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Juvenile Hormone, Ecdysteroids, and Insulin Signaling Operate as an Integrated Regulatory Network Connecting Development and Reproduction

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ABSTRACT

Juvenile hormone (JH), ecdysteroids, and insulin/IGF-like signaling (IIS) are often described as separable endocrine systems controlling insect development, metabolism, and reproduction. Evidence from selected insects instead reveals regulatory connections among these systems, but it does not support a single invariant endocrine cascade. This article develops an original molecular-physiological synthesis in which JH, ecdysteroid, and IIS components form a proposed conditionally reconfigurable regulatory network. Directly supported relationships include endocrine control of insulin-like peptide transcription, nutrient-dependent differentiation of IIS outputs, IIS-associated modulation of JH reproductive physiology, JH-effector repression of ecdysteroid biosynthesis, and convergence of insulin and ecdysteroid signaling on reproductive effectors. The same literature also identifies critical boundaries: regulatory direction changes with target gene and developmental state, endocrine sources can remain unresolved, and IIS-dependent oogenesis can occur without detectable alteration of JH or ecdysteroid signaling in at least one model. We therefore distinguish coupling, hierarchy, convergence, reciprocal regulation, and conditional independence as different network states rather than treating endocrine integration as obligatory. Developmental and reproductive decisions are interpreted as context-dependent outputs of these changing relationships across tissues, stages, nutritional states, sexes, and taxa. The resulting synthesis generates experimentally distinguishable predictions while retaining explicit limits on cross-species and organism-level generalization.

Keywords: Juvenile hormone, Ecdysteroids, Insulin/IGF signaling, Endocrine crosstalk, Metamorphosis, Vitellogenesis

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Introduction

Development and reproduction in insects are conventionally partitioned into endocrine topics, yet their regulators need not operate as isolated programs. In adult female *Rhodnius prolixus*, feeding-associated physiology involves interactions among nutritional state, insulin signaling, JH, and ovarian ecdysteroid processes, providing direct evidence that multiple endocrine axes can be physiologically coupled within one reproductive cycle [1]. This model does not establish an insect-wide topology, but it makes separation of the three systems an insufficient starting assumption.

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Coupling is also demonstrable at the transcriptional level. In female *Aedes aegypti*, JH- and 20-hydroxyecdysone (20E)-responsive regulators directly affect insulin-like peptide (ILP) genes, with gene-specific rather than uniform responses [2]. Thus, cross-talk can occur before a downstream phenotype is produced: one endocrine pathway can alter the molecular composition of another pathway's signal output.

Importantly, sharing a regulator does not imply sharing its function. Krüppel homolog 1 (Kr-h1), a major JH-responsive factor, can recruit different cofactors according to developmental state, supporting an anti-metamorphic role in juveniles and a different vitellogenic function in adults [3]. The regulatory problem is therefore not simply which molecules are present, but which molecular relationships are available in a particular state.

Nutritional signaling adds another state variable. In larval *Drosophila melanogaster*, cholesterol availability can be linked through tissue nutrient sensing and IIS to growth and maturation-related processes [4]. This evidence supports a connection between resource state and developmental timing without implying that cholesterol is a universal maturation cue in insects.

At the pathway level, JH signaling, ecdysteroid production and secretion, and ILP regulation each possess established molecular organization while also exhibiting substantial stage-, tissue-, environmental-, and taxon-dependent variation [5–7]. Treating them either as fully independent pathways or as equivalent branches of a single cascade therefore obscures the relevant mechanistic heterogeneity.

Developmental interpretation further requires a stage-identity framework. The metamorphic gene network, including temporally structured relationships among Kr-h1, E93 and Broad-Complex, provides such a framework, although its implementation varies with metamorphic mode [8]. Building on these observations, this article proposes that endocrine integration is best analyzed as a set of conditional regulatory decision nodes. "Decision node" here denotes an analytical point at which molecular states constrain subsequent developmental or reproductive trajectories; it is not assumed to be a discrete anatomical structure. The central question is consequently where JH, ecdysteroid and IIS signals become coupled, hierarchically ordered, convergent or partly autonomous, and how those configurations change between development and reproduction.

