**Is retinoic acid a functional hormone in crustaceans?**

**what is known and what is to be known**

**Abstract**

Vitamin A metabolism and its biological role in vertebrates is well studied. Comparatively less understood, there is an increasing recognition of retinoic acid signalling in invertebrates including crustaceans. The presence of retinoids and some of their functional aspects in the biological framework of crustaceans have been demonstrated. This review aims at giving a comprehensive overview of the retinoid system and various physiological events such as glucose homeostasis, regulation of reproduction, and limb regeneration regulated by retinoic acid. Finally, perspectives on current and possible research are offered.

**Key Words**: Crustaceans, retinoids, reproduction and hormones

**Introduction**

Vitamin A also known as retinol (ROL) is one of the important nutrient factors associated with proper development of an organism starting from embryonic period (Menezes and Almeido, 2024). A wealth of studies till date focused on the retrospective, perspective and prospective facets of retinoid system in biological framework of vertebrates and we cite a few of the major ones here, just as an entry point (Theodosiou et al., 2010; Al Tanoury et al., 2013; Andre et al., 2014; Hammerling et al., 2016; Canete et al., 2017; Das et al., 2019; George, 2019; Wołoszynowska-Fraser et al., 2020; Yee et al., 2021; Niranjana and Supriya, 2024). The role of retinoid signalling in the regulation of biological processes, such as differentiation, embryogenesis, cellular proliferation, apoptosis, normal vision, induction of neural differentiation, motor axon outgrowth and neural patterning, immune based functions, regulation of carbohydrate and lipid metabolism, reproduction and fertility is well appreciated in vertebrates (Maden and Hind, 2003; Md Noh et al., 2019; Carazo et al., 2021; Kim et al., 2021; Gudos, 2022; Chen et al., 2023; Menezes and Almeido, 2024). In animals, vitamin A is not synthesized *de novo* and relies exclusively upon ROL, retinyl esters (REs) and pro-vitamin A (mainly beta-carotene) dietary sources (Theodosiou et al., 2010). As retinoid system and its signalling are key in the regulation of various physiological events, retinoid homeostasis is instrumental. This is accomplished by a cascade of enzymes and proteins that mediate metabolic and signaling pathways of retinoids (Theodosiou et al., 2010) (Fig. 1). Depending on the homeostatic requirements of retinoids, ROL can undergo a) oxidation to form retinoic acid (RA), the biological active metabolite or b) esterification to form retinyl esters (REs) for storage (Theodosiou et al., 2010). Finally, oxidation of RA leads to its inactivation (Theodosiou et al., 2010). The retinoid system is well understood in chordates as compared to the basal metazoans. Thanks to advanced molecular and analytical techniques that paved a way to the discovery of retinoid system counterparts in basal metazoans also.

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**Figure 1**: Schematic representation of key players involved in synthesis, transport, catabolism and signaling of retinoids

**Synthesis:** β,β-carotene1058 15,15’-monooxygenase (BCO-I), β,β-carotene 9-10’-dioxygenase (BCO-II), alcohol dehydrogenases (ADHs), short-chain dehydrogenases/reductases (SDRs), retinaldehyde dehydrogenase (ALDH). **Storage and mobilization:** lecithin:retinol acyltransferase (LRAT), acyl-CoA:retinol acyltransferase (ARAT), acetyl-CoA-retinol acyltransferase (DGAT1), retinyl ester hydrolases (REHs). **Catabolism:** cytochrome P450 family 26 (CYP26). **Transport:** Stimulated retinoic acid protein 6 receptor (STRA6), transthyretin (TTR), retinol binding protein (RBP), cellular retinoic acid binding protein (CRABP), and cellular retinol binding protein (CRBP). **Genomic actions:** Retinoic acid receptors; Retinoic acid receptor (RAR) and retinoic acid X receptor (RXR).

Now it is clear that the retinoid system and its signalling mechanisms also exists in basal metazoans like non-chordate invertebrates and protostomes (Albalat and Cañestro, 2009; Cañestro et al., 2006; Theodosiou et al., 2010; Gesto et al., 2012; 2013). Even though the retinoid system and the physiological significance of retinoids is not yet been fully characterized in invertebrates, some functions are evolutionary conserved and thus could be susceptible targets for endocrine disrupting chemicals (Gesto et al., 2013; Lima et al., 2011; Theodosiou et al., 2010; Andre et al., 2014).

The central objective of this review is to provide insights into the retinoid system of crustaceans (ecdysozoan group and phylum arthropoda) which occupy a strategic position as one of the key elements of food sectors like fisheries. Considering the facts that a) one of the remarkable features of crustaceans is the accumulation of carotenoids during ovarian development wherein the colour of the ovary changes as the animal progress from immature stage to mature stage, b) vitamin A and carotenoids are used as feed additives and given to crustaceans and c) several studies in crustaceans revealed the occurrence of vitamin A metabolites, and its signalling cascade, understanding retinoid system will definitely provide meaningful insights into the utilization of vitamin A as a tool to sustain crustacean aquaculture industry.

Based on the literature available on retinoids in crustaceans, this review presents three major aspects. First aspect deals with biochemistry of retinoid signalling in crustaceans based on the vertebrate background. Second, appreciating the significance of retinoid signalling in crustaceans can be greatly enhanced by integrating our work on crustaceans with other invertebrates and vertebrates. Finally, perspectives on current and possible future research are offered.

**Vitamin A: biotransformation, transport proteins and retinoid receptors**

Retinoids are primarily derived from the dietary intake of carotenoids found in plant pigments, such as ß-carotene, and retinyl esters (RE) found in animal sources such as fish liver oils, eggs, milk, and butter. The retinoid system can be broadly viewed by considering three components in general: synthesis, storage and signalling aspects of retinoids. To gain insights into the crustacean retinoid system, a brief background of vertebrate retinoid system and it’s signaling cascade is presented here. For a detailed account on the subject please refer to Theodosiou et al. (2010) and Andre et al. (2014).

