



Homeostasis Regulation by Potassium Channel Subfamily K Member 3 (KCNK3) in Various Fishes

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Potassium channels are important for K⁺ transport and cell volume regulation, which play important roles in many biological processes such as hormone secretion, ion homeostasis, excitability, and cell development. In mammals, a total of 15 potassium channels were identified and they were divided into six subfamilies, including TALK (TALK1, TALK2, TASK2), TASK (TASK1, TASK3, TASK5), TREK (TREK1, TREK2, TRAAK), TWIK (TWIK1, TWIK2, KCNK7), THIK (THIK1, THIK2) and TRESK. TASK1, also known as potassium channel subfamily k member 3 (KCNK3), is the first member identified in the TASK subfamily. This K_{2P} channel has potential applications in fish breeding and aquaculture industry due to its important roles in various physiological processes. Despite its functional role has been well studied in mammals; however, it is less known in fishes. In this review, we systematically summarize recent research advances of this critical potassium channel in representative fishes, such as gene number variation, tissue distribution, phylogeny, and potential homeostasis regulation role. This paper provides novel insights into the functional properties of these fish *kcnk3* genes (including osmoregulation, energy homeostasis maintenance and fatty acids metabolism regulation), and also expands our knowledge about their variations among diverse fishes.

Keywords: potassium channel, *kcnk3*, osmoregulation, energy maintenance, fish

INTRODUCTION

Potassium channels are the largest ion channel family with more than 78 genes encoding pore-forming subunits in the human genome (Feliciangeli et al., 2015). This family consists of three structure-differential subclasses including inward rectifiers (K_{ir}), voltage-gated K⁺ (K_v) channels and two-pore domain K⁺ (K_{2P}) channels (Goldstein et al., 2001; Gutman et al., 2005; Gonzalez et al., 2012). Different from the other two subclasses, K_{2P} channels were originally identified from DNA database mining without any clues about their electrophysiological and functional properties (Lesage et al., 1996). Thus far, a total of 15 genes have been identified to encode K_{2P} channels that are involved in the development and excitability of many cell types (Mathie, 2007;

Feliciangeli et al., 2015). These channels are modulated by a wide range of chemical and physical stimuli, and they have been widely used as the targets of various drugs such as neuroprotective, anti-depressive and anesthetics agents (Talley and Bayliss, 2002; Olschewski et al., 2017). These K_{2P} channels can be divided into six subfamilies comprising Two P-domain in a weakly inward rectifying K^+ channel (TWIK1, TWIK2, KCNK7), TWIK-related acid-sensitive K^+ channel (TASK1, TASK3, TASK5), TWIK-related alkaline-sensitive K^+ channel (TREK1, TREK2, TRAAK), Tandem pore domain halotane-inhibited K^+ channel (THIK1, THIK2) and TWIK-related spinal cord K^+ channel (TRESK), according to their structural and functional properties (Feliciangeli et al., 2015; Wen et al., 2019).

Thus far, various K_{2P} channels have been well studied in mammals. However, only a few counterparts were preliminarily characterized and investigated in zebrafish, an well-established model for human diseases (Shin and Fishman, 2002). The TREK2 is the first K_{2P} channel identified in zebrafish, and this channel exhibits similar structural and functional properties as human TREK2 (Gierten et al., 2012). Meanwhile, TRESK was characterized in zebrafish, and functional experiments revealed that this channel shares similar functions as its counterpart in human, such as open rectification properties, inhibition by barium, and regulation by signaling molecules including protein kinases PKC & PKA and phospholipase C (Rahm et al., 2014). Additionally, zebrafish TASK2 channel was determined to be inhibited by increased CO_2 and intracellular acidification (Pena-Munzenmayer et al., 2014). Interestingly, two isoforms of TASK1 channels were identified in zebrafish, and they were proposed to contribute to an atrial substrate for arrhythmogenesis (Liang et al., 2014). Similarly, two paralogs of *kcnk10* were identified in zebrafish, which were predicted to play important roles in regulation of reproduction (Loganathan et al., 2017). Recently, another two paralogs of TWIK related potassium channels, *Kcnk2a* and *Kcnk2b*, were reported and they were proved to exhibit similar functional traits as their counterpart in human (Nasr et al., 2018). Furthermore, two THIK1 isoforms are newly identified in zebrafish, and they were considered to exhibit similar structural and functional properties as human THIK1, due to their activation by arachidonic acid and reduction by barium, mexiletine, lidocaine, and inhibited phospholipase C (Staudacher et al., 2019).