Juvenile hormone signaling

JH signaling illustrates why a regulatory axis cannot be reduced to hormone concentration alone. In *Helicoverpa armigera*, JH promotes phosphorylation of Methoprene-tolerant 1 (Met1), increasing its interaction with Taiman and facilitating JH-responsive transcription [9]. Receptor-state modification can therefore alter signaling competence downstream of ligand availability, although the particular phosphosite mechanism cannot be assumed to apply identically across insects.

Biochemical receptor evidence provides a complementary but narrower level of inference. Met–Tai receptor complexes from *Prorhinotermes simplex* and *Blattella germanica* bind JH III and juvenile-hormone agonists [10]. Such binding supports ligand–receptor competence but does not, by itself, establish downstream reproductive or developmental outcomes. Network interpretation must keep receptor engagement separate from organismal phenotype.

The sign of a downstream JH response is likewise not fixed. In adult female *A. aegypti*, Kr-h1 functions as both a transcriptional activator and repressor depending on the target promoter [11]. Describing the JH branch simply as "activating" or "repressing" therefore loses mechanistic information. In the proposed network terminology, target identity changes the effective direction of a JH-responsive edge.

Whole-organism state adds another layer. In the cabbage beetle *Colaphellus bowringi*, manipulation of JH biosynthetic genes and JH signaling supports a causal contribution of reduced JH state to reproductive diapause under the tested photoperiodic conditions [12]. This is evidence for an environmentally contingent reproductive switch, not for a universal JH rule governing insect diapause.

Reproductive outputs also branch after JH reception. In female *R. prolixus*, JH signaling through its receptor complex supports several post-feeding reproductive processes, while downstream components do not contribute identically to every output [13]. Reception, transcriptional mediation, vitellogenic physiology, and egg production should consequently remain distinguishable analytical levels.

Finally, JH chemistry itself can alter biological performance. Genetic disruption of JH epoxidation in *A. aegypti* demonstrates that conversion to epoxidated JH materially affects developmental and reproductive performance, although methyl farnesoate retains partial biological capacity [14]. The result supports functional importance of JH chemical architecture in this system; it does not by itself establish a universal evolutionary advantage or an

invariant history of endocrine adaptation. Together, these observations define JH signaling as a regulated, branching axis whose effective network role depends on receptor state, transcriptional target, physiological state, and taxon.

Ecdysteroid signaling

Ecdysteroid signaling is similarly heterogeneous at both production and response levels. Functional disruption of ecdysteroid biosynthetic enzymes in the rice planthopper *Nilaparvata lugens* reveals differentiated contributions to molting and reproductive processes rather than simple interchangeability among steroidogenic components [15]. Steroid production should therefore be represented as an internally regulated module, not as a single undifferentiated input.

Downstream response is also tissue-dependent. In the panoistic ovary of *B. germanica*, EcR perturbation produces multiple ovarian effects, including responses that cannot all be collapsed into a single canonical transcriptional program [16]. The consequence of an ecdysteroid signal thus depends on receptive tissue and physiological state as well as on circulating hormone.

Even the origin of an endocrine signal may remain uncertain. During *Drosophila* pupal–adult development, the source of the relevant ecdysteroid pool has been critically reassessed, with competing interpretations including steroid recycling and alternative source models [17]. None should be converted into established fact without direct resolution. For network analysis, this uncertainty is biologically important: an observed hormonal state can be well supported while the tissue-level route producing it remains incompletely identified. Ecdysteroid nodes must therefore distinguish synthesis, source, circulation, receptor engagement, and downstream effect.