Following ingestion, intestinal mucosal enzymes hydrolyse retinyl esters (REs) to ROL, whereas carotenoids are cleaved into retinal (RAL) and then reduced to ROL or oxidised to retinoic acid (RA). Retinol homeostasis is tightly regulated and as a result, much of the ROL synthesised is converted back into REs for storage in hepatocytes and stellate cells in the liver. These esters are cleaved and released into the bloodstream as ROL when needed (Marill et al., 2003; Ambrosio et al., 2011). Two enzymes viz., retinol ester hydroxylases (REHs) and ß-carotene 15,15-oxygenase 1 (BCO1) play a key role in the hydroxylation of REs to ROL and symmetrical cleavage of beta carotene to RAL and its subsequent conversion to ROL, respectively. The later cleavage pathway which was discovered in zebrafish (Andre et al., 2014). This pathway, thought to have originated from early chordates and is primarily found in marine fishes, wherein retinaldehyde and carotenoids from the yolk of the egg serve as the body main sources of retinoids during development (Lampert et al., 2003). Depending on the homeostatic requirements, ROL can undergo either esterification in the form of REs to promote retinoid storage and/or converted into retinal (RAL) and retinoic acid (RA), a biologically active metabolite. With regards to storage of retinoids, liver acts as the storage organ for retinoids. During storage of retinoids, transport proteins viz., cellular retinol binding proteins I and II (CRBP1 and II) plays a key role in the transport of ROL to target tissues such as liver. ROL in the enterocytes binds with CRBPII and re-esterified to REs by lecithin:retinol acyltransferase (LRAT) before its secretion into the lymph and circulating REs are transported to the liver for storage. In the hepatocytes, hydroxylation of REs to ROL occurs and binds to CRBPI which in turn transported to hepatic stellate cells. ROL is esterified by LRAT thereby its storage in liver. On the other hand, to sustain retinoid levels during inadequate levels of vitamin A, REs stored in the liver are mobilized and converted into ROL by REHs and binds retinol-binding protein 4 (RBP4) before its release into the circulation. Transthyretin, an evolutionary conserved protein is strategic to prevent the excretion of ROL-RBP4 complex. At the peripheral tissues, a transmembrane receptor known as stimulated by retinoic acid 6 receptor (STRA6) facilitates the ROL cellular uptake followed by its conversion into RAL. This step is mediated by two enzyme family members *viz*., the cytosolic alcohol dehydrogenases belonging to the medium-chain dehydrogenase/reductases family and the microsomal retinol dehydrogenases included in the short-chain dehydrogenases/reductases family (Pares et al., 2008), while RAL oxidation occurs via retinaldehyde dehydrogenases (Niederreither and Dolle, 2008; Theodosiou et al., 2010). Alternatively, ROL and RA can also result from symmetrical and asymmetrical cleavage of β-carotene by β,β carotene 15̍-15̍ monooxygenase and β,β carotene 9̍-10̍ monooxygenase, respectively. Accordingly, different isoforms of RA have been discovered such as all-*trans*, 9-*cis* and 13-*cis* RA and their biological significance in vertebrates are also well documented (Andre et al., 2014). Furthermore, studies of Wang (1996) demonstrated that the biotransformation of ß-carotene to RA occurs without the involvement of ALDHs in rabbits. Cell culture studies have shown that cytochrome P450 subunit CYP1B1 catalyses the conversion of retinol to retinaldehyde and RA (Andre et al., 2014). The RA binds with cellular RA binding proteins (CRABPs) and transported to the cell nucleus where RA exerts its genomic actions via retinoid receptors viz., retinoic acid receptors (RAR) and retinoic acid X receptor (RXR). RA mediated non-genomic actions via cell surface receptors have also been demonstrated in vertebrates.

It is well known that the homeostasis between synthesis and catabolism of RA are equally important. The later step is mediated by cytochrome P450 family 26 (CYP26), wherein oxidation of RA leads to metabolites such as 4-hydroxy retinoic acid, 4-oxo retinoic acid, 18-hydroxy retinoic acid that are polar, and less potent in nature (Blomhoff and Blomhoff, 2006; Theodosiou et al., 2010).

Studies of Hopkins (2001) measured the levels of retinoid isomers such as all trans retinoic acid (ATRA) and 9-cis retinoic acid (9CRA) in the regenerating limb of *Uca pugilator* and also demonstrated the occurrence of enzymes that convert retinaldehyde to RA in the extracts of *U. pugilator* blastemas. Studies of Hopkins et al. (2008) quantified all-*trans* RA, retinal (RAL), 13-*cis*-RAL, ATRA and 9CRA in blastema’s of regenerating limbs in the fiddler crab, *Uca pugilator* by using HPLC and GC/MS. Studies of Paniagua-Michel and Linan-Cabello (2000) and Linan-Cabello et al. (2003) using diode array spectrophotometer and HPLC quantified the ROL, RAL and β-carotene (provitamin A) in the ovary of the shrimp, *Litopenaeus vannamei*. Studies of Venne et al. (2016) reported the occurrence of endogenous retinoic acid isomers (9CRA and ATRA) in daphnia by using liquid chromatography-triple quadrupole mass spectrometry. We also demonstrated the occurrence of two vitamin A metabolites such as 9CRA and ATRA in the ovaries of mud crabs, *Scylla serrata* using HPLC analysis (Venkaiah et al., 2019). Studies of Durica et al. (2006) demonstrated that the β,β carotene 15̍-15̍ monooxygenase cDNAs have been identified in an EST library of crab blastema tissues. Studies of Huang et al. (2022b) showed that vitamin A in the hemolymph of chinese mitten crab, *E. sinensis* supplemented with vegetable oil, palm oil that is rich in beta carotene. These results tempted us to suggest that the crustaceans can able to convert beta carotene to vitamin A catalyzed by β carotene 15̍-15̍ monooxygenase. This notion needs further authentication. Studies of Gauthier et al. (2023) demonstrated the identification of RA metabolites (all-*trans* 4-oxo and 13-*cis* 4-oxo RA), RA isomers (all-*trans* and 13-*cis* RA) as well as retinaldehyde (RALD) isomers (all-*trans*, 11-*cis,* and 13-*cis* RALD) using liquid chromatography-tandem mass spectrometry in an amphipod crustacean, *Gammarus fossarum*. Studies of Gu et al. (2002) reported that a member of retinoid/fatty acid binding-like protein family, that displayed characteristics of both CRABP and CRBP that can able to bind RA and RAL with similar affinity was isolated from the crustacean *Metapenaeus ensis*. Based on the homology modelling, studies of Ma et al. (2020) have shown that the lipocalin 1 and lipocalin 3 exhibit similarity to retinoic acid binding protein in the ridgetail white prawn, *Exopalaemon carinicauda*. It is noteworthy to mention that the retinoid receptors such as retinoic acid X receptor has been cloned from several crustaceans (Andre et al., 2014). The genome of *Daphnia pulex* also demonstrated the occurrence of RXR ortholog, yet machinery required for retinoid storage, transport and mobilization are missing (Theodosiou et al., 2010). Further, genes related to vertebrate type ALDH1a (an enzyme responsible for RA synthesis) were predicted, while CYP26 homologues, which mediate RA oxidative clearance are also missing from the genome of *D. pulex* (Andre et al., 2014).

