

JUVENILE HORMONES IN DEVELOPMENT OF IXODOID TICKS: A SHORT REVIEW OF CURRENT CONTROVERSIAL SITUATION IN TICK ENDOCRINOLOGY

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ABSTRACT: The problem of juvenile hormones (JHs) in ixodoid ticks is quite controversial and disputable due to contradictions in data on effects of JHs, juvenoids and their antagonists in these chelicerate arthropods. It remains unsolved until now even after recent studies by R.M. Roe's group (USA), whose conclusion that JHs are absent in ticks and do not control their metamorphosis and reproduction (Roe et al. 1999b, 2001; Neese et al. 2000), was supported by some insect physiologists (Gilbert et al. 2000; Wilson 2004). However my investigations on limb regeneration in ticks have demonstrated specific morphogenetic effects of JH-agonists and antagonists upon sensillar sets in Haller's organ regenerates (Belozеров 1999a, 2001 a,b,c, 2003a,b, 2004). They provided evidence of similarity between ticks (as chelicerate arthropods) and insects (as mandibulate arthropods) in regard to JHs and their function as "*status quo*" factors in the control of developmental processes. This is confirmed also by the retinoic acid (RA) juvenilizing effects known in insects (Nemec et al. 1993), and discovered recently in ixodid ticks (Belozеров 2003a, 2004a). Action of RA in morphogenetic processes in ticks is revealed also by its specific teratogenic effect through axial duplication of some compartments in Haller's organ regenerates. The study of Haller's organ regeneration in ticks provides positive perspectives for investigations in tick endocrinology and developmental biology, particularly in bioassaying of compounds with JH-activity for chelicerate arthropods.

Key words: ixodid ticks, juvenile hormones, regeneration, Haller's organ

INTRODUCTION

The study of hormonal mechanisms controlling development and reproduction in chelicerate arthropods, and ixodoid ticks in particular, reveals its definite lag behind the progress in endocrinology of mandibulate arthropods (e.g. insects and crustaceans). In lesser degree this concerns molting ecdysteroid hormones that are common in insects and ticks in regard to both their general function (primary initiation of apolysis followed by the whole cascade of molting events — Diehl et al. 1986; Stauffer and Connat 1990; Lomas and Rees 1998), and to their action at the cellular and molecular level (through participation of specific nuclear hormonal receptors, namely EcR and RXR — Palmer et al. 1999).

The situation with another group of developmental hormones, the so-called juvenile hormones (JHs), is much more unclear and contradictory in ticks. These hormones are of the sesquiterpenoid nature with the function of "*status quo*" factors in the insect development at the immature stages (Riddiford 1996), and reproductive regulation at the adult stage (Wyatt 1997). However, for ixodid and argasid ticks the problem of the presence and function of JHs remains unsolved (Solomon et al.

1982; Lomas and Rees 1998), and represents the subject of much controversy and arguments. The current situation with JHs and possible approaches in further investigations of JHs in ixodid ticks are considered in the present paper*.

CURRENT DOMINANCE OF NEGATIVE IDEAS CONCERNING THE JUVENILE HORMONE PROBLEM IN TICKS

Many investigations dealing with effects of insect JHs (either natural or their synthetic mimics and antagonists) have demonstrated that in ixodoid ticks these compounds exert, as a rule, common non-specific, toxic action (mortality of eggs, engorged larvae and nymphs, reduction of female fecundity etc.). There are no contradictions for such non-specific JH-effects in ticks (Table 1, 1). However, the results of investigations in regard to the possibility of specific, gonadotropic and morphogenetic effects of JHs in ticks are very contradictory, being confirmed by some students and rejected by others (Table 1, 2–3). The same controversies exist regarding the presence of JHs in ticks (Table 1, 4). Table 1 gives an emphatic, but objective illustration of this conflicting situation with deep contradiction between positive and negative results.

* The contribution was presented at the 5th EURAAC symposium in Berlin (July 2004). The manuscript was reviewed and recommended for publication by two anonymous reviewers and was revised by the author according to their comments. Unfortunately the author was not able to send the revised copy to the Editors of the 5th EURAAC Proceedings (G. Weigmann, G. Alberti, A. Wohltmann and S. Rugosa), and therefore submit it for publication in "ACARINA" (with consent of the Proceeding's editors).

