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REVIEW DERLEME

Fish derived bio-active peptides and their metabolic effects

Balık kaynaklı biyo-aktif peptidler ve metabolik etkileri

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Özet: Diğer tüm organizmalar gibi, balıklar da, araştırmalarda antimikrobiyal, antihipertensif, antioksidan ve antitümör aktivitelerine odaklanılan bio-aktif bileşiklerin zengin kaynağıdırlar. Bunlar, sadece yüksek besin değeri nedeniyle değil, özellikle son yirmi yılda geliştirilen analitik yöntemlerle elde edilen peptidleri açısından da kullanılabilirler. Akuatik canlılar dünya üzerinde en fazla tür sayısına sahiptir, dolayısıyla bunlardan bio-aktif peptidlerin eldesi diğerlerine göre oldukça olasıdır ve bu, önceki çalışmalarda açıkça ortaya konmuştur. Doğal peptidler ve uzun zincirli polipeptidlerden uygun enzimatik yöntemlerle elde edilen peptidler tıp alanında yeni ufuklar açabilirler.

Anahtar kelimeler: *Balık, peptidler, bio-aktif, metabolik etki, sağlık*

Abstract: Like many other organisms, fishes are also rich sources of bio-active compounds which were well studied by research focused on their antimicrobial, antihypertensive, antioxidant and antitumor activities. They can be used not only for good nutritional value, but also for peptides obtained with analytic processes that were developed in last decades. Aquatic organisms total the highest number of species in world, therefore discovering bio-active peptides in them is more possible than in others, which was clearly shown in previous studies. Abundance of native and obtained peptides from long chain polypeptides with proper enzymatic methods may open new horizons for medical research.

Keywords: *Fish, peptides, bio-active, metabolic effect, health*

INTRODUCTION

In last decades many high-cost, time consuming studies were focused on fish derived peptides, their metabolisms and physiological effects on human health. They can be isolated from various foods like soy bean, milk and fish. Peptides are inactivated in main protein blocks till they are separated by enzymatic process and act as hormones in organisms. Bio-active peptides have gained importance with their potential for disease prevention and complex metabolic effects. Urotensin 1-2-3, adrenomedullin, melanin-concentrating hormone (MCH), piscidin and other novel peptides were obtained from various fish species. They, their receptors and human homologues are being investigated in last decade for human health topics for cancer, diabetes, hypertension, obesity, psychological and cardiovascular diseases. In this review, recent studies were presented about fish derived bio-active peptides, their human homologues and possible future targets which may develop new therapies for diseases, discussed. Definitely too many peptides are involved in metabolic processes. Hydrolysis is main procedure to obtain bio-active peptides from polypeptides with steps included hydrolysis, determining metabolic effects, purification, size separation, MS detection and sequencing of smaller than 10 kDa (Ryan et al., 2011). According to Takahashi and Kawauchi (2004), fish peptides have important impacts on human physiology like appetite control, circulation, cell differentiation and on metabolic pathologies included cancer, metabolic syndrome and cardiovascular problems. They asked related question as 'if all living things began in water?' and stated that more studies should be carried out on his road to clarify relationships of these peptides with diseases to develop more effective therapies.

Melanine-Concentrating Hormone (MCH)

MCH is a regulating hormone for skin color of teleost fishes. It also can be found in mammalians central nervous system as a cyclic neuropeptide which has roles in complex network of stress-regulating system and appetite stimulating (Kawauchi et

al., 1983; Flier, 2004; Takahashi et al. 2004). Takahashi et al.(2004) have reported salmon and human MCH sequencing (Fig.1). MCH is stimulator on food intake, may cause to obesity. Moreover, its role on homeostatis and brain activity was shown (Shi, 2004).

By binding to seven membrane receptors, neuropeptide MCH mediate its functions as neurotransmitter and regulator on food intake in mammals (Kawauchi, 2006). Matsuda et al. (2006) have reported that their results suggest that MCH influences feeding behavior, but not spontaneous locomotor activity, in the goldfish, and may exert an anorexigenic action in the goldfish brain, unlike its orexigenic action in mammals.