Taken together, the complete picture of retinoid system is not yet fully characterized in crustaceans. However, occurrence of retinoids (RAL, RA isomers and RA metabolites), signaling cascade (RXR), transport proteins such as retinoid/fatty acid binding-like protein and biotransformation enzymes such as beta carotene 15̍-15̍ monooxygenase in crustaceans at least in part indicate the occurrence of retinoid metabolism.

**Genomic and non-genomic actions of retinoic acid**

 RA mediated genomic occurs via retinoic acid receptors and non-genomic actions occurs via cell surface receptors in vertebrates.

**Genomic actions**

Nuclear receptors are ligand activated transcription factors that control important functions involved in development, growth, cell differentiation, proliferation, apoptosis, and the maintenance of homeostasis (Mangelsdorf et al., 1994, Chambon, 1996; Wu et al. 2011). In general, the NRs comprised of four domains that perform various modular functions: a) DNA-binding domain (DBD) is stabilized by two zinc fingers, which are required for DNA identification and binding to specific response elements (Kumar and Thompson, 1999); b) the ligand-binding domain (LBD) allows the NRs to regulate transcription following ligand binding. The C-terminus of LBD contains an activation function 2 (AF-2) sub-domain that promotes ligand-dependent transcription by binding to coactivation factors (Warnmark et al., 2003). In most NR proteins, the A/B-domain, or N-terminal domain, is variable and contains an AF-1 motif that may induce ligand-independent transcription.

Retinoic acid receptors (retinoic acid receptors: RAR and retinoic acid x receptors: RXR) belong to the nuclear receptor (NR) family II. RAR and RXR exhibit typical NR structure elements (A/B domain, DBD, hinge region, LBD domains). The members of this family can able to bind ligands such as steroids, thyroid hormones, ecdysteroids, and retinoic acid. The retinoid signal is transduced by two nuclear receptor families, the retinoic acid receptor (RAR) family, which includes three isotypes, RARα, RARβ, and RARγ, and the retinoid X receptor (RXR) family, which also includes three isotypes, RXRα, RXRβ, and RXRγ. RARs are activated by all-*trans* retinoic acid and its stereoisomers, 9-cis-retinoic acid and 13-cis-retinoic acid, whereas RXRs are activated by 9-*cis*-RA. RARs function as RAR/RXR heterodimers. In addition, RXR also heterodimerizes with other nuclear receptors such as thyroid receptors, peroxisome proliferator-activated receptor, and vitamin D receptors and interfere with the transactivation processes of its heterodimeric partner (Matsuda and Kitagishi, 2013; Evans and Mangelsdorf, 2014). To interact with its cognate receptor, all-t*rans* and 9-*cis* retinoic acid is transported into the nucleus by binding with CRABP. During transactivation of the target genes, they dimerize and bind retinoic acid response elements (RAREs) located in the regulatory regions of the target genes (Moutier et al., 2012; Andre et al., 2014). By binding to specific RAREs [direct repeat (DR) type2: infrequent and DR-5 type: frequent], the ligand-receptor complexes function as inducible transcription regulators of several genes. Co-activators and co-repressors play an important role in executing the regulation of target genes of retinoid receptors during ligand bound and ligand unbound conditions (Altucci and Gronemeyer, 2001).

RAR in any of the ecdysozoan family members is not yet characterized (Andre et al., 2014). Interestingly, RXR orthologs have been demonstrated in several crustaceans *Celuca pugilator* (Durica et al., 2002), *Gecarcinus lateralis* (Kim et al., 2005), *Marsupenaeus japonicas* (Asazuma et al., 2007), *Daphnia magna* (wang et al., 2007), *Fraxinus chinensis* (Priya et al., 2009), *Carcinus maenas* (Nagaraju et al., 2011), *Homarus americanus* (Tiu et al., 2012) and *Scylla serrata* (Girish et al., 2015). Crustacean RXRcDNA homologs containing intact sequences of DNA binding, hinge, ligand binding, and terminal domains (C-F domains) were isolated (Wang et al. 2007; Nagaraju et al., 2011). Occurrence of RXR transcripts in the embryos of *D. magna* might also indicate the critical role of RXR during embryonic development (Wang et al., 2007).

Ecdysteroid hormones play a key role in the regulation of several physiological processes in crustaceans (Subramoniam, 2000). It has been suggested that they can able to bind their cognate partner, ecdysone receptor (EcR), a member of the NR family II. In response to ecdysteroid hormones (e.g. 20-hydroxy-ecdysone and ponasterona A), EcR can able to form obligate heterodimer with RXR [(which is also known as ultraspiracle (USP) in insects] (Techa et al., 2013) and mediate physiological functions like development, metamorphosis, molting, regeneration of appendages, and reproduction (Hall and Thummel, 1998; Hopkins et al., 2008; Lafont and Koolman et al., 2009; Nakagawa et al., 2007; Nowickyj et al., 2008). Studies of Hopkins et al. (2008) suggested that the affinity of ecdysteroids towards its cognate EcR enhance during heterodimerization with RXR in the crab, *U. pugilator*. Their studies also revealed that the two RXR splice variants were capable of binding 9-cis-RA, methyl farnesoate and farnesoic acid and also showed to alter the sensitivity of EcR towards the ponsaterone A but no other ecdysteroids suggesting differential actions of EcR/RXR signaling cascade in *U. pugilator* (Hopkins et al., 2008). Surprisingly, studies of Wang and LeBlanc, (2009) in *D. magma* demonstrated that RXR can able to bind 9CRA and methyl farnesoate (a terpenoid synthesized and produced by mandibular organs) *in vitro* might indicate EcR-independent RXR signalling pathways. However, such ligand bound RXR might induce transactivation signals or not is yet to be addressed.