Table 1

The presence of juvenile hormones (JHs) in ticks (Ixodoidea) and effects of insect JHs, their agonists and antagonists on ticks (summary of results)

Effects	Results	References
1. Non-specific, toxic effects	a. Positive results (mortality of eggs, of engorged larvae and nymphs, or reduction of female fecundity)	Bassal 1974; Ioffe et al. 1977, 1979; McDaniel and Oliver 1978; Solomon and Evans 1978; Leahy and Booth 1980; Khalil et al. 1984; Abdelmonem et al. 1986; Teel et al. 1996; Donahue et al. 1997
	b. Negative results (normal development of eggs)	Slusser and Sonenshine 1996
2. Specific gonadotropic effects	a. Positive results (stimulation of gonad development)	Bassal and Roshdy 1974; Pound and Oliver 1979; Obenchain and Mango 1980; Connat et al. 1983
	b. Negative results (absence of stimulation)	Chinzei et al. 1991; Lunke and Kaufman 1993; Chinzei and Taylor 1994; Li and Jiang 1995; Friesen and Kaufman 2004
3. Specific morphogenetic effects	a. Positive results (juvenilization or imaginization as a response to JH analogs or JH antagonists)	Belozеров 1999a,c; Liu et al.1999; Belozеров 2001a,b,c; Belozеров 2002, 2003a,b, 2004a,b,c
	b. Negative results (no specific structural changes after treatment by JH)	Obenchain 1979; Solomon and Evans 1978; Solomon et al. 1982
4. Presence of JH in ticks	a. Positive results (analytical, indirect)	Venkatesh et al. 1990; Roe et al. 1993, 1999a; Lomas et al. 1996
	a. Positive results (analytical, direct)	Sonenshine et al. 1989; Roe et al. 1992, 1993; Liu et al. 1997, 2002
	b. Negative results (analytical, direct)	Neese et al. 1998, 2000; Roe et al. 1999b, 2001
	b. Negative results (bioassays)	Neese et al. 1998, 2000; Roe et al. 1999b, 2001

[from Belozеров (2001c) with supplementary references]

Several current reviews on JHs in arthropods (Gilbert et al. 2000; Wilson 2003) favor the hypothesis of the absence of JHs in ixodoid ticks. This can be explained by the results in recent investigations of R. Mike Roe' group (USA) with *Dermacentor variabilis* and *Ornithodoros parkeri* (Neese et al. 1998, 2000, 2001; Roe et al. 1999b, 2001), demonstrating that ixodoid ticks "do not have the ability to make the common insect juvenile hormones, and these juvenile hormones do not regulate tick metamorphosis or reproduction as hypothesized in literature" (Neese et al. 2000, p.477), though the opposite conclusion on the presence of JHs in ticks was expressed in their previous publications (Sonenshine et al. 1989; Venkatesh et al. 1990; Roe et al. 1992, 1993, 1999a). The negative conclusion appears to be more convincing, as it is evidenced through modern analytical approaches, bioassays and radiobiosynthesis methods, while the opposite posi-

tive conclusion of the same authors was based mostly on a possibility of JH-degradation by endogenous esterases and hydrolases. The idea that ticks do not have JHs and that JH is not a "*status quo*" hormone regulating nymphal-adult metamorphosis and vitellogenesis was repeated at the X International Congress of Acarology as a new perspective in tick endocrinology (Roe et al. 2001; Neese et al. 2001). M. Roe's conclusion (no insect juvenile hormones in Acari!) was declared by him and his colleagues in their review on the results of the VII International conference on juvenile hormones (Gilbert et al. 2000, p.631), with the assumption that both metamorphosis and reproduction in ticks appear "to be controlled by a hormone other than the common insect JH" (ibid., p.626), though with reservation that this is "not the final word on the subject of JH in ticks", inasmuch as "the structure of this hormone and its origin remain conjectural" (ibid., p.632).