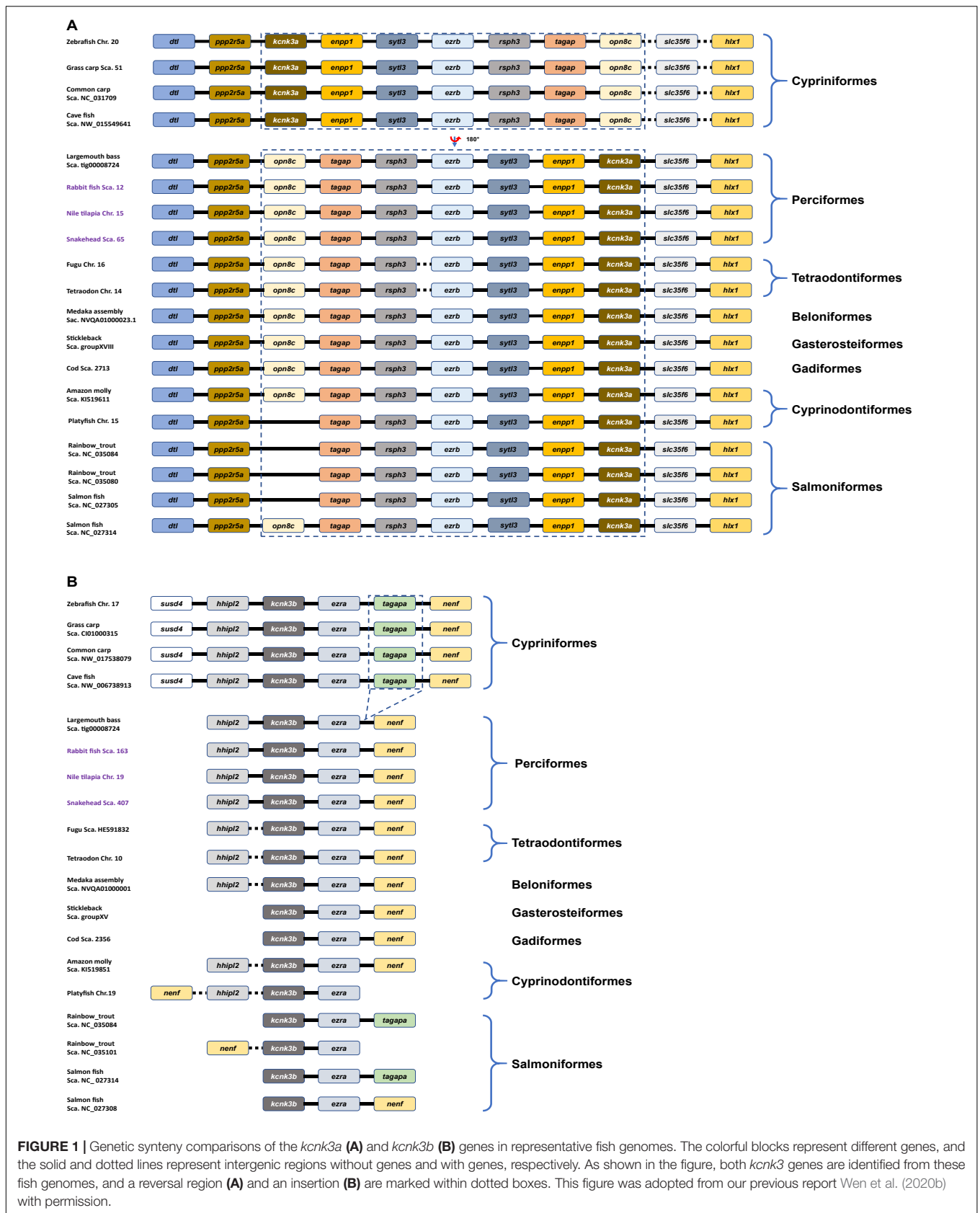
TASK1, also known as potassium channel subfamily k member 3 (KCNK3) or $K_{2P3.1}$, is the first member identified in the TASK subfamily to participate in regulation of resting membrane potential in several cell types (Olschewski et al., 2017; Lambert et al., 2018, 2019). This channel is characterized by four transmembrane domains and two pore domains per subunit (Ma et al., 2013; Feliciangeli et al., 2015). KCNK3 channels are primarily expressed in the central nervous system (CNS) but also in periphery tissues including heart, adrenal gland, and pulmonary arterial smooth muscle (PASM) (Lesage and Barhanin, 2011; Lambert et al., 2018). KCNK3 is modulated by a variety of biochemical agents, such as unsaturated fatty acids (UFAs), extracellular pH, hypoxia, and anesthetics (Olschewski et al., 2017; Wen et al., 2020b). Due to these physiological