**Non genomic actions**

Non genomic actions of RA have been demonstrated wherein RA mediated actions does not mediate nuclear receptors instead mediate cell surface signal mechanisms. RA control and coordinate transactivation of genes via non-transcriptional effects through the phosphorylation activities via activation of mitogen-activated protein kinase MAPK signaling pathway and observed in fibroblasts, mouse embryo carcinoma cells, mammary breast tumor cells, and leukemia cells (Piskunov and Rochette-Egly, 2012). Further, RA mediated signaling kinases such as MAPK and extracellular signal regulated kinases subsequent to the activation of upstream signal transduction events such as Rho GTPases, phosphatidylinositol-3-kinase and protein kinase B suggest the non-transcriptional effects of RA similar to that described for steroid nuclear receptors (Al Tanoury et al., 2013).

With regards to the non-genomic actions of RA, so far, no information is available in crustaceans. Studies of Ren et al. (2023) have shown that the MAPK signaling pathway involved in the regulation of lipid metabolism may play an important role in ovarian development of mud crabs, *S. paramamosian*. The studies of Ren et al. (2023) also demonstrated the occurrence of vertebrate type peroxisome proliferator activated receptor (PPAR) viz., ecdysone related proteins (*Sp-Eip75B* and *Sp-Eip78C*). It has been shown that the proteins E75B and E78C from *D. melanogaster* are orthologs of mammalian PPARγ (Blommer et al., 2021; Hong et al., 2010; King-Jones et al., 2005; Zipper et al., 2020). Studies of Ren et al. (2023) showed a probable link between MAPK signaling pathway involved during the regulation of ovarian lipid metabolism and PPAR signaling pathway in the regulation vitellogenesis. In vertebrates, ligand bound PPAR heterodimerizes with RXR in regulation of genes related to lipid metabolism. Therefore, whether the EP75B and EP78C from *S. paramamosian* would bind RXR and influence lipid metabolism and vitellogenesis and if so, what could be role of RA. Thus, studies in this direction provides key insights into the non-genomic actions of RA in crustaceans.

**Physiological significance of retinoids**

Retinoic acid is a pleotropic molecule and exhibits versatile functions. The mode of action of retinoic acid via genomic (nuclear receptor mediated) and non-genomic actions are well appreciated in mammals and other vertebrates, however, limited information is available with regards to crustaceans. This section covers the available information on receptor mediated and non‐receptor mediated effects of retinoic acid in crustaceans and compared with vertebrate retinoic acid functions for better understanding of retinoid signalling. This section also encompasses the physiological role of retinoic acid in crustaceans.

Hormonal control of physiological events limb regeneration, carbohydrate metabolism and reproduction in crustaceans are well established. Diverse nature of hormones are synthesized by neural and non-neural glands in crustaceans to control and coordinate complex biological processes in crustaceans. Several studies have shown that these endocrine mediated processes are influenced by retinoic acid in crustaceans suggesting a crosstalk between the involvement of retinoic acid signaling and endogenous hormones (Mantiri et al., 1995; Hopkins and Durica, 1995; Durica et al., 2002; Linan et al., 2004; Zou and Bonvillian, 2003; Reddy and Sainath, 2008; Reddy and Srilatha, 2015; Venkaiah et al., 2019; 2023).

***Glucose metabolism***

Glucose homeostasis in crustaceans is a fundamental process in a constantly changing environment and regulated by a peptide hormone known as crustacean hyperglycemic hormone (CHH) released from the X-organ sinus gland complex located in the eyestalks of crustaceans (Fanjul Moles, 2006). The chemical nature, mode of action and the target sites of CHH have been extensively studied in several crustaceans (Böcking et al., 2002; Katayama et al., 2002). However, the mechanism of release of CHH into circulation in coordination with other endogenous signals is not clearly understood (Webster et al., 2012). Studies of Zou and Bonvilliain, (2003) and Reddy and Sainath, (2008) have shown that the administration of 9-CRA into the crabs, *U. pugilator* and *O. senex senex,* respectivelyinduced hyperglycemia. Further, Reddy and Srilatha (2015) also demonstrated that 13-CRA injection significantly increased hemolymph glucose levels in *O. senex* in intact crabs in a dose-dependent manner and also an increase in the CHH mRNA.Studies of Venkaiah et al. (2023) demonstrated that the injection of 9-cis-retinoic acid elevated glucose levels accompanied by increased expression levels of CHH mRNA in the freshwater edible prawn, *M. malcolmsonii*. The key finding of the research on retinoid system in the prawn, *M. malcolmsonii* suggests that 9CRA induces hyperglycemia in intact but not in eyestalk‐less crabs by activating the enzyme glycogen phosphorylase, in hepatopancreas and muscle tissues. Since hyperglycemia is induced by 9CRA in intact prawns, Venkaiah et al. (2023) concluded that 9CRA‐induced hyperglycemia in prawn, *M. malcolmsonii* at least in part depends on CHH. Studies have shown that the CHH from the eyestalks target hepatopancreas and muscle tissue thereby through G protein coupled receptors activate cAMP (Sainath and Reddy, 2011). This step subsequently activates the phosphorylase kinase through protein kinase A which in turn activates glycogen phosphorylase, thereby induces glycogenolysis (Davidson and Sittman, 1999). The glucose resulted from glycogenolysis leaks into hemolymph resulting in hyperglycemia (Sainath and Reddy, 2010).

