 s at 95°C and 20 s at 60°C for 40 cycles.

In the middle-aged mice, the mRNA levels of ACMSD in the striatum of QPRT KO mice were lower than those in the WT group (P = 0.036). In contrast, no significant differences in the mRNA expression levels were seen in other KP enzymes (Figure 5).

On the other hand, the aged groups showed the opposite results for ACMSD expression. The mRNA levels of ACMSD in the QPRT KO mice were increased significantly compared to those of WT mice (P = 0.0088). However, in both the middle-aged and aged groups, there were no significant changes in any of the other KP enzymes between the WT and KO mice.

4.2 The gene expression levels of NMDAR subunits in the striatum of WT and QPRT KO mice

We next investigated the effects of QPRT deletion on the glutamatergic pathway. The mRNA expression of NMDAR subunits in the striatum of middle-aged and aged WT and QPRT KO mice were analyzed by real-time PCR (Figure 6). In the middle-aged QPRT KO group, the NR2B subunit mRNA expression level increased approximately two-fold compared to the WT group (P = 0.002). In addition, the NR2A subunit genes in the KO mouse striatum showed a tendency toward an increased expression compared to the WT group. However, there were no significant differences for any other subunits.

In the aged KO mouse group, the mRNA expression levels of the NR1, NR2A and NR2B subunits were significantly higher than those of the WT group (P = 0.016, 0.049 and 0.044, respectively). KO mice also showed two-fold increased expression of the NR2D subunit (P = 0.015). However, the NR2C subunits did not show any significant differences in expression between WT and KO mice.

These results about NMDAR expression levels suggested that there were similar propensities with regard to about the expression of NR2A and NR2B subunits in the middle-aged and aged groups, but that more subunits were affected by QPRT deficiency in the aged group.