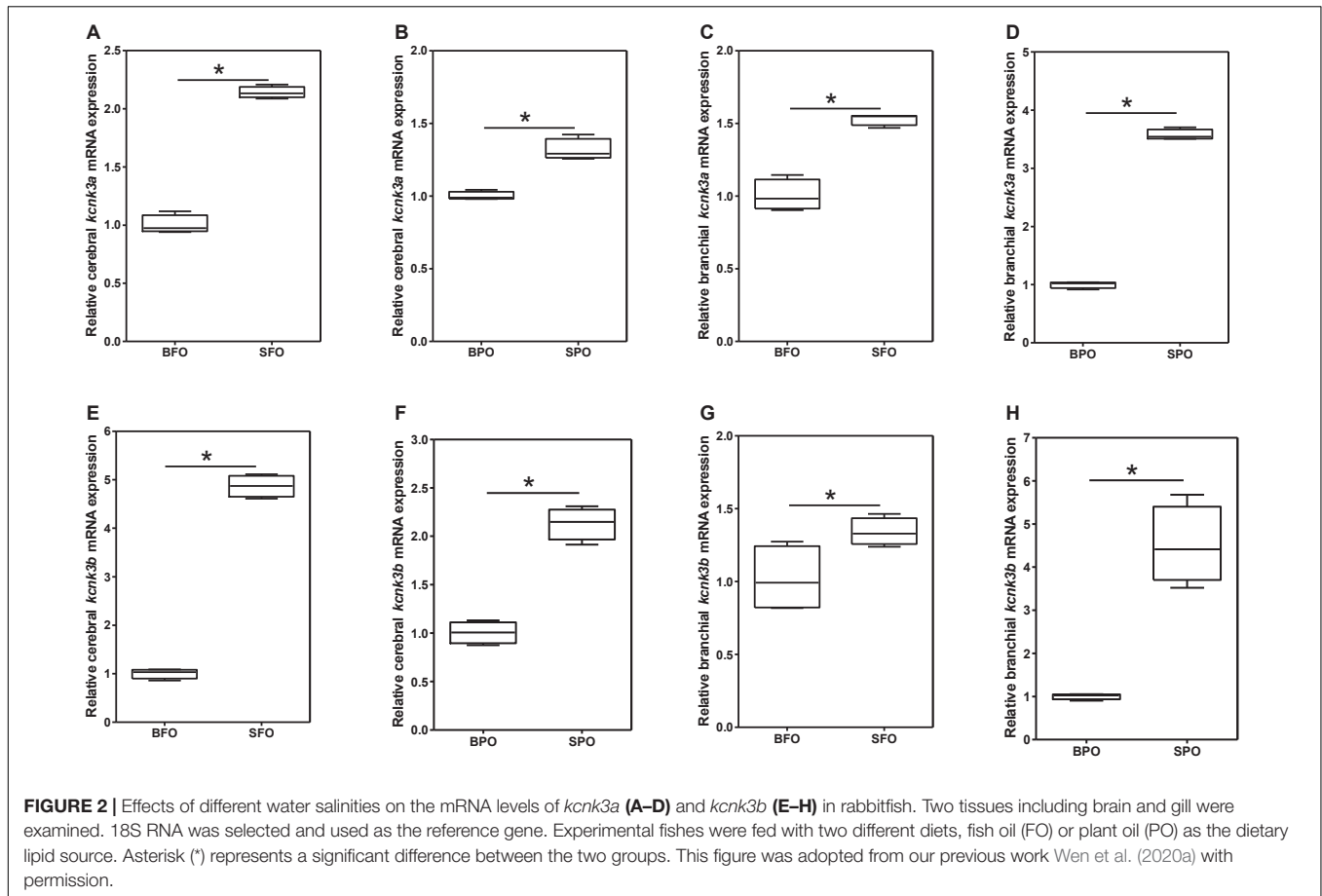
traits, KCNK3 has been proposed to mediate central as well as peripheral chemoreception, such as sensing O_2 and CO_2 in glomus cells (Mulkey et al., 2007) and smooth muscle cells of pulmonary arteries (Olschewski et al., 2006). Meanwhile, KCNK3 is also considered as a nutrient sensor for sensing glucose in hypothalamic orexin neurons (Burdakov et al., 2006). Simultaneously, KCNK3 plays important roles in adrenal gland development and aldosterone secretion (Czirjak et al., 2000; Czirjak and Enyedi, 2002), and mineralocorticoid hormone stimulates K^+ excretion and Na^+ reabsorption in the kidney, contributing to fluid volume and blood pressure control (Lesage and Barhanin, 2011). Additionally, one of the most important functions of KCNK3 is involved in regulation of neuronal excitability with pH variations by affecting ion channel activity (Linden et al., 2006; Lesage and Barhanin, 2011). Moreover, KCNK3 also plays critical roles in other physiological process, such as protecting brain against ischemia (Meuth et al., 2009), regulating thermogenesis through the mineralocorticoid receptor pathway (Pisani et al., 2016) and cAMP-PKA signaling (Chen et al., 2017).