Regulation of glucose metabolism by retinoic acid in vertebrates is well documented (Matsuoka et al., 2019). Experimental studies in rodents show that vitamin A affect liver carbohydrate metabolism and also affect key energy related processes such as glycolysis, gluconeogenesis and glycogenesis (Kane et al., 2010; Chen and Chen, 2014; Blaner, 2019; Napoli, 2022). Several genes associated with hepatic enzymes that mediate glycolysis, and gluconeogenesis at least in part regulated by retinoids (Chen and Chen, 2014). Studies in INS1 cell lines have shown that retinoids could be associated with both stimulation of insulin secretion and expression of the glucose transporter 2 gene (Blumentrath et al., 2001; Rhee and Plutzky, 2012). Both ATRA and 9CRA play vital roles in the regulation of glucose homeostasis (Rhee and Plutzky, 2012). Therefore, it is expected that their interactions with their cognate receptors could be pivotal in the regulation of several biological functions. Studies of Cabrera-Valladares et al. (1999) demonstrated that the RA could mediate its genomic effects via its cognate receptors on the gene expression of glucokinase and insulin in primary culture of pancreatic islets. The antidiabetic effects of retinoids are believed to be mediated through the retinoic acid receptor homodimer (Chertow et al., 1997) or RAR/PPARγ heterodimer (Cha et al., 2001; Singh et al., 2001). Further, it has been shown that RA regulation of carbohydrate metabolism also mediate the expression of transcription factors hepatocyte nuclear factor4 (HNF)4α, carbohydrate response element-binding protein (ChREBP), sterol response element binding protein (SREBP), peroxisome proliferator-activated receptor (PPAR)γ and liver X receptor (LXR) (Matsuoka et al., 2019). Studies from murine beta and alpha pancreatic cell lines revealed that raldh3 (which catalyses the conversion of 13cis-retinaldehyde to 13cis-RA) acts as a novel factor in the regulation of insulin and glucagon levels (Rhee and Plutzky, 2012). Studies also indicated that 9CRA at least in part mediate RXR in the regulation of insulin levels (Chertow et al., 1997; Lenhard et al., 1999; Kane et al., 2010).

Taken together, in vertebrates, the regulation of glucose metabolism by vitamin A is wired with genomic and non-genomic actions (Kane et al., 2010; Chen and Chen, 2014; Blaner, 2019; Chen, 2022; Napoli, 2022). Such specific actions of vitamin A in the regulation of glucose metabolism in crustaceans needs to be clarified. Since administration of either CRA induced hyperglycemia in intact crabs/prawns but not in eyestalk ablated crabs/prawns might augment the likelihood of interaction of CRA with its cognate receptor in the eyestalk of crustaceans. Interestingly, expression of RXR has been demonstrated in the eyestalks of crustaceans (Gong et al., 2016; Kluebsoongnoen et al., 2021). Since the RXR isolated from crab has been found to bear a close resemblance to vertebrate RXRs in the ligand-binding domain it is very likely that RA may also have a high affinity to its receptor in eyestalks of the crab. Whether treatment with combination with a 9CRA and RXR blocker or RXR antagonist abolishes the occurrence of 9CRA-induced hyperglycemia needs to be investigated until then the regulation of RA on glucose homeostasis is not clear.

***Lipid metabolism***

There is no question about the importance of lipids to the life of the organism. Not only do they play a metabolic role and provide energy for almost all endergonic processes, but they are of utmost importance in maintaining the structural and physiological integrity of cellular and sub-cellular membranes as they serve as structural constituents of biological membranes, acts as insulators of cells, acts as coenzyme factors, precursors of hormones and vitamins (Perona et al., 2017). In addition, their role in transport of substrates via the circulatory system in both vertebrates and invertebrates is believed to be vital. Many factors interfere with lipid metabolism and available literature showed that vitamin A is one such factor that could affect lipid anabolic and catabolic aspects in mammals and fishes (Bonet et al., 2012; He et al., 2013; Chen and Chen, 2014; Liu, et al., 2016; Yang et al., 2017; Harnandez and Hardy, 2020; Huang et al., 2022). Published reports have shown that vitamin A can able to influence bile acid synthesis, fatty acid synthesis, steroid hormone synthesis, and phospholipid synthesis in vertebrates (Wang and Yan, 2017; Li et al., 2021; Yang et al., 2021; Huo et al., 2023). In crustaceans, lipids contribute to normal growth, stress resistance and reproduction (Cahu et al., 1994; Jannathulla et al., 2019; Ouraji et al., 2010) and few studies showed a link between lipid metabolism and vitamin A supplementation (Shiau and Chen, 2000; Huang et al., 2022a, b and c). Experimental studies have shown that supplementation of vitamin A caused significant effects on growth performance, lipid metabolism and antioxidant capacity in juvenile chinese mitten crabs, *Eriocheir sinensis* (Huang et al., 2022a and b). Lipid synthesis, its transport and lipid catabolic aspects are three important routes associated with lipid metabolism. Studies of Huang et al. (2022a) suggested that vitamin A (6000 IU/kg) exhibited lipid lowering effects in juvenile crabs *E. sinensis* fed with lipid diet (either at 7 or 13% of lipids) and such lipid lowering effects induced by vitamin A could be associated with elevated lipid catabolism and lipid transport accompanied by inhibition of lipogenesis (Howell and Chen, 2012; Zhao, et al., 2012; Lin, et al., 2021). It is well accepted that the fatty acids β-oxidation is crucial for lipid catabolism in animals (Karagianni and Talianidis, 2015). During the process of β-oxidation, the key enzymes are acyl-CoA oxidase (aco), a rate-limiting enzyme in peroxisomal fatty acid oxidation (Zeng, et al., 2017), carnitine palmitoyltransferase 1a (Cpt1a), an enzyme involved in fatty acid oxidation in mitochondria (Li et al., 2021a) and carnitine palmitoyltransferase 2, an enzyme involved in long-chain fatty acid oxidation in the mitochondria (Pereyra, et al., 2020). Vitamin A supplementation elevated the levels of *aco,cpt1a* and *cpt2* mRNA in high lipid diet fed crabs over its respective controls suggesting enhanced lipid catabolism (Huang et al., 2022a). In mouse model, ATRA induced up-regulation of fatty acid oxidation genes in the liver tissue has been reported (Kang, et al., 2007; Amengual, et al., 2012). Microsomal triglyceride transfer protein (mttp) is a lipid transport protein as it plays a key role in the assembly and secretion of triglyceride carrier, VLDL (Newberry, et al., 2021; Li, et al., 2021b; Lin, et al., 2021). Studies of Huang et al. (2022a) indicated that elevated *mttp* mRNA levels and VLDL levels associated with a reduction in the levels of TG in the hepatopancreas of crabs subjected to both vitamin A and high fat diet over high fat diet alone group supports the notion that vitamin A supplementation promote VLDL secretion to overcome lipid accumulation under high fat diet. Regulation of lipid metabolism is tightly linked to vitamin A in mammals and fishes (Bonet, et al., 2012; Chen and Chen, 2014; Howell and Chen, 2012). Interestingly, supplementation of vitamin A at 30444 IU/kg in diet revealed down regulation of genes (*ATP-citrate synthase, fatty acid synthase, long-chain-fatty-acid--CoA ligase ACSBG2, sterol regulatory element-binding protein-1, long-chain fatty acid elongase protein 6, acetyl-CoA carboxylase and acyl-CoA delta-9 desaturase*) related to lipid synthesis and upregulation of genes related to lipolysis (*gastric triacylglycerol lipase, intracellular triacylglycerol lipase, inactive pancreatic lipase related protein 1, pancreatic lipase-related protein 2, pancreatic lipase*), β oxidation (*carnitine O-acetyltransferase, carnitine O-palmitoyltransferase 1a, very long-chain specific acyl-CoA dehydrogenase, mitochondrial*), genes related to immunity and antioxidant capacity (*crustin-1, crustin-2, lysozyme, glutathione S-transferase, heme oxygenase 1-like*, and *catalase isozyme 1-like*) (Huang et al., 2022b) in crabs over controls. Supplementation of vitamin A induced elevation of antimicrobial peptide-related gene expression in the liver and lysozyme content in grass carp (*Ctenopharyngodon idella*) occurred via activating the NF-κB signals (Zhang, et al., 2017). Vitamin A (3155 IU/kg dietary vitamin A) supplementation also showed to elevate the GPx activity in gibel carp compared with the control group (Shao, et al., 2016) and also caused a reduction in the lipid peroxidation levels in *Rhamdia quelen* relative to control group (Battisti, et al., 2017). Vitamin A significantly improved the SOD and GPx activities in cows (Jin, et al., 2014). Nuclear factor-E2-related factor 2 (Nrf2) is a key regulator of the antioxidant genes (i.e., SOD, GPx, GST, CAT, HO-1) (Taguchi, et al., 2011; Wang, et al., 2014; Wang, et al., 2018) and studies have shown that vitamin A could alleviate oxidative stress through Nrf2 activation (Wang, et al., 2014). Further, these authors showed a positive effect on growth performance and most notably elevated total antioxidants, superoxide dismutase and catalase associated with decreased lipid peroxidation levels in Vitamin A supplemented juvenile crabs treated with high lipid diet (Huang et al., 2022a and b).