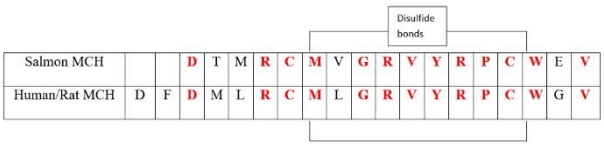

Figure 1. Aminoacid (AA) sequences of human and fish MCH (Takahashi, 2004)

Epinecidin

An antimicrobial fish peptide Epinecidin-1 has also an antitumor effect in human fibrosarcoma cells. Effects of epinecidin-1 on cell membranes of tumor cells were shown (Lin et al. 2009; Hoskin and Ramamoorthy, 2008). 21 AA contained (GFIFHIIKGLFHAGKMIHGLV) peptide epinecidin-1 (Rajanbabu and Chen, 2011) was evaluated by various study and researches for its spesifications mentioned above. Fish can regulate their defense system while cytokine expressions, bacterial infection consequences and protect them from death by injection of epinecidin-1 peptide just before inoculation of *V.vulnificus* according to Pan et al. (2007). Same infection were prevented in grouper (*Epinephelus coioides*) and zebrafish (*Danio rerio*) by epinecidin-1, reported Pan et al. (2012).

Adrenomedullin (AM)

Adrenomedullin is a member of Calcitonin Gene Related Peptide (CGRP) family. Five paralogues of AM are identified in teleost fishes (Fig 2a). One of these, AM2, may be more advantageous than AM to respond quickly to changes in blood flow and oxygen content in the coronary artery. If this is actually the case, then AM2 can be used as a diagnostic marker for the initial stage of ischemic heart failure (Fig 2b) (Takei et al., 2004a). Comparative genomic analyses concluded that mammalian AM2 is an ortholog of pufferfish AM2 (Takei et al., 2004b).

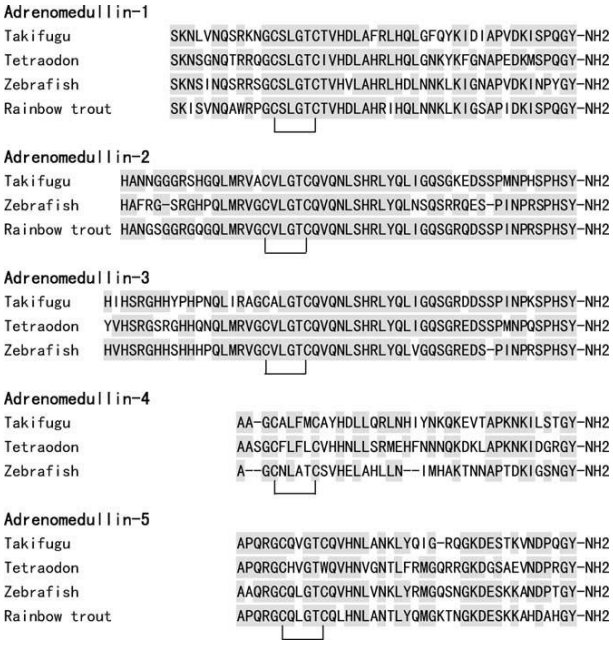

Figure 2a. Amino acid sequences of five putative mature peptides of the adrenomedullin (AM) family identified in teleost fish (Takei et al., 2004a)

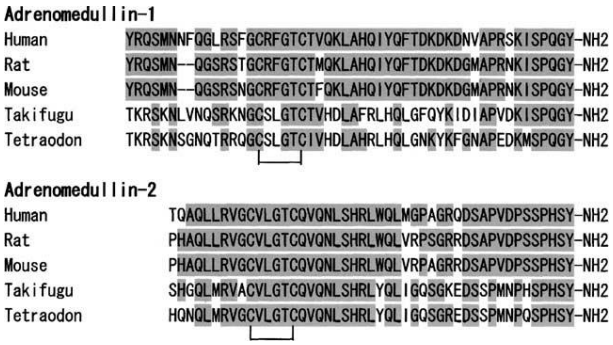

Figure 2b. Amino acid sequences of adrenomedullin (AM) 1 and 2 in human, rat, mouse and two species of pufferfish (*Takifugu rubripes* and *Tetraodon nigroviridis*) (Takei et al., 2004a)

Ghrelin

Ghrelin was isolated from goldfish and it is naturally secreted by stomach and hypothalamic neurons now recognized as a multifunctional peptide for human feeding, cardiovascular and pshycological metabolisms (Currie et al., 2008; Miura et al., 2009). Ghrelin has also electrophysiological effects on pedunculopontine tegmental neurons in rats (Kim et al., 2009).