Different with mammals, studies focusing on *kcnk3* are rarely reported in fishes. The fish KCNK3 channels were first identified and investigated in zebrafish (*Danio rerio*) in 2014 (Liang et al., 2014), but no further related results were reported in other fishes. Until recently, we systematically examined the functional properties of this channel in three representative fish species including freshwater carnivorous Northern snakehead (*Channa argus*) (Wen et al., 2019), euryhaline omnivorous Nile tilapia (*Oreochromis niloticus*) (Wen et al., 2020b) and marine herbivorous rabbitfish (*Siganus canaliculatus*) (Wen et al., 2020a). In this review, we are planning to summarize the gene copy number variation, tissue distribution pattern, phylogeny, and potential homeostasis regulation role of *kcnk3* genes in various fishes. Our works will not only provide novel insights into the functional properties of these fish KCNK3 channels, but also establish guidelines for related studies and applications in diverse fishes in the coming future.

Gene Copy Variations in Vertebrates

Thus far, only a single copy gene of KCNK3 was identified in mammals. However, two *kcnk3* paralogs were discovered in zebrafish, the first teleost that was reported to possess *kcnk3* gene (Liang et al., 2014). Consistently, our further studies showed that two *kcnk3* genes (*kcnk3a* and *kcnk3b*) were also existed in many other fishes such as Northern snakehead (Wen et al., 2019), Nile tilapia (Wen et al., 2020b) and rabbitfish (Wen et al., 2020a) by a comparative genomics strategy (Figure 1). These findings suggest that two copies of *kcnk3* genes might be widely existed in teleost, and this phenomenon may be caused by the specific whole genome duplication (WGD) event in teleost (Hughes et al., 2018; Xu et al., 2019; Wen et al., 2020c). Additionally, a more complex situation of the gene copy numbers may have occurred in cypriniformes and salmoniformes fishes (Figure 1), because of an additional WGD event in these two lineages (Lien et al., 2016; Xu et al., 2019). These gene copy variations of the *kcnk3s* implies that the functional properties of this channel could be also variable in various vertebrates, especially in the numerous fishes.