Vitamin A induced effects are mediated by its active metabolite, retinoic acid. Both genomic and non-genomic actions of RA induced regulation of lipid metabolism have been demonstrated in mammals (Amengual, et al., 2010). Non-genomic effects of RA include phosphorylation of p38 MAPK activation eventually leading to the inhibition of transcription of *srebp1* and showed a suppressive role in hepatic lipogenesis (Bonet, et al., 2012; Xiong, et al., 2007; Su et al., 2015). Moreover, the role of vitamin A in lipogenesis was also affected by “genomic effects” (Ziad, et al., 2013) and mediated by RXR which served as heterodimeric partners (Bonet, et al., 2012; Feng, et al., 2019; He et al., 2013; Howell & Chen, 2012). In mammals, the RARE was found inside the promoter of *srebp1* gene, and the expression of which could be induced by activation of RXR (Li, et al., 2011; Repa, et al., 2000). Studies of Huang et al., (2022a) indicated that the RXR mRNA level and *srebp1* mRNA levels are corresponding to each other under high lipid level.

***Limb regeneration***

Now evidences indicated that the role of retinoid signaling in the regulation of metamorphosis, regenerative growth and limb regeneration in cnidarians, arthropods (lower insects: Eg: *Locusta migratoria* and crustaceans) and non-chordate deuterostome, echinoderms (Hopkins et al., 2008; Nowickyj et al., 2008; Andre et al., 2014; Fuchs et al., 2014; Yamakawa et al., 2018). In order to grow in size, crustaceans must shed their old exoskeleton and then expand a new soft, paliant exoskeleton which has been formed beneath the old one and this process is known as molting or ecdysis (Sainath et al., 2013). Many factors affect molting process including nutritional status and whether or not the animal is generating a limb (Hopkins, 2001). In crustaceans, autotomy is a response against injury or predation which ensures that the limb is cast off at a predetermined point at the base of all walking legs and the lost appendages are regenerated before the next molt. Thus, both limb bud regeneration and molting are obligatory linked to each other. Regeneration of limbs following autotomy occurs in two phases. The first phase immediately follows the loss of the limb and is called basal growth. Basal growth can take place at any time during the molt cycle. The second phase is called proecdysial growth and occurs only as the animal is preparing for ecdysis. In crustaceans, limb regeneration and molting are interdependence processes controlled and coordinated by molt hormone. The molting and growth are regulated by ecdysteroids. In insects and crustaceans, ecdysteroids are synthesized and secreted by prothoracic glands and the Y organs, respectively. Ecdysteroids comprised of 25-dexoyecdysone and ecdysone which subsequently converted to ponasterone A and 20-hydroxyecdysone in peripheral tissues of crustaceans. Ecdysone acts via its cognate nuclear receptor, ecdysteroid receptor (EcR). EcR forms heterodimer partner with ultraspiracle, a homolog of RXR in insects, while in crustaceans, EcR pairs with RXR.

As the loss of limbs at the predetermined point ensures the most efficient and fastest regeneration and interdependence on molting events, several scientists focused on the effect of ecdysteroids on regeneration in crustaceans and insects. With regards to insects, it is well known that a neuropeptide prothoracicotropic hormone (PTTH) released from the brain stimulate the prothoracic gland or molting gland to synthesize and secrete ecdysone which eventually involved in molting and regeneration events. Studies from *Drosophila* *melanogaster* indicated that retinoids inhibit the gene expression of *ptth* and thereby delayed development in response to tissue damage (Halme et al., 2010). Thus, inhibition of PTTH could be linked to the low levels of ecdysone (Halme et al., 2010). *In vitro* studies showed that the DNA binding activity of EcR/USP (a homolog of RXR in insects) did not respond to hormones ecdysteroids and 9CRA, while DNA binding activity of EcR/RXR was found to be influence by selected hormones in mammalian cell lines, CV1 and Hela cell lines (Thomas et al., 1993). Interestingly, though juvenile hormones can directly regulate the activity of EcR/USP heterodimer complex in insects, exogenous 9CRA and juvenile hormones did not activate EcR/RXR complex in cultured Sf9 cells (Fang et al., 2005). In flies and moths, molting is mediated by a heterodimer ecdysone receptor consisting of the ecdysone monomer (EcR) and an RXR homolog, ultraspiracle (USP); the latter is believed to have diverged from its RXR origin. However, in *Locusta migratoria*, RXR is more similar to human RXRs than to USPs (Nowickyj et al., 2008). LmRXR transcripts and retinoids like 9CRA and ATRA were confirmed using HPLC and MS in the embryos of *L. migratoria*. Recombinant LmRXRs bound 9CRA and ATRA with high affinity (IC(50) = 61.2-107.7 nM; K(d) = 3 nM), similar to human RXR was also demonstrated (Nowickyj et al., 2008). Thus, it is conceivable that the signalling of retinoids is evolutionary conserved at least in primitive insects and the binding of 9CRA to its cognate receptor is relatively evolutionary conserved.