AN OPPOSITE APPROACH TO THE JUVENILE HORMONE PROBLEM IN TICKS AND ITS POSSIBLE SOLUTION

An opposite approach to the solution of the JH-problem in ticks has re-emerged from studies of regeneration of Haller's organs in prostriate and metastriate ixodid ticks (Leonovich and Belozеров 1992; Belozеров and Leonovich 1995; Belozеров et al. 1997; Belozеров 2000, 2001a,c). These complex, paired sensory organs located on the tarsi of tick forelegs of ixodoid ticks, are characterized by the high stability and species-specificity of their structure in terms of the number and topography of sensillar hairs. Their sets in Haller's organ compartments (the capsule, the distal, pre- and postcapsular parts) display strong regular ontogenetic changes. These changes involve all the compartments and are especially remarkable in prostriate ticks (*Ixodes*) (Fig. 1, A–C). The most drastic changes occur during larval-nymphal metamorphosis (duplication of distal and central postcapsular sensilla, appearance of additional sensilla in the capsule and in the precapsular compartment, usually called the anterior pit). Minor changes (duplication of the bordering postcapsular sensilla only) occur at the adult stage. Much less change occurs in metastriate ticks (e.g. *Hyalomma* and *Haemaphysalis*) that usually show only duplication of the postcapsular sensilla at the nymphal stage (Belozеров and Leonovich 1995; Belozеров 2001a, 2004a; Leonovich and Belozеров 2004).

Regenerates of Haller's organ in the nymphal and adult ticks, with the left foreleg amputated at the larval and nymphal stage, respectively, show specific and regular structural modifications of their sensillar sets (Belozеров 2001a) and strongly depend on the life-cycle stage when the regeneration took place (Fig. 1, D,E). Adult regenerates (developed after a foreleg amputation at the nymphal stage) are characterized by an increased number of sensilla, *i.e.* by their atavistic multiplication, while nymphal regenerates (after foreleg amputation at the larval stage) demonstrate opposite changes with a reduction in the number of sensilla and with restoration of larval traits, *i.e.* juvenilization of regenerates (Belozеров 2001a). This regularity is characteristic to all ixodid ticks, with some differences in prostriate and metastriate ticks (Belozеров et al. 1997; Belozеров and Leonovich 1995). Adult Haller's organ regenerates in prostriate ticks are characterized by an increase in the number of porous sensilla both in the distal compartment (from normal two to three-four in 58 and 84% of regenerates in *Ixodes ricinus* and *I.*

rubicundus, respectively), and in the precapsular compartment (from normal one to two-four in 100% of regenerates in *I. ricinus* and from one to two-five in 96% of regenerates in *I. rubicundus*) (Belozеров et al. 1997; Leonovich and Belozеров 1992). In contrast, 40% of nymphal regenerates in *I. ricinus* (and 65% of them in *I. rubicundus*) retained the larval number and topography of the distal sensilla. Also, 46% of nymphal regenerates in *I. rubicundus* (and 70% of them in *I. ricinus*) retained the larval sets of the postcapsular sensilla (Belozеров et al. 1997; Belozеров 1999b, 2001a).

The observed structural changes in the nymphal and adult Haller's organ regenerates have received satisfactory explanation in the hypothesis (Belozеров et al. 1997), suggesting that the character of regenerative processes is determined by the level of intrinsic JHs (high at the larval, but low at the nymphal stage) in correspondence with the role played by these hormones as “*status quo*” factors in the insect metamorphosis. This hypothesis was confirmed by special experiments with juvenoids and antijuvenoids (see Fig. 2) and their impact on Haller's organ regeneration in ixodid ticks (Belozеров 1999a,c, 2000, 2001a,b,c, 2002c, 2003a, 2004a,b,c).

The first data evidencing the *status quo* function of insect JHs in developmental events of ixodid ticks were received in experiments with an impact of JH agonists (methoprene and fenoxycarb) on reparative regeneration of adult Haller's organ after amputation of left foreleg in nymphal ticks (Belozеров 1999a). In these experiments, methoprene produced the specific juvenilizing effect on development of Haller's organ regenerates in adults of *I. ricinus* (Fig. 1, G), namely the restoration of the larval traits in the sensillar sets of the distal compartment (in 30% of adult regenerates) that was never observed without juvenoid treatment, and of postcapsular area (in 46–77% of adult regenerates), as well as the suppression of multiplication of the porous anterior-pit, precapsular sensilla (in 42% of adult regenerates). This effect was less distinct in the metastriate ticks — *Hyalomma* (Belozеров 1999a) and *Haemaphysalis* (Belozеров 2004). Methoprene by its juvenilizing effect is considerably superior to other juvenoids — fenoxycarb (Belozеров 1999a) and pyriproxyfen (Belozеров 2003a). All three juvenoids (Fig. 2) had no effect on Haller's organ formation of the intact right foreleg.