Insulin/IGF signaling

IIS is not a unitary nutritional readout. In blood-fed female *A. aegypti*, amino-acid state is translated through TOR, GATA factors and associated regulators into differential control of ILP genes; high- and low-nutrient conditions do not simply move all ILPs in the same direction [18]. Signal identity therefore matters within the insulin-family system itself, making “IIS activity” an incomplete description when individual peptide outputs can diverge.

Functional differentiation persists at the reproductive level. In *A. aegypti*, ILPs and ovary ecdysteroidogenic hormone have distinct effects on physiological processes involved in egg formation [19]. Their reproductive functions cannot be inferred from membership in a broad neuroendocrine class, and convergence on egg production does not imply peptide interchangeability.

Evidence from another insect order reinforces the participation of IIS in reproductive activation without establishing an invariant mechanism. In the Asian citrus psyllid *Diaphorina citri*, ILPs and their receptors contribute to ovarian development and oviposition-related physiology under laboratory host-feeding conditions [20]. These findings support taxonomic breadth for an IIS–reproduction connection, but not a quantified field-population consequence.

Interactions with JH are particularly informative because they can be nonuniform. In adult female *B. germanica*, nutritional state and JH influence ILP expression in gene- and tissue-dependent ways, and several responses do not conform to a simple linear JH→ILP relationship [21]. A change in one ILP transcript therefore cannot be treated as a proxy for global IIS or as proof of a fixed upstream endocrine hierarchy.

More importantly, coupling is not obligatory. In *Propylea japonica*, disruption of the IRS1–FOXO axis impairs oogenesis and vitellogenesis without detectable corresponding alteration of JH or 20E titres or the measured pathway markers [22]. This constitutes direct negative evidence against requiring JH or 20E mediation for that IIS-dependent reproductive phenotype in this model. It does not establish general independence of IIS. Instead, it defines a critical boundary condition for the present synthesis: an integrated network must permit conditional autonomy as well as endocrine coupling.

Molecular crosstalk

The strongest case for a network interpretation comes from mechanistically distinct forms of cross-talk rather than from any single three-way pathway. One form is downstream convergence. In *Bactrocera dorsalis*, insulin and 20E signaling both promote expression of the small GTPase Rab40C, and Rab40C perturbation affects ovarian development and fecundity-related outcomes [23]. Rab40C therefore provides a demonstrated convergence point in this species, but it should not be elevated to a universal insect reproductive hub.

A second form is upstream endocrine hierarchy. In female *Spodoptera litura*, InR perturbation alters JH-associated signaling, ovarian state and fecundity-related measures, supporting a route in which IIS can influence a JH-associated reproductive program [24]. Interpretation nevertheless requires methodological caution because exogenous mammalian insulin was among the experimental tools; the work supports coupling but does not completely resolve the endogenous topology.

A third form reverses the apparent direction of control. Kr-h1 can directly repress transcription of steroidogenic enzymes in larval steroidogenic tissues of *Drosophila* and *Bombyx*, establishing a molecular route from the JH-responsive program to suppression of ecdysteroid biosynthesis [25]. This direct mechanism shows why JH and ecdysteroid axes cannot always be represented as parallel independent inputs. Its direction, however, is bounded by developmental and tissue context.

A fourth form involves redeployment of developmental regulators within reproductive tissue. In the brown planthopper *N. lugens*, E93 and Kr-h1 directly interact and exert antagonistic effects during ovarian development [26]. The finding links components best known from metamorphic stage-identity regulation to adult reproductive physiology, but the ovarian interaction remains model-specific rather than proof of a conserved reproductive circuit.

Taken together, these mechanisms support a more discriminating synthesis. Multi-axis coordination has been demonstrated in the feeding-linked reproductive physiology of *R. prolixus* [1]. Direct JH/20E control of ILP transcription demonstrates cross-system regulation at the gene level in *A. aegypti* [2]. Yet JH–ILP relationships vary by gene and tissue in *B. germanica* [21], while IRS1–FOXO-dependent oogenesis in *P. japonica* proceeds without detectable JH or 20E mediation [22]. This article therefore proposes that molecular crosstalk be classified by network state rather than by the mere co-occurrence of endocrine pathways: receptor gating, target-dependent polarity, upstream hierarchy, downstream convergence, reciprocal or antagonistic regulation, and conditional independence are mechanistically different configurations. The configuration observed in one tissue, stage or species should not be presumed to persist in another.