On other hand, the current knowledge on the role of retinoids in the regulation of crustacean molting is still in its infancy (Hopkins and Durica, 1995, Hopkins et al., 2008). The effect of retinoids on limb regeneration has been demonstrated in *Uca pugilator* as crustacean model. During limb regeneration, proliferation and differentiation of blastema cells are the major events which are controlled by factors such as fibroblast growth factors (FGF) and ecdysteroids. FGF is required for the formation of myoblasts in blastema and ecdysteroids are involved in mobilizing pre-myoblast cells during basal growth and stimulate hypertrophic muscle protein synthesis in those same cells during early proecdysial growth. The concentration of ecdysteroids also affect the limb bud regeneration in crabs. At low concentrations, ecdysteroids promote basal growth of limbs, while at higher concentrations, ecdysteroids inhibit basal growth of limbs. On the other hand, exogenous retinoids indicated that a) proliferation of balstema cells but not their differentiation; b) high levels of RXR mRNA in the blastema cells and modulate the FGF during limb bud regeneration (Hopkins, 2001). Limb bud regeneration in crustaceans is linked to several molecular events. During basal growth the EcR mRNA levels also remain low, suggesting that low levels of ecdysteroids and its cognate receptor (Hopkins, 2001; Hopkins et al., 2008). Blastema of *U. pugilator* contains retinoids such as 13cis-retinaldehyde and all-trans-retinaldehyde, which can serve as precursors for 9CRA and ATRA and relatively, aldehyde forms were found to be abundant over RA isomers in *Uca* blastemas (Hopkins et al., 2008). The role of MF in molting, reproduction, osmoregulation and behaviour is well studied in crustaceans (Nagaraju, 2007). Surprisingly, both RA and MF may act as ligands for RXR in Uca pugilator (Hopkins et al., 2008). Studies of Hopkins et al. (2008) indicated the effect of different ligands and their crosstalk with EcR/RXR (isoforms). The findings revealed that EcR binds with ponasterone A with high affinity when it partners with RXR isoform (-33 amino acids) in the presence of ligands 9CRA and methyl farnesoate (MF: a terpenoid synthesized and secreted from mandibular organs in crustaceans and ring gland in insects), while low affinity was observed when EcR partners with RXR isoform (+33 amino acids) in the presence of ligands 9CRA and MF in *U. pugilator* blastemas (Hopkins et al., 2008). In vertebrates, the synergy occurs in RXR/RAR, RXR/thyroid hormone receptor, and RXR/PPAR pairs (Rastenijad, 2022). During synergy of receptors, the transactivation of effects occurs by only one ligand, though both the dimer partners (EcR and RXR) of *U. pugilator* were ligand bounded implying that the RXR subunit of EcR/RXR could be bound to low affinity ligands to maximally ‘sensitize’ the transcriptional activity of the EcR to discrete variation in the concentration of the cognate ligand of its heterodimer partner i.e. EcR (Hopkins et al., 2008).

Recent findings of Xing et al. (2024) showed that innexin genes play a vital role in the morphological and molecular changes during limb regeneration of shrimp, *Exopalaemon carinicauda* (Xing et al., 2024). Innexin are cell to cell gap junction proteins that are required for tissue polarity, electrical signalling, directional movement and germ cell maintenance and development (Yue et al., 2023). Studies of Wang et al. (2022) found upregulation of six *Innexin* genes in *E. sinensis*, eight *Innexin* genes in *L. vannamei*, six *Innexin* genes in *M. rosenbergii*, and four *Innexin* genes in *M. nipponensis* after autotomy at 1 day post autotomy. Intriguingly, the effect of retinoic acid on innexin genes during modulation of electrical signals between the cell junctions has been demonstrated in invertebrate, *Lymnaea stagnalis* (Rothwell et al., 2017).

Taken together, at least two questions arise at this juncture, a) which factors regulate the levels of ecdysteroids during limb bud regeneration; b) how retinoids interfere with endogenous hormones thereby limb bud regeneration; c) whether or not the interaction of retinoids and innexins could play a key role in limb bud regeneration. This studies in this direction may provide additional insights into the role of retinoids in the regulation of limb bud regeneration in crustaceans.