Another essential evidence for morphogenetic function of JH in ticks was received in the study of effects produced by the JH-antagonist, precocene II (Fig. 2), on Haller's organ regeneration after ampu-

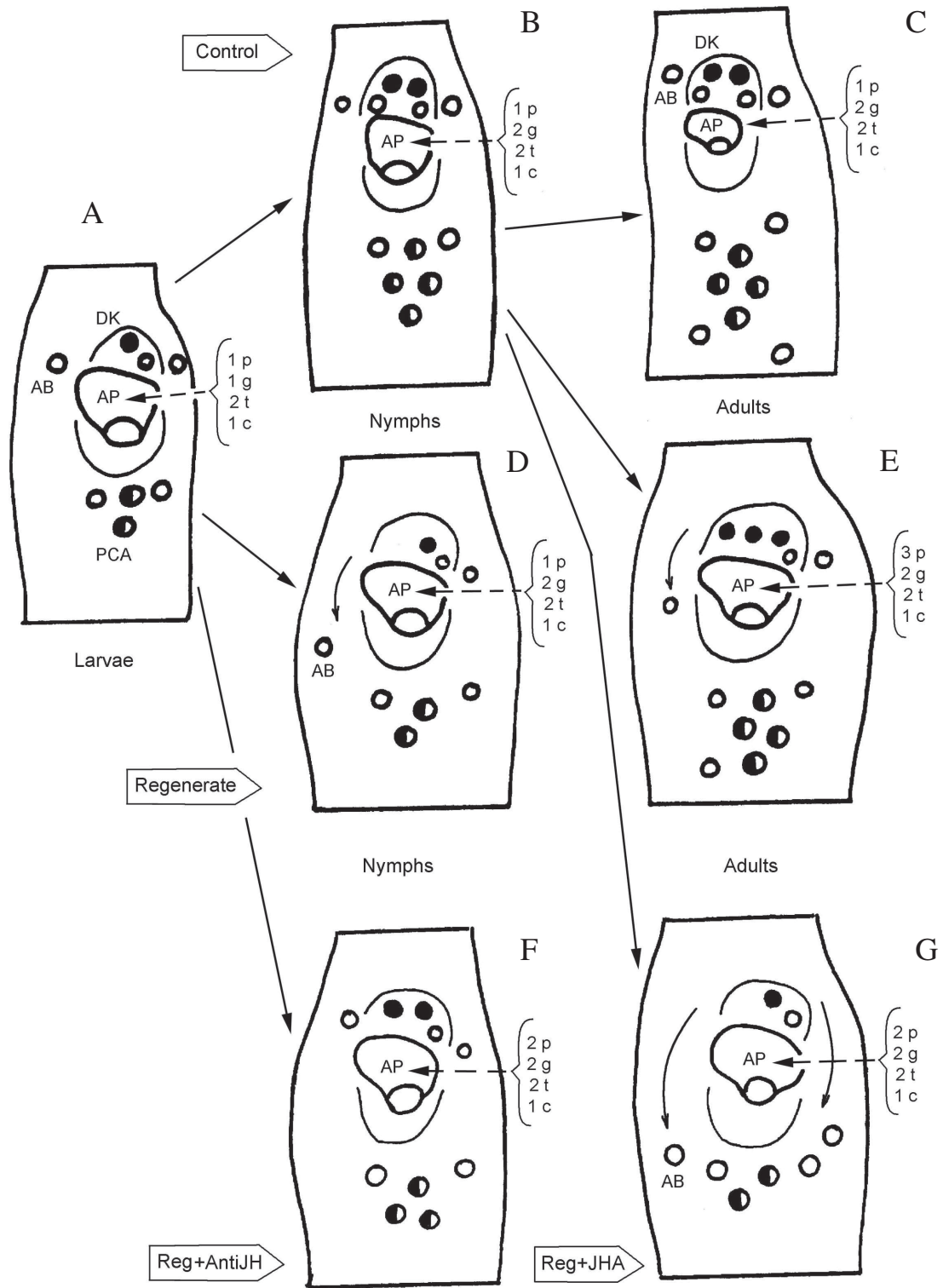


Fig. 1. Ontogenetic changes in the external structure of the *Ixodes ricinus* Haller's organ during normal development (A–C), after regeneration without additional treatment (D–E), with treatment by the antijuvenoid, precocene II (F), and by the insect juvenile hormone analog, methoprene (G). DK — distal compartment with long porous (●) and short smooth (○) sensilla; AP — anterior-pit (precapsular) compartment with its set of porous (p), grooved (g), thin (t) and conical (c) sensilla; PCA — postcapsular area with central, pc (●) and bordering, pb (◊) sensilla; AB — anterior bordering sensilla (arrows show their shift after regeneration) (from: Belozero 2001c).