Tissue Distribution Traits in Vertebrates

In mammals, KCNK3 is primarily distributed in the CNS, but also expressed in certain periphery tissues and cells, such as heart, adrenal gland, glomus cells and smooth muscle cells of pulmonary arteries (Olschewski et al., 2006; Mulkey et al., 2007; Lesage and Barhanin, 2011). Similarly, both *kcnk3* paralogs were proved to be highly transcribed in the CNS and heart in zebrafish by combining whole-mount *in situ* hybridization and real-time quantitative PCR (Liang et al., 2014). Meanwhile, we observed that *kcnk3a* and *kcnk3b* showed a similar distributed pattern, and both genes were widely transcribed in Nile tilapia and rabbitfish with the highest transcription levels in heart (Wen et al., 2020a,b). However, *kcnk3a* was mainly transcribed in heart, while *kcnk3b* was highly expressed in gill, brain and kidney in Northern snakehead (Wen et al., 2019). These findings suggest that the distribution patterns of *kcnk3* genes are variable in various fishes, although we found a common trait that these channels are primarily expressed in the excitable tissues including CNS and heart. Meanwhile, the extensive distribution of *kcnk3* genes implies diverse functions of these channels in various fishes, which needs to be further explored with in-depth investigations.

Heart Rhythm Regulation Role in Fishes

Previous studies have shown that a variety of atrium-specific K^+ and Ca^{2+} channels are crucial in shaping the atrial action

potential in the heart, including $K_v1.5$, $K_{2p3.1}$ (KCNK3)/ $K_{2p9.1}$ (KCNK9), $K_{ir3.1}/K_{ir3.4}$, and $K_{Ca2.x}$ channels (Bertaso et al., 2002; Wettwer et al., 2004; Limberg et al., 2011; Schmitt et al., 2014; Skarsfeldt et al., 2016). In human, KCNK3 contributes to action potential repolarization and the resting membrane potential of atrial cardiomyocytes (Le Ribeuz et al., 2020). Knockdown of KCNK3 in human-induced pluripotent stem cell (iPSC)-derived cardiomyocytes results in a significant prolongation of action potential duration, suggesting that KCNK3 also contributes to action potential repolarization in human ventricular cardiomyocytes (Chai et al., 2017). Meanwhile, KCNK3-knockout mice showed a ventricular phenotype with prolonged QT interval, wide QRS, reduced heart rate variability (HRV) and increased ventricular action potential duration (Donner et al., 2011). Similarly, knockdown both *kcnk3a* and *kcnk3b* genes resulted in lower heart rate and higher atrial and ventricular diameters in zebrafish (Liang et al., 2014), indicating that inactivation of *kcnk3* may have diverse effects on atrial size and electrophysiological properties that can contribute to an arrhythmogenic substrate.

However, a recent study revealed that KCNK3/KCNK9 and $K_{Ca2.x}$ channels do not appear to be involved in regulation of the action potential in the zebrafish heart (Skarsfeldt et al., 2016). Despite the controversial results were obtained in zebrafish, the important roles of the KCNK3

channels in heart rhythm regulation should be noticed and more investigations are required to illustrate the detailed functions in both mammals and fishes.

Osmoregulation Roles in Fishes

Different from mammals, most fishes reside in various water environments and they must address the problem of ion-homeostasis between the body and the waters, especially for euryhaline fishes. As an important ion channel family, potassium channels may highly play potential roles in osmoregulation in fishes. Indeed, a previous transcriptomic study in Mozambique tilapia (*Oreochromis mossambicus*) revealed that *kcnk3s* could be involved in osmoregulation (Lam et al., 2014). In order to validate this speculation, we explored the potential osmoregulation roles of both *kcnk3a* and *kcnk3b* genes in euryhaline Nile tilapia and marine rabbitfish (Wen et al., 2020a,b). In tilapia, both *kcnk3* genes in the gill were proved to have a similar transcriptional change pattern in response to two-week acclimation in various salinity of seawater (0, 5, 10, and 20 psu) with the lowest transcription levels in 10 psu (Wen et al., 2020b), implying that these two channels might be involved in osmoregulation. Meanwhile, three putative transcription factors (TF) including *arid3a*, *arid3b*, and *arid5a* exhibited a similar transcription pattern with the two *kcnk3* genes, implying their positive regulatory roles in osmoregulation by targeting these two *kcnk3* genes (Wen et al., 2020b). Consistently, our further study in rabbitfish showed that both *kcnk3* genes had higher transcription levels in sweater in comparison with that in brackish water (Figure 2), which further confirmed that these two channels are involved in osmoregulation in fishes (Wen et al., 2020a). However, the exactly regulated mechanisms are still unknown, which are required for further investigation.