Because those configurations differ in direction, biological level, and evidential strength, prose alone risks making mechanistically distinct relationships appear equivalent. **Table 1** therefore separates the crosstalk states that must remain distinct when inferring how JH, ecdysteroid, and IIS components jointly regulate insect physiology.

Table 1. Molecular crosstalk states that distinguish conditional endocrine-network configurations from a fixed JH–ecdysteroid–IIS cascade

Evidence	Interpretive consequence · Limits and uncertainty	Research or test · Synthesis standing	Biological setting
Met–Tai receptor gating			
JH-dependent Met phosphorylation enhances Tai interaction; functional receptor complexes display ligand binding	Ligand presence and receptor competence are separable dimensions of JH-network input Particular phosphorylation mechanism is not demonstrated as universal; binding alone does not specify organismal outcome	Resolve whether receptor-state modification changes cross-pathway coupling in other stages and taxa Evidence-derived mechanism; network-gain interpretation is proposed	Larval lepidopteran JH signaling; receptor-level evidence also available from termite and cockroach systems
Kr-h1 transcriptional polarity			
Kr-h1 can activate some JH-responsive targets and repress others	A JH-responsive branch cannot be assigned one invariant regulatory sign Direction depends on promoter and molecular context	Perturb identical regulators across defined target sets rather than inferring pathway-wide activation or repression Evidence-derived mechanism; polarity-state classification is proposed	Adult female mosquito JH response
AA–TOR–GATA ILP partitioning			
Nutrient state differentially regulates distinct ILP genes	IIS input structure is internally heterogeneous and nutrient-state dependent Blood-meal physiology and individual ILP identities limit transferability	Measure peptide-specific output alongside upstream nutrient sensors and downstream endocrine states	Blood-fed adult female mosquito

		Evidence-derived mechanism; partitioned-input category is proposed	
Insulin–20E downstream convergence			
Both endocrine inputs stimulate Rab40C-associated reproductive regulation	Separate pathways can converge on a shared reproductive effector without becoming one pathway Rab40C is not established as a universal convergence node	Test whether convergence survives tissue-specific or temporally separated disruption of each input Evidence-derived convergence; convergence-node class is proposed	Adult female fruit fly reproductive physiology
InR→JH-associated hierarchy			
InR perturbation alters JH-associated molecular/endocrine measures and reproductive outputs	IIS can occupy an upstream position relative to a JH-associated reproductive state Endogenous topology is not completely resolved; exogenous mammalian insulin introduces a methodological caveat	Use endogenous, tissue-resolved IIS perturbation with direct JH synthesis, titre, receptor, and ovarian readouts Evidence-derived coupling; hierarchy classification is proposed	Adult female moth reproduction
Kr-h1→steroidogenic repression			
Kr-h1 directly represses transcription of steroidogenic enzymes	A JH-responsive effector can directly constrain ecdysteroid production Direction is established in selected developmental tissues, not across all adult or reproductive states	Compare the same regulatory edge across developmental and adult steroidogenic contexts Directly supported regulatory edge	Larval fly and silkworm steroidogenic tissues
E93–Kr-h1 ovarian antagonism			
Protein interaction and perturbation reveal antagonistic reproductive effects	Metamorphic gene-network regulators can be redeployed as interacting reproductive regulators One reproductive tissue and taxon; conservation of the edge is unresolved	Test whether developmental-state and ovarian cofactors alter interaction sign or strength across orders Evidence-derived antagonism; redeployment interpretation is proposed	Adult female brown planthopper ovary
IRS1–FOXO conditional independence			
IIS disruption impairs reproductive processes while measured JH/20E titres or pathway markers remain unchanged	An IIS-dependent reproductive route need not require detectable JH or 20E mediation in every state Null mediation evidence is model- and measurement-specific and does not prove general independence	Simultaneously perturb IIS and each endocrine alternative while resolving tissue and temporal responses Evidence-derived boundary; "conditional independence" is a proposed network-state category	Adult female ladybird oogenesis and vitellogenesis