5. Discussion

In this study, we generated QPRT gene deficient mice (QPRT knockout mice) and confirmed that the mRNA and protein expression of QPRT were not detected in the tissues of the QPRT KO mice. Therefore, it is expected that endogenous QA cannot be degraded by QPRT in these mice, allowing for the possible accumulation of QA. According to the "quinolinate hypothesis" and other previous studies utilizing animal models of neurodegenerative disorders, the accumulation of QA was associated with remarkable abnormal phenotypes such as defects in growth and development, such as were observed in a mouse model of Huntington's disease (HD) (Dellen, 2008). However, the QPRT KO mice exhibited normal phenotypes. In our long-term follow-up study, the changes in the body weight and intake of food were almost the same in the QPRT KO mice as in the wild type (WT) mice (data not shown). These results made us wonder why the QPRT KO mice did not show any effects in their growth and development. We assumed that there were two possibilities that needed to be investigated. First, there was the possibility that the QA concentrations in the brains of QPRT KO mice were decreased to nontoxic levels due to changes in the expression levels of kynurenine pathway metabolic enzymes. The second possibility was that there might have been a change in the mechanism of NMDARs-mediated QA excitotoxicity in the presence of excessive QA. Based on these possibilities, we investigated the mechanisms of QA accumulation, degradation and excitotoxicity in QPRT KO mice.