Energy Homeostasis Maintenance Role in Fishes

In mammals, hypothalamic orexin neurons are able to sense extracellular glucose concentration to trigger adaptive responses in response to low body energy level, including wakefulness and food-seeking behavior, by inhibiting a background K^+ current that can promote depolarization and enhanced excitability (Burdakov et al., 2006; Burdakov and Lesage, 2010). This phenomenon suggests that *kcnk3* may play important roles in nutrients and energy homeostasis regulation in vertebrates. However, no related reports were provided in fishes. In order to explore the potential regulatory role of *kcnk3* in energy homeostasis maintenance, we examined the transcription patterns of both *kcnk3a* and *kcnk3b* genes in response to different feeding status in Northern snakehead (Wen et al., 2020a). Our results showed that two *kcnk3* genes in the brain presented totally opposite change patterns in response to both short- (24 h) and long-term (2 weeks) food deprivations, implying that both snakehead *kcnk3a* and *kcnk3b* might form a negative feedback control during the physiological process of appetite regulation, and the former potentially serves as an orexigenic factor while the latter may play as an anorexigenic factor. Anyway, our findings indicate that the two *kcnk3* genes in the snakehead fish

might function differentially, while with cooperation, in appetite regulation and energy homeostasis maintenance.

Long Chain Polyunsaturated Fatty Acids Metabolism Regulation in Fishes

K_{2P} channels have been regarded as important biochemical and medical sensors since they are sensitive to natural and chemical effectors, such as extracellular acidification (Duprat et al., 1997), volatile anesthetics (Patel et al., 1999; Talley and Bayliss, 2002), hypoxia (Kemp et al., 2004), and long chain polyunsaturated fatty acids (LC-PUFA) (Felicciangeli et al., 2015). Several previous studies have shown that LC-PUFA can induce activation of the K_{2P} channels, such as TREK1 (Fink et al., 1998), TREK2 (Bang et al., 2000), and TRAAK1 (Lesage et al., 2000). However, whether *kcnk3* is sensitive to LC-PUFA has not yet well studied. Our research in rabbitfish showed that fishes fed diets with fish oil as dietary lipid (rich in LC-PUFA) induced higher mRNA levels of the two *kcnk3* genes in comparison with those in fishes fed with plant oil diet (lack of LC-PUFA) at two different salinity environments (32 and 15‰), suggesting that LC-PUFA also can stimulate the activation of the KCNK3 channels, and thus these channels may play important roles in LC-PUFA metabolism regulation in various vertebrates, including fishes. However, more studies are required to explore the exact mechanisms of this phenomenon.

CONCLUSION

The KCNK3 potassium channels are crucial for many biological processes. Although the structural and functional properties of KCNK3s have been well investigated in mammals, the genetic variations and functional traits of the counterparts are still rarely known in fishes. A previous study revealed that two *kcnk3* genes are existed in zebrafish and they may play important roles in heart beating. Our further works on three representative fishes with different environments and feeding habits showed that two *kcnk3* paralogs (*kcnk3a* and *kcnk3b*) are widely existed in diverse fish species, and these two channels are involved in heart rhythm regulation, osmoregulation, energy homeostasis maintenance, and LC-PUFA metabolism regulation. However, extensive distribution of the two channels in various fishes implies that they may play important roles in different tissues. Therefore, more in-depth studies are required to further investigate the genetic and functional traits of these channels, which can be selected as potential targets for molecular breeding in practical fish industry, such as developing new variants that can survive healthily in broader salinity environments.

AUTHOR CONTRIBUTIONS

Z-YW and QS conceived the project. Z-YW wrote the manuscript. C-JQ, Y-YL, Y-PL, Y-CZ, and S-TG provided assistance in the manuscript preparation. QS revised the manuscript. All authors contributed to the article and approved the submitted version.

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