Unniappan and Peter (2005) have indicated about ghrelin functions on fish as regulator of food intake, growth hormone production, reproduction and other physiological metabolisms as well as in mammals similar pathways and still need to be researched for endocrinology database to better understanding. According to Kang et al. (2011) stated about differencies in metabolism of ghrelin on same or different teleost fishes like energy intake, locomotor mechanisms and fat deposition. Further studies to be needed about effects on homeostatic function.

Urotensin

Urotensin 1 was first isolated in pure form from an extract of urophyes of the white sucker (*Catostomus commersoni*). Its human homologues urocortins (UCNs) produces a hypotensive response, acts as a mediator of the effects of stress on food intake and may play protective roles against cardiovascular stress (Conlon, 2000; Inada et al., 2009). Urotensin 2 is a cyclic peptide also isolated from fish and expressed in some tumor cells, and stimulates proliferation of them (Takahashi et al., 2004). UCNs have also functions in energy, gastrointestinal, immune, reproductive systems and hearing (Fekete and Zorilla, 2007).

Hepcidin

Hepcidin is well known peptide that has roles in iron metabolism and defense mechanism against bacterial infections (Rodrigues et al., 2006). Chen et al. (2009) have indicated that Tilapia hepcidin (TH2-3) may be promising candidate for treatment of cancer with its cytotoxic effects on destructive impact on membranes of cancer cells and downregulation of apoptosis gene expression, blocking invasion to prevent metastasis, especially on human fibrocarcinoma cells (Chen et al, 2009). Rodrigues et al. (2006) have detected 8 copies of hepcidin gene in sea bass genome and determined its functions on iron regulation and infection response.

Piscidin

Piscidins are one of the elements in antiviral defence system of fish. They can also act like antibiotics and help fighting viruses in human body. Peptide antibiotics, host-produced antimicrobial defenses that have been isolated from all types of organisms, from plants to mammals, possess a number of characteristics that make them attractive drug candidates. An example of the diversity and potential for new discoveries in this area is a novel family of peptide antibiotics named "piscidins," which have been recently isolated from fish. Piscidins have potent, broad-spectrum *in vitro* activity against many pathogens, including multidrug-resistant bacteria (Noga and Silphaduang, 2003). Sung et al. (2008) have stated that piscidin 1 (P1) has more effective in fungicidal and hemolytic activities than piscidin 3 (P3), in addition, P1 also have higher ability to permeabilize phospholipids membranes where action of peptides performed. Antimicrobial effects of P1 and P3 by minimum concentration were summarized at Table1 (Chekmenev et al, 2006).

Table 1. Minimum inhibitory concentration of P1 and P3 on microorganisms. (Chekmenev et al., 2006)

Microorganism	P1-MIC (μM)	P-3-MIC (μM)
Gram (+) *Staphylococcus aureus* *Bacillus cereus*	 0-2 0-2	 0-2 2-10
Gram (-) *Escherichia coli* *Proteus vulgaris*	 2-10 2-10	 10-20 2-10

Calcitonin (CT)

Calcitonin is a member of CGRP (Calcitonin Gene-Related Peptides) superfamily like amylin, adrenomedullins and CRSPs (Calcitonin receptor-stimulating peptides). Calcitonin, a 32 aa peptide, was initially isolated from fish. Fish CT has higher affinity to mammalian CT receptor (CTR), and has activity on calcium homeostatis. Therefore, fish CT has been used as a drug for treatment of human bone diseases (Nag et al, 2007). Pufferfish and mammalian CTR genes have miR-489 coding region in intron 3. Although the function of miR-489 has not been clarified yet. Its expression was detected in brain and eye (Kloosterman et al., 2006). Its suggesting role in nervous system (Nag et al, 2007).

MCH (Melanin Concentrating Hormone) stimulates apetit which leads to obesity may cause diabetes mellitus which prevented by U-II (Urotensin II) that also has cardiovascular control and inhibiting effect on tumoral cell growth. Possible relations, interactions of fish derived peptides to human physiology and diseases with other mechanisms were shown at Fig 3 (Takahashi, 2004).