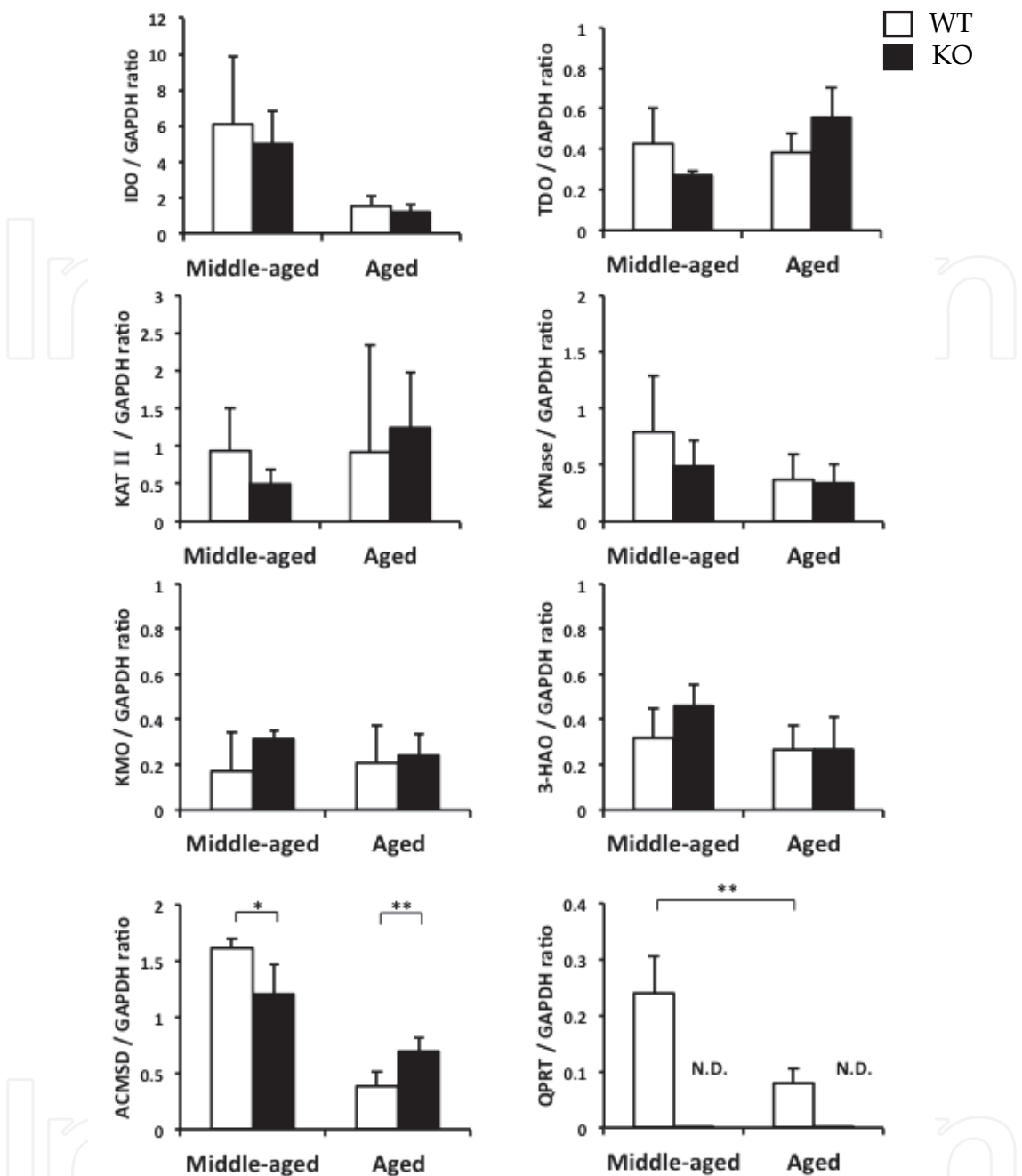
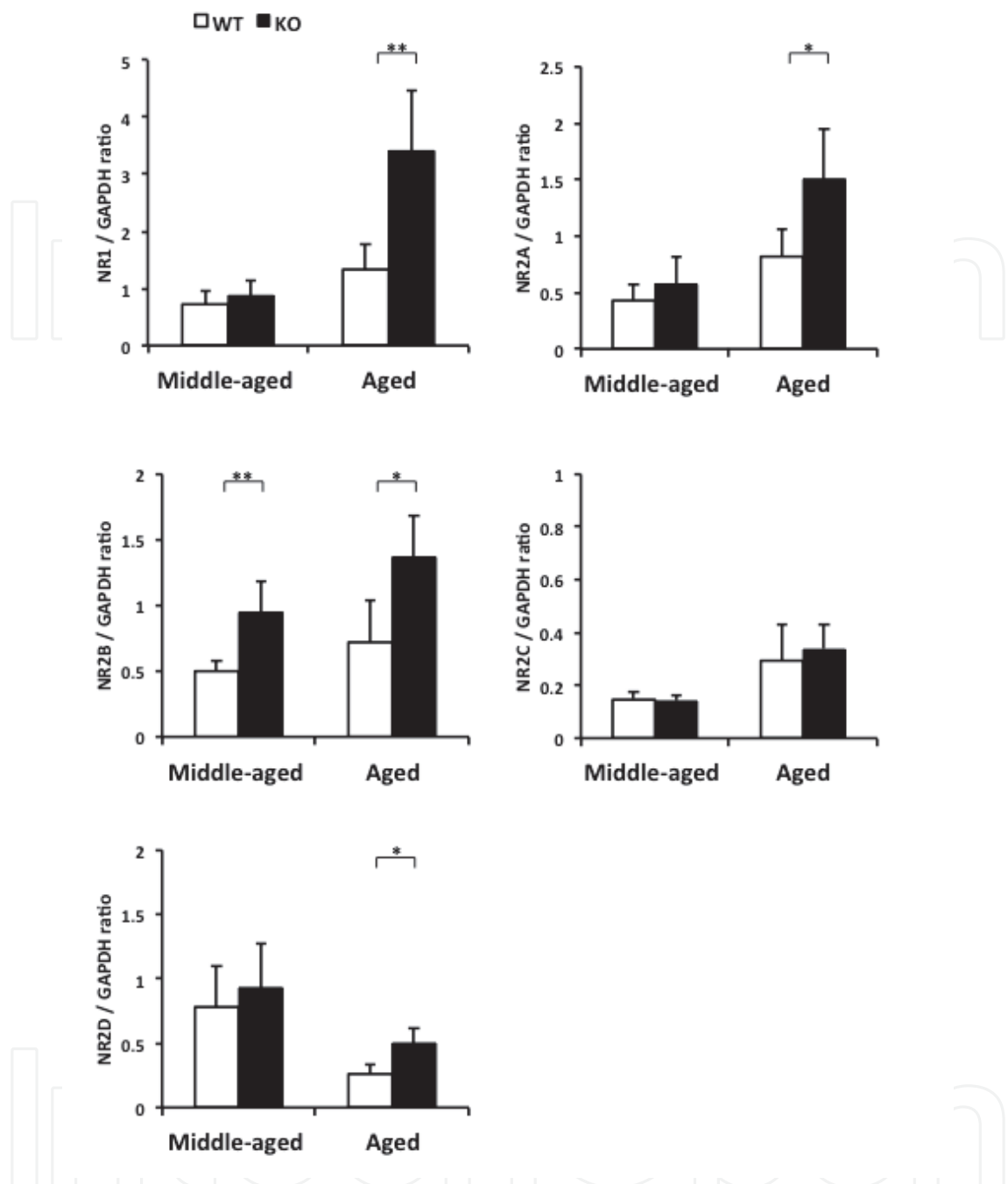Fig. 5. The mRNA expression levels of KP enzymes in the striatum tissue samples of WT and QPRT KO mice. WT, wild type mice; KO, QPRT knockout mice. Total RNA extracted from middle-aged (14~22-week-old) and aged (68-week-old) mouse striatum samples was subjected to real time quantitative RT-PCR. The figures show the gene expression levels of KP enzymes IDO (middle-aged,WT: n = 4, KO: n = 8, aged, WT: n = 3, KO: n = 6), TDO (middle-aged, WT: n = 4, KO: n = 6; aged, WT: n = 3, KO: n = 5), KATII (middle-aged,WT: n = 3, KO: n = 6; aged, WT: n = 3, KO: n = 6), KYNase (middle-aged,WT: n = 4, KO: n = 6; aged, WT: n = 3, KO: n = 6), KMO (middle-aged,WT: n = 3, KO: n = 4; aged, WT: n = 3, KO: n = 6), 3-HAO (middle-aged,WT: n = 3, KO: n = 7; aged, WT: n = 3, KO: n = 6), ACMSD (middle-aged,WT: n = 3, KO: n = 6; aged, WT: n = 3, KO: n = 6) and QPRT (middle-aged,WT: n = 3, KO: n = 7; aged, WT: n = 3, KO: n = 6). The values are shown as the ratios of KP enzymes / GAPDH (internal standard). The data are presented as the means ± S.D. *, $p < 0.05$, **, $p < 0.01$. (Student's t-test).