Developmental decision nodes

Developmental transitions illustrate why endocrine integration is better represented as conditional gating than as hormone-by-hormone control. In *Drosophila melanogaster*, nutrient-dependent endocycling in steroidogenic tissue influences metamorphic timing, demonstrating that cellular state within an endocrine organ can function as a developmental checkpoint [27]. Such a checkpoint does not imply that steroidogenic endocycles universally govern insect commitment; it establishes one mechanism by which nutritional history can alter competence to execute an endocrine transition.

Commitment itself can be distinguished from size-dependent permissive conditions. In *Tribolium castaneum*, increased E93 expression can trigger metamorphosis independently of the conventional threshold-size explanation [28]. Body size therefore need not be identical to the molecular event committing an animal to transition. Comparative interpretation remains essential because metamorphic architectures differ among insect lineages [29]. The Kr-h1/E93 stage-identity logic is consequently best viewed as reusable but context-sensitive rather than structurally invariant across metamorphic modes [3, 8, 29].

We therefore propose a developmental decision node as a temporally bounded configuration in which nutritional competence, steroidogenic capacity, JH-responsive stage identity, ecdysteroid signaling, and commitment machinery jointly constrain which transition remains available. The concept describes regulatory integration, not a newly discovered anatomical switch.

These distinctions are difficult to recover from a linear pathway diagram because competence, endocrine signaling, and commitment can overlap in time while remaining mechanistically separable. **Figure 1** therefore represents developmental regulation as a temporal signal-integration field with conditional cross-links and explicit boundaries.