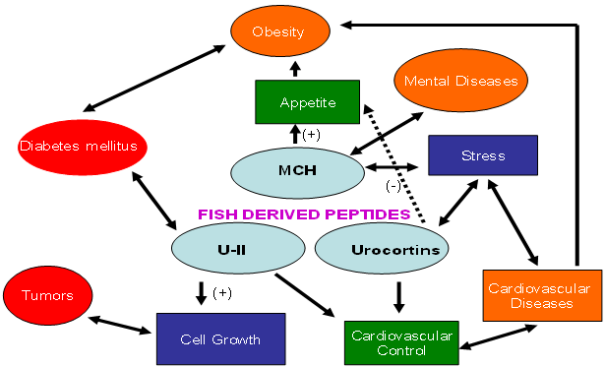

Figure 3. Possible relations, interactions of fish derived peptides and related metabolic processes (Takahashi, 2004)

Novel Peptides

The *in vitro* colony formation activity of established human tumor cells (HT-29: Colon cancer cells, MDA-MB-231: Breast cancer cells) is greatly reduced or diminished by treatment with rtEa-4, one of trout pro-IGF-I E-peptides. The invasive activity of HT1080 (invasive cancer line cells) is reduced three to fourfold by treatment with the same peptide (Chen et al., 2002).

The peptide MY isolated from sardine, stimulates antioxidant protein HO-1 (heme oxygenase) activity (Erdmann et al., 2006).

18 fish protein hydrolysates from Atlantic salmon (*Salmo salar*), Atlantic cod (*Gadus morhua*), plaice (*Pleuronectes platessa*), bluewhiting (*Micromesistius poutassou*), Atlantic emperor (*Lethrinus atlanticus*), pollack (*Pollachius pollachius*) and Portuguese dogfish or siki (*Centroscymnus coelolepis*) were measured on 2 human breast cancer lines grown in vitro. They were identified as significant growth inhibitors on the two cancer lines (Picot et al., 2006).

The fish muscle hydrolysate of 300-700 Da molecular weight showed high ACE (Angiotensin Converting Enzyme) inhibitory

(regulation of blood pressure) and radical scavenging activity. Coho salmon is the most effective sample to obtain bio-active compounds (Nakajima et al., 2009)

Protein hydrolysate from blue whiting (*Micromesistius poutassou*) by-product, stimulates CCK (Cholecystokinin) secretion in the STC-1 (intestinal edocrine cells) and appetite-suppressive effect to control the body weight (Cudennec et al., 2008).

The acidic mucus extracts of brook trout, haddock and hagfish showed antibacterial activity against a wide range of fish and human pathogens (Subramanian et al., 2008).

Oral administration of fish protein concentrates (FPC) enhances gut-associated non-specific immunity without an inflammatory outcome and that this effect would be induced by the products appeared during the fermentation process. FPC is an immunomodulating food with a demonstrated capacity to enhance non-specific host defence mechanism (Duarte et al., 2006)

With the hydrolysate obtained from fresh sample, the bioactive molecules around 1850 Da also interacted with the CGRP receptor in rat liver membranes. We can conclude they are structurally very similar to human CGRP. The obtained molecules (gastrin/CCK-and- CGRP-like peptides) could make the cod hydrolysates useful for incorporation in functional foods (Slizyte et al., 2009).

Song et al. (2012) have discovered peptides (MLTTPPHAKYVLQW, LRSKAAAPAEQYE, TPGALLEHPTL, SHAATKAPPKNGNY, LATVSVGAVELCY, PTAGVANALQHA, QLGTHSAQPVPF, VNVDERWRKL, NPEFLASGDHLDNLQ, PEVVYECLHW) from half-fin anchovy (*Setipinna taty*) and reported that pepsin hydrolysate of the marine fish half-fin anchovy contained antibacterial peptide fractions. HAHp2-3-I, an antibacterial peptide fraction whose molecular weight ranges from 1,100 to 1,700 Da was isolated and characterized. Peptides sequences prediction showed that HAHp2-3-I contained net charged peptides, which could form extended strands, random coils and alpha helix structures. HAHp2-3-I might exert its antibacterial activity via a membrane disruptive model in the “carpet” model way.