Fig. 6. The mRNA expression levels of NMDAR subunits in striatum tissue samples from WT and QPRT KO mice. WT, wild type mice; KO, QPRT knockout mice. Total RNA was extracted from middle-aged (14~22-week-old) and aged (68-week-old) mouse striatum samples, and the mRNA expression levels of NMDAR subunits was determined by real time quantitative RT-PCR. The figures show the gene expression levels of NMDAR subunits NR1 (middle-aged,WT: n = 6, KO: n = 7; aged, WT: n = 3, KO: n = 6), NR2A (middle-aged,WT: n = 5, KO: n = 7; aged, WT: n = 3, KO: n = 6), NR2B (middle-aged,WT: n = 5, KO: n = 8; aged, WT: n = 3, KO: n = 6), NR2C (middle-aged,WT: n = 5, KO: n = 8; aged, WT: n = 3, KO: n = 6), and NR2D (middle-aged,WT: n = 5, KO: n = 7; aged, WT: n = 3, KO: n = 6). The values are shown as the ratio of NMDAR subunits/GAPDH (internal standard). The data are presented as the means ± S.D. *,$p < 0.05$. (Student's t-test).

We first tried to visualize the intrastriatal QA in mouse brain sections to clarify whether QA accumulated in the brains of the QPRT KO mice. In human and rat brains, QA is present at concentrations in the high nanomolar range (Wolfensberger, 1983). An HD study revealed that QA levels were increased (by 300-400%) in the neostriatum of human with early stage HD compared to controls (Guidetti, 2004)]. By an immunohistochemical analysis using an anti-QA polyclonal antibody, we observed that the number of QA-positive cells in the striatum of middle-aged QPRT KO mice was higher than in WT mice. This result suggested that QA does indeed accumulate in the QPRT KO mice. An *in vitro* study showed that prolonged exposure of rat organotypic cortico-striatal cultures to as little as 100 nM QA results in characteristic excitotoxic damage (Whetsell & Schwarcz, 1989).

Using immunohistochemical detection of QA, we tried to validate the existence of neurodegenerarion in the striatum of middle-aged QPRT KO mice. Several previous studies demonstrated that selective striatal neuronal damage occurs in the striatum of HD patients. Therefore, we and others have postulated that a pathological elevation of QA levels may produce excitotoxic neurodegeneration in HD. We used fluoro-jade C staining for detection of neuronal degeneration. As a result, there were an increased number of degenerated neurons in the striatum of QPRT KO mice compared to WT mice. These results were consistent with QA accumulation in the striatum of the QPRT KO mice. We hypothesized that the neuronal degeneration in the striatum of KO mice might have been induced by the high levels of QA due to the QPRT deficiency.

We revealed significant differences in the gene expression levels of KP enzymes between WT and QPRT KO mice. The expression levels of ACMSD, which degrades the QA precursor α-amino-β-carboxymuconate-ε-semialdehyde (ACMS) in the striatum of middle-aged QPRT KO mice were lower than those of WT mice. In middle-aged QPRT KO mice, this change in KP metabolism might promote QA production, because QA is non-enzymatically derived from ACMS (Figure 1). This is consistent with the results of our immunohistochemical staining for QA. However, the results in the aged groups showed the opposite, with an increase in expression in the QPRT KO mice compared to the WT mice. This may reflect the acquisition of a defense mechanism against accumulation of QA in the aged QPRT KO mice, and we expected that this mechanism was established during the aging process. A reciprocal relationship between ACMSD mRNA and enzymatic activity was described by previous studies; the fluctuation of hepatic ACMSD mRNA expression was followed by that of ACMSD activity (Tanabe et al., 2002), and in the mouse brain, the changes in ACMSD expression at the message levels are shown to be highly correlated to those at the enzyme activity levels. This suggests that the quantification of the message levels with the real-time PCR technique is useful to address the regulation of ACMSD expression and QA levels (Fukuoka et al., 2002). Although we have not measured the enzymatic activities in the different groups of mice, based on the previous studies, we speculated that the mRNA expression levels of ACMSD observed in our present study were reflective of the enzymatic activity.