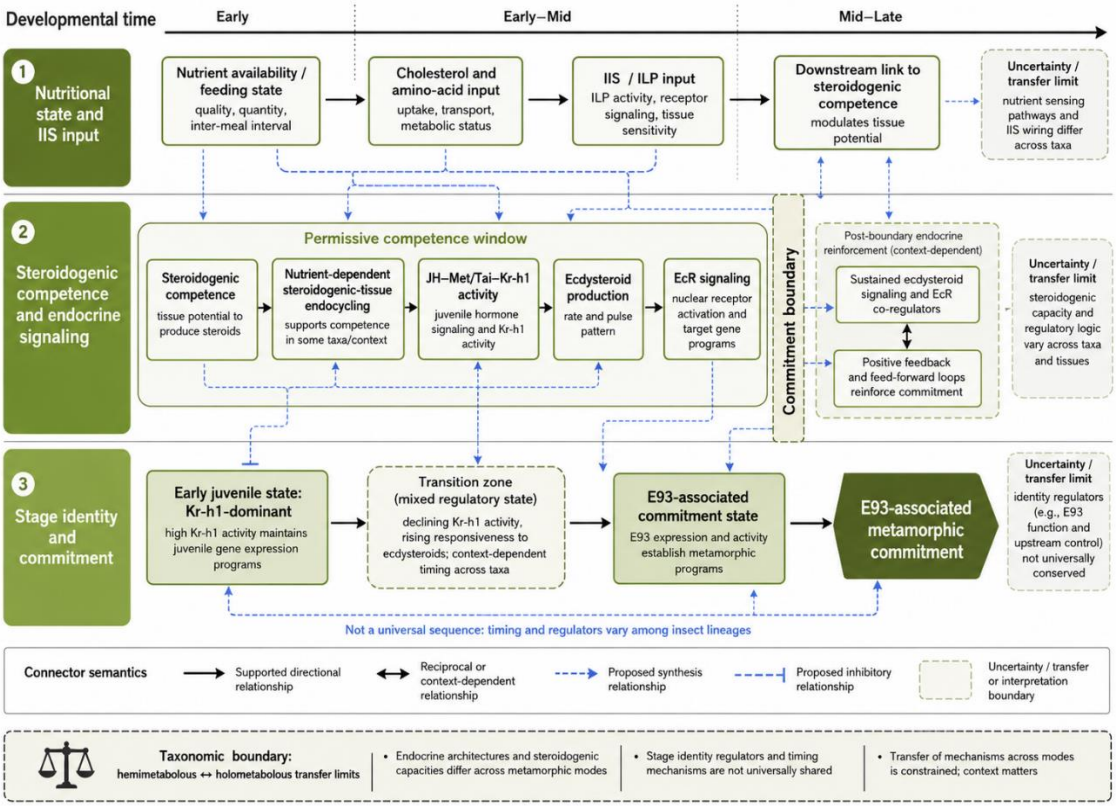


Figure 1. Competence, stage identity, and commitment occupy separable temporal states during endocrine control of insect developmental transition

Reproductive decision nodes

Reproduction reuses developmental regulators while adding nutritional, ovarian, and post-transcriptional control. Endocrine integration extends beyond transcription because miRNAs, alternative splicing, and related post-transcriptional mechanisms can participate in reciprocal regulation of metamorphic and oogenic pathways [30]. Evidence for individual RNA-level edges remains uneven among taxa, so these mechanisms should enlarge the network's possible regulatory levels without licensing invented universal loops.

In blood-fed *R. prolixus*, nutritional and endocrine state become coordinated during reproduction [1], while JH receptor signaling supports differentiated reproductive outputs [13]. In *A. aegypti*, insulin-family signals and ovarian endocrine signals perform non-equivalent functions during egg formation [19]. Other insects expose different topologies: JH regulation of ILPs is nonuniform in *B. germanica* [21]; IIS-dependent oogenesis can remain detectably independent of JH and 20E changes in *P. japonica* [22]; insulin and 20E converge on a reproductive effector in *B. dorsalis* [23]; and IIS influences a JH-associated reproductive state in *S. litura* [24].

Accordingly, a reproductive decision node is proposed here as a state-dependent regulatory configuration linking resource information to ovarian activation, vitellogenesis, diapause, or oviposition. It is an analytical construct rather than a discrete anatomical organ.

The same nominal reproductive outcome can therefore arise from different endocrine configurations. **Table 2** separates those configurations so that convergence, hierarchy, branching, and independence are not mistaken for equivalent mechanisms.

Table 2. Reproductive regulatory states that distinguish alternative routes to ovarian activation, vitellogenesis, diapause, and oviposition

Reproductive decision state	Nutrient-coupled reproductive activation	Branched JH reproductive output	Endocrine division of labor	Seasonal reproductive suppression	Downstream convergence	Conditional independence
Evidence · Mechanistic interpretation	Feeding-associated IIS, JH, and ovarian endocrine responses Resource acquisition can reorganize several endocrine branches together	Met/Tai-dependent reproductive processes with differentiated downstream requirements JH reception does not imply one uniform downstream route	Insulin-family and ovarian endocrine signals have non-equivalent physiological effects Multiple signals can contribute to egg formation through distinct tasks	Reduced JH-associated state under controlled photoperiod promotes diapause physiology Environmental state can redirect reproductive endocrine configuration	Insulin and 20E regulate a shared reproductive effector Different pathways can converge without becoming interchangeable	IRS1–FOXO perturbation impairs reproduction without detectable JH/20E change IIS-dependent reproduction need not always require measurable JH/20E mediation
Limits and uncertainty · Perturbation implication	Pulsed blood feeding is not representative of all insects Resolve tissue and temporal ordering after feeding	Component dependence varies by reproductive output Separate receptor activation from each ovarian endpoint	Signal functions are species- and cycle-specific Perturb signals individually before testing combinations	Photoperiodic and taxonomic restriction Cross photoperiod manipulation with pathway-specific perturbation	Shared effector not demonstrated universally Test whether simultaneous disruption produces additive or non-additive effects	Measurement- and species-bounded null result Test mediation with tissue- and time-resolved dual perturbation
Evidential standing	Evidence-derived; node interpretation proposed	Evidence-derived	Evidence-derived	Evidence-derived; state-classification proposed	Evidence-derived; convergence class proposed	Evidence-derived boundary; independence class proposed
Biological setting	Blood-fed hemipteran female	Female blood-fed bug	Mosquito gonotrophic cycle	Female beetle diapause	Adult fruit-fly ovary	Ladybird oogenesis