***Reproduction***

Though mechanisms are poorly understood, studies have shown that exogenous supplementation of vitamin A and its metabolite retinoic acid have significant role in crustacean reproduction. The role of vitamin A in spermatogenesis, oogenesis, and embryonic growth of crustaceans has been demonstrated (Mantiri et al., 1995). Linan et al. 2004 observed that the ovarian maturation in *L. vannamei* is due to the trigger of retinol palmitate. Injection of vitamin A metabolites i.e 9-cis retinoic acid and 13-cis retinoic acid in the regulation of ovarian maturation of crustaceans has been demonstrated (Nemec et al., 1993; Girish et al., 2018). With respect to the crustacean reproduction, few studies have indicated that both EcR and RXR at least in part have implications in the regulation of vitellogenesis in crustaceans. Studies of Durica et al., (2002) and Nagaraju et al., (2011) have shown that the reduction in RXR and vitellogenin mRNA levels in the crab, *C. maenas* following treatment with RXR dsRNA and fluctuations in RXR mRNA expression in ovaries during reproduction suggest that RA acts as a reproductive hormone. Nagaraju et al. (2011) showed that the stimulatory effect of MF on vitellogenin expression in the hepatopancreas and ovary of *C. maenas* is greatly reduced when the expression of RXR is knocked down. It was also discovered that RXR forms a heterodimer with the ecdysteroid receptor (EcR) (Nagaraju et al., 2011). This RXR-EcR complex can bind to RA, ecdysteroid (E), or methyl farnesoate (MF) to form a heterotrimeric complex (RXR-EcR-RA/E/MF) and thus regulate a variety of physiological aspects in crustaceans. Studies of Gong et al., (2016) demonstrated that rather than complying with ecdysone or the insect JH, both MF and RXR are thought to play important roles in controlling VTG expression and ovarian development in *S. paramamosain*. Further, Gong et al. (2016) have shown that RXR may be involved in the MF signaling pathway in two routes: a) interacting with EcR through the stimulatory effects of MF and b) interact directly with MF. Studies of Asazuma et al., (2007) investigated that RXR in *M. japonicus* mediates a specific hormonal signal related to reproduction. Studies by Shirley et al. (2012) on the interaction between RXR and farnesoic acid/MF and their effects on target tissues throughout the reproductive cycle, should provide insights into gonad maturation manipulation. Experiments of Cui et al. (2013) indicated that RXR transcripts in the mature ovary of *M. ensis* act as maternal signals for controlling early molting processes during embryonic development. Interestingly, Girish et al. (2015) suggested that the heterodimer, RXR-EcR and its target E75 are important for controlling the synthesis of VTG in the hepatopancreas, whereas in the ovary, NR dimers are crucial for controlling the uptake of VTG from the haemolymph, more likely by regulating the levels of VTG-receptor. *In vivo* and *in vitro* studies of Jakkapong et al. (2021) hypothesized that RXR may be an activator protein that modifies VTG expression in shrimp, *P. monodon* ovary by binding to RARE. Based on the aforementioned data, literature related to the effect of vitamin A and its metabolite retinoic acid is limited to few crustaceans only and in particular data pertaining to the role of retinoic acid in the regulation of crustacean reproduction is still at its infancy.

**Ligands for Crustacean RXR?**

It is well known that 9-cis retinoic acid is a canonical ligand for RXR in vertebrates (Mangelsdorf and Evans, 1995). In vertebrates, the regulation of limb regeneration is controlled and coordinated by retinoic acid signaling including an interplay between 9-cis retinoic acid and RXR (Tabin, 1991). Intriguingly, the regulation of limb regeneration in *U. pugilator* by 9-cis retinoic acid has been demonstrated (Hopkins et al., 2001). Another study by Chung et al. (1998) have shown that the elevated levels of RXR could be associated with limb regeneration followed by exogenous administration of 9-cis retinoic acid. These studies provide a cue towards the occurrence of retinoid signaling pathway in crustaceans. In support to this notion, studies of Hopkins et al. (2008) provided evidence for binding of 9-cis-retinoic acid and MF with RXR.

**Conclusion**

Hormones of diverse nature in several crustaceans exhibit multifunctional properties. For example, peptide hormones of eyestalk XO-SG complex like hyperglycemic hormone which is primarily involved in glucose homeostasis and molt inhibiting hormone which is primarily involved in the regulation of molt cycle participates in molt‐inhibiting activity and glucose metabolism, respectively. Ecdysteroids of the Y-organs which are involved in the regulation of ecdysis/growth also possess morphogenic activity at embryonic stage and also involved in color change and gonadal maturation in crustaceans (Chang et al., 2001). Another cogent example of this trend is the methyl farnesoate of the mandibular organs which are fundamentally involved in morphogenesis at larval period and act as a gonadotropin in adults. These pleiotropism exhibited by crustacean endocrine factors illustrates the amazing economy of nature—a single hormone with multiple functions at different life stages (Chang et al., 2001).

Retinoic acid in crustaceans is another molecule exhibiting multiple biological actions such as regulation of glucose homeostasis, limb regeneration, lipid metabolism and reproduction. At this juncture, an important question arises; how these hormonal signals crosstalk with other endocrine factors and signalling factors to perform many functions in crustaceans during different developmental stages remained to be answered. This is an extremely fertile area for study and may show ultimately unique about the RA that has been conserved during evolution.

Piecing these studies, it can be concluded that the following observations could be deduced: a) endogenous occurrence of retinoids and its metabolites in crustaceans is evident; b) retinoid signalling cascades i.e. CRABPs and RXRs have been identified in crustaceans; c) exogenous supplementation of vitamin A and its metabolite, though limited to few crustaceans only, have demonstrated the physiological significance of retinoids in crustaceans; d) precise regulation of ovarian development by retinoids in crustaceans is still at its infancy and e) elucidation of role of retinoids in the regulation of crustacean reproduction could act as a tool to control ovarian development in brood stocks in captivity and also act as an alternative tool against the eyestalk ablation technique.

Though some physiological role of RA was reported in crustaceans, they are limited to few crustaceans only and hence, its modus operandi is still remaining a puzzle and a reasonably clear picture of the action of RA is still to be emerged. Endocrine factors have a remarkable feature as such several physiological processes may be acted upon by single hormone or several hormones may act on the same physiological process, exhibiting pleiotropism. As such, the need for a poly‐hormonal approach rather than a mono‐hormonal approach appears a logical necessity and such an approach might enable us in gaining a clear concept of the endocrine control physiological process in crustaceans. As RA exerts its effects via genomic involving retinoid receptors and non-genomic actions, poly-hormonal approaches involving RA might be helpful to get clear cut picture of its endocrine role in the biological framework of crustaceans.

Recent findings of Feng et al. (2019) suggested that vitamin A supplementation ameliorate the antioxidant capacity and immunity in crabs, *E. sinensis* against aroclor 1254, a polychlorinated bisphenol. Studies of Gauthier et al. (2023) demonstrated that some chemicals such as juvenile hormone analogs like Methoprene and RA inhibitors like citral might disrupt the RA signalling in an amphipod female crustacean, *G. fossarum*. Tributyltin, a potent agonist of RXR was found to disrupt lipid and carbohydrate metabolism in crustaceans via RXR signalling and CHH, respectively (Vogt et al., 2018). Thus, understanding the retinoid system and its signalling may be helpful in understanding the mechanisms underlying endocrine disrupting chemicals that involve retinoid signalling.

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