Because QA is known as a selective N-methyl-D-aspartate receptor (NMDAR) agonist, we determined the mRNA expression levels of NMDAR subunits to evaluate the mechanism underlying the neurotoxicity of endogenous QA.

The expression of functional recombinant NMDARs in mammalian cells requires the co-expression of at least one NR1 and one NR2 subtype. The stoichiometry of NMDARs has not

yet been established conclusively, but the current consensus is that NMDARs are tetramers that most often incorporate two NR1 and two NR2 subunits of the same or different subtypes. In the case of middle-aged QPRT KO mice, only the NR2B subunit expression levels were significantly increased compared to the levels in WT mice. In contrast, the expression levels of both the NR2A and NR2B subunits were increased in the aged QPRT KO mice compare to the aged WT mice. Previous studies have elucidated that the pharmacological and functional properties of NMDARs depend heavily on the NR2 subunit composition. Moreover, other groups have confirmed that the critical factor affecting the NMDAR activity is the subunit composition: NR2B-containing NMDARs promote neuronal death, while NR2A-containing NMDARs promote neuronal survival. Heng et al. created double-mutant mice by crossing a murine genetic model of HD to a transgenic mouse overexpressing the NMDAR–NR2B subunits (Tang et al., 1999; Heng et al., 2007) and their recent study showed that the double-mutant mice exhibited a significant decrease in striatal neuron number and striatal volume. This result demonstrated that the overexpression of the NR2B subunit leads to the degeneration of striatal neurons. Based on these previous studies and our present findings, we believe that the high sensitivity of striatal neurons in the middle-aged mice to damage was due to their high expression of the NR2B subunit. Similarly, we believe that the aged QPRT KO mice expressed high levels of the NR2A subunit as an adaptive neuroprotective mechanisms.

6. Conclusion

In summary, our study detected the presence of endogenous QA accumulation and QA-induced neurodegeneration in the striatum of middle-aged QPRT KO mice. Our results raised the possibility that QPRT KO mice are able to be used as a model of endogenous QA accumulation mimicking various human neurodegenerative conditions. Although it was difficult to demonstrate the "quinolinate hypothesis" in previous *in vivo* studies, the new QPRT KO mouse model will therefore be a useful model for further investigating this hypothesis.

7. Acknowledgements

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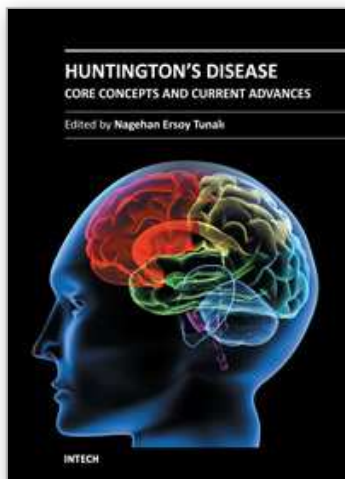
Huntington's Disease - Core Concepts and Current Advances

Edited by Dr Nagehan Ersoy Tunali

Huntington's Disease is one of the well-studied neurodegenerative conditions, a quite devastating and currently incurable one. It is a brain disorder that causes certain types of neurons to become damaged, causing various parts of the brain to deteriorate and lose their function. This results in uncontrolled movements, loss of intellectual capabilities and behavioural disturbances. Since the identification of the causative mutation, there have been many significant developments in understanding the cellular and molecular perturbations. This book, "Huntington's Disease - Core Concepts and Current Advances", was prepared to serve as a source of up-to-date information on a wide range of issues involved in Huntington's Disease. It will help the clinicians, health care providers, researchers, graduate students and life science readers to increase their understanding of the clinical correlates, genetic aspects, neuropathological findings, cellular and molecular events and potential therapeutic interventions involved in HD. The book not only serves reviewed fundamental information on the disease but also presents original research in several disciplines, which collectively provide comprehensive description of the key issues in the area.

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