Kumanesan et al. (2015) have reported that a novel antimicrobial peptide had been derived from goose type lysozyme (LyzG) which was identified from the cDNA library of freshwater fish *Channa striatus* (Cs). The identified lysozyme cDNA contains 585 nucleotides which encodes a protein of 194 amino acids.

Sila et al. (2014), evaluated the mode of action of new peptides (Gly-Val-His, Trp-His-Arg, Trp-His-Phe, Pro-Pro-Ser-Ser, Ala-Ala-Ala-Leu, Ala-Ala-Gly-Gly-Val, Ala-Ala-Val-Lys-Met, Ala-Ser-Ser-Ser), previously characterized, from barbel (*Barbus callensis*) protein hydrolysates against *Listeria monocytogenes* via a membrane damage mechanism. Prediction of peptide secondary structure indicated that these peptides should have random coil structures and high content of hydrophobic amino acids (Table 2).

Table 2. Antibacterial activity of synthetic peptides (1mg/1ml) (Sila et al., 2014)

Peptide	MW (Da)	Inhibitory Effects on Microorganisms					
		Bacillus cereus	*Staphylococcus aureus*	*Enterobacter sp.*	*Escherichia coli*	*Listeria monocytogenes*	*Micrococcus luteus*
GVH	275	-	-	-	-	-	-
WHR	433	+++	-	-	-	-	++
WHF	452	++	-	-	-	+	+++
PPSS	350	-	+	+	+	-	++
AAAL	308	++	-	+	+	+	++
AAGGV	337	+++	+++	++	++	+++	+++
AAVLM	482	++	++	+	+	+++	+++
ASSS	314	+	-	++	++	+	++

Àlvarez et al (2014) have reported on antimicrobial activity of trout hepcidin and stated that peptide showed an alfa-helix conformation in reduced state and the characteristic beta-sheet conformation in the oxidized state. Antimicrobial activity assays showed that the oxidized peptide is more effective than the reduced peptide against *Escherichia coli* and the important salmon fish pathogen *Piscirickettsia salmonis*.

Valero et al. (2015) have reported that they characterized the antimicrobial response triggered by nodavirus (VNNV) in the testis of European sea bass (*Dicentrarchus labrax*), a very susceptible species of the virus, and in the gilthead seabream, which acts as a reservoir, both in vivo and in vitro, and compared with that present in the serum and brain (target tissue of VNNV). First, their data show a great antiviral

response in the brain of gilthead seabream and in the gonad of European sea bass. In addition, for the first time, their results demonstrate that the antimicrobial activities (complement, lysozyme and bactericidal) and the expression of AMP genes such as complement factor 3, lysozyme, hepcidin, dicentracin, piscidin or b-defensin in the gonad of both species are very different, but generally activated in the European sea bass.

Wang et al. (2015), characterized the gene structure and expression of MHC class II (Lunar-DAA) and II (Lunar-DAB) of mangrove red snapper (*Lutjanus argentimaculatus*). Both genes shared, respectively, a high similarity and typical features with other vertebrate MHC class II α and II β. The phylogenetic analysis of the deduced peptides revealed that both Lunar-DAA and Lunar-DAB were located in the teleost subclass. Western blotting analyses indicated that both MHC class II α and II β were expressed ubiquitously in immune-related cells, tissues and organs, and that MHC class II α and II β chains existed mainly as heterodimers. While it was highly expressed in gills, thymus, head kidney (HK), spleen, head kidney macrophage and spleen leucocytes, MHC class II β chain was expressed with a low abundance in skin, intestine, stomach and heart.

Lassoued et al. (2015) have used Neutrase and Alcalase to obtaine thornback ray (*Raja clavata*) muscle hydrolysates (TRMH). They have reported that TRMH-Neutrase exhibited the highest antioxidant activity in DPPH (2,2-diphenyl-1-picrylhydrazyl) scavenging, reducing power and inhibition of β-carotene bleaching tests. However, in the total antioxidative efficacy, TRMH-Crude exhibited the highest activity. TRMH-Crude and TRMH-Neutrase were the most potent to prevent DNA oxidation by Fenton reagent. Concerning anti-ACE activity, TRMH-A26 and TRMH Neutrase exhibited the highest activity with 87% at 5mg/ml.