Network-level integration

Environmental conditions can alter inter-organ regulation of metabolism, growth, and endocrine state, as extensively characterized in *Drosophila*-centered literature [31]. Such plasticity provides context for endocrine-network reconfiguration but does not itself demonstrate adaptive benefit in natural populations.

The synthesis proposed here therefore treats network topology as conditional. Direct transcriptional coupling exists [2], direct JH-effector control of steroidogenesis exists [25], and state-dependent reuse of Kr-h1 exists [3]. Conversely, an endocrine source can remain unresolved [17], and a reproductive IIS route can operate without detectable JH/20E mediation [22]. These observations are compatible only if "integration" permits both connected and partly autonomous routes.

Biological levels must also remain separate. Molecular interaction, hormone production, tissue response, ovarian development, and organismal reproduction are linked levels, not interchangeable measurements. The resulting network is consequently a state-, tissue-, stage-, sex-, and taxon-dependent synthesis whose individual edges require separate empirical justification.

Predictions and perturbation tests

The proposed architecture is useful only if it can be falsified. First, coupling should be tested with factorial disruption of more than one endocrine branch. A directly demonstrated cross-link such as JH/20E regulation of

ILP transcription [2] should be contrasted with a system showing conditional independence [22] and with direct JH-effector repression of steroidogenesis [25]. If all perturbations produce the same hierarchy regardless of state, the proposed reconfigurable topology would be weakened.

Second, temporal and tissue resolution should distinguish hierarchy from coincident activation. Multi-axis physiology in *R. prolixus* provides a relevant starting system [1], whereas stage-dependent Kr-h1 function demonstrates why identical components cannot be assumed to carry identical meanings through time [3]. Downstream convergence [23] and IIS-associated JH regulation [24] should therefore be tested by staggered, tissue-specific perturbations.

Third, equivalent perturbations should be compared between developmental and reproductive states. Stage-dependent Kr-h1 activity [3], JH-dependent reproductive diapause [12], adult JH reproductive functions [13], and the steroidogenic endocycle checkpoint [27] predict that network position may shift even when a regulator is reused.

Finally, conservation of a molecule should not be treated as conservation of its regulatory edge. Comparative stage-identity evidence [8], reproductive IIS evidence from a psyllid [20], metamorphic diversity [29], and environment-dependent endocrine integration [31] make cross-order replication essential before assigning an invariant topology. Validation should therefore prioritize matched perturbations across tissues, stages, sexes, feeding regimes, and metamorphic modes rather than merely accumulating additional pathway associations.

Conclusion

JH, ecdysteroids, and IIS are best interpreted neither as isolated endocrine systems nor as components of a mandatory three-axis cascade. The evidence supports multiple forms of connection—hierarchy, convergence, antagonism, reciprocal regulation, and stage-dependent reuse—while also documenting uncertainty and conditional independence. This article therefore proposes a reconfigurable regulatory network in which developmental and reproductive outcomes depend on the configuration of endocrine relationships available in a particular biological state. Its value lies in making those alternative configurations explicit and experimentally distinguishable. The architecture remains a synthesis requiring tissue-resolved, temporally resolved, and cross-taxonomic testing before any specific topology can be considered broadly conserved.

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