Liu et al. (2014) have reported comprehensive analysis and characterization of LEAP-2 gene from miiuy croaker (*Miichthys miiuy*). In their study, cDNA of miiuy croaker was completely analysed and determined LEAP-2 gene as 2360 bp, contained 170 bp at 5'terminal untranslated region (UTR), an part of open reading frame (ORF) of 312 bp, 1878 bp at 3' terminal (UTR).

LEAP-2 of this fish has shown anti-microbial activity on *Aeromonas hydrophila*. Moreover, with evolutionary analysis to predict selective constraints. It was determined that no positive selection detected for sequences of LEAP-2 gene.

Chalamaiah et al. (2015) have use eggs of common carp (*Cyprinus carpio*) to obtain hydrolysates by using pepsin, trypsin and Alcalase. Its determined that all hydrolysates significantly boosted proliferation of spleen lymphocytes where pepsin hydrolysate (0.5 g/kg body weight) has significant impact on increasing the cytotoxicity of splenic killer cells and IgA too. Alcalase hydrolysate enhanced the percentage of CD4+ and CD8+ cells in spleen.

Henda et al. (2015) have investigated effects of previously known peptides on proliferation, differentiation and maturation of human white pre-adipocytes. They indicated that adipocytes can be affected in different stages of their life cycle by some marine peptides but this is not correlated with their inhibiting ability on ACE (Angiotensin Converting Enzyme). (Leu-Lys-Pro) and (Val-Tyr) have high ACE inhibiting capability but no proliferation or differentiation effect on adipocyte cells. Inhibition of preadipocytes growth could be induced during proliferation by three peptides sequenced as (Ala-Pro), (Val-Ala-Pro) and (Ala-Lys-Lys). In other stage; differentiation, number of preadipocytes may decreased by two peptides as (Lys-Trp-Trp) and (Val-Trp). By restriction of factors for adipocyte specific transcription, (Gly-Pro-Leu) or (Ile-Tyr) could inhibite adipogenesis.

Azuma et al. (2014) have extracted fish scale collagen peptide and investigated its anti-inflammatory effects in the dextran sulfate sodium induced acute ulcerative colitis model and stated that their results indicate that fish scale collagen peptides could be a new functional food for patients with inflammatory bowel disease.

Fe(II)-binding activity ability of fish scale collagen peptides were detected by Huang et al. (2015) as primary study on this concept, also indicated that scales could be proper source for fish collagen.

Salampessy et al. (2015) have produced three bioactive peptides from hydrolyzation of trevally (*Pseudocaranx* sp.), investigated their ACE-Inhibitory effects and stated that fractionation with RP-HPLC gave three most active peptide fractions labelled as TBS1, TBS2, and TBI2 which showed high potential as ACE-inhibitory agents. Sequences of active peptides were detected as

AR, AV, and APER, with molecular weights of 245.28, 188.23, and 471.51 Da, respectively. Their stability in gut were shown by simulated gastrointestinal enzyme degradation.

Ennaas et al (2015) have obtained four bioactive peptides from Atlantic mackerel (*Scomber scombrus*) hydrolizate, that sequenced as SIFIQRFTT (P4), RKSGDPLGR (P8.1), AKPGDGAGSGPR (P8.2) and GLPGPLGPAGPK (P11). They reported that P8.1, P8.2 and P11 exhibited partial inhibition, P4 totally inhibited tested Gram-positive (*Listeria innocua*) and Gram-negative (*Escherichia coli*) bacterial strains.

García-Moreno et al (2015) have identified 14 novel ACE-inhibitory peptides in horse mackerel and small-spotted catshark hydrolysates. The peptide VAMPF, identified in fraction D of smallspotted catshark hydrolysate, is evaluated as one of the most promising peptides.

CONCLUSION

Fish derived bio-active peptides are gaining importance among all scientific community that related human health like pharmacy, biochemistry and medicine. Their high nutraceutical, pharmaceutical and disease prevention potentials may make possible to produce products in food industry like nourishment

support and in medicine like vaccines. New modelling concepts on the way with developing techniques to solve their structures and creating artificial active forms of polypeptide subunits as mimicked oligopeptides and peptides. It's clearly that humankind could find solutions for pathologies in nature by completing billion pieces puzzle where bio-active peptides takes leading roles as big part by future visions with sophisticated methods and devices.

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