tation of the left foreleg in *I. ricinus* larvae (Belozero 2001b). The effect of precocene was revealed in preventing the juvenilization of the nymphal

Haller's organ regenerates (Fig. 1, F) that resulted in the development of additional distal and postcapsular sensilla in 29% and 42% of regenerates,

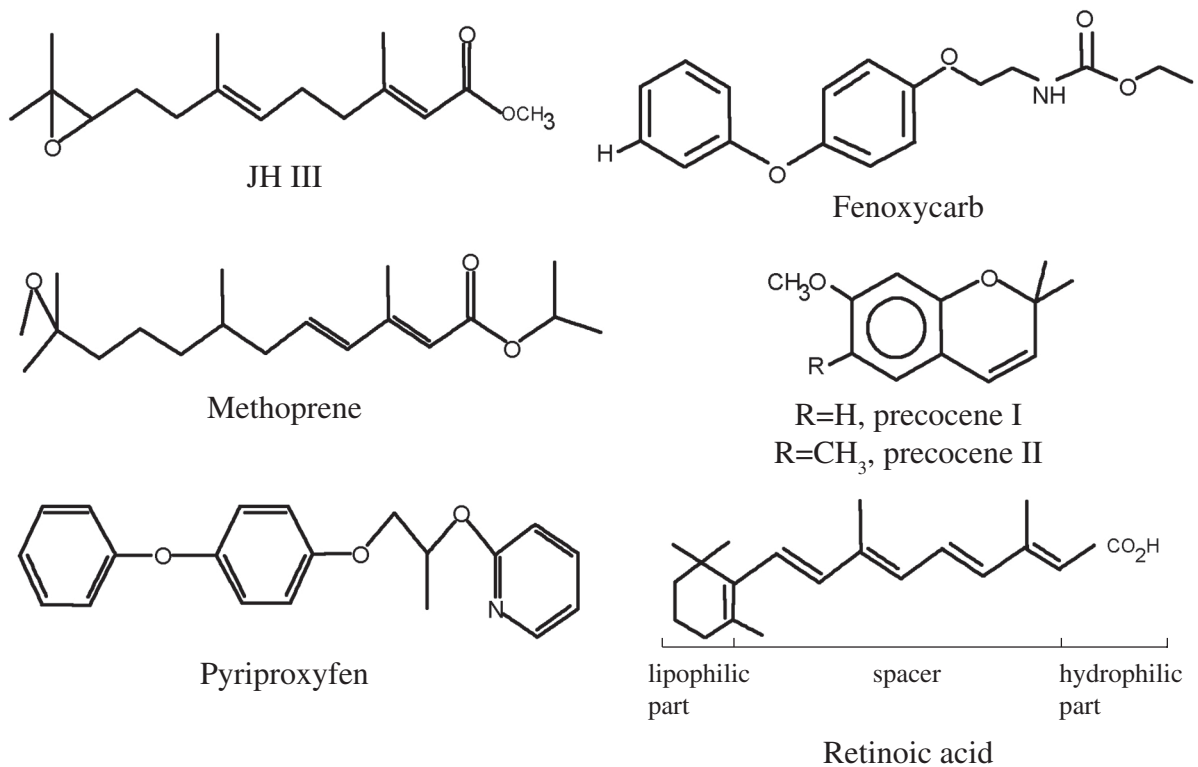


Fig. 2. Chemical structure of insect juvenile hormone (JH III), three juvenoids (methoprene, pyriproxyfen and fenoxycarb), antijuvenoid (precocene), and a retinoid (retinoic acid) studied in the described experiments on JH effects on Haller's organ regeneration.

respectively. It is of interest that precocene (in contrast to juvenoids) affects specifically not only reparative regeneration, but also normal developmental processes (this is evidenced by multiplication of distal porous sensilla in Haller's organ of the right intact foreleg in 29% of nymphs). All the mentioned effects of precocene are in strong agreement with its antijuvenoid action, and confirm the idea of morphogenetic function of JH-like compounds in ixodid ticks.

A novel evidence for participating sesquiterpenoid compounds in hormonal control of development and metamorphosis in ixodid ticks was received in experiments with Haller's organ regeneration under the influence of retinoic acid (RA) (Belozero 2003b, 2004a,c). This retinoid, possessing high morphogenetic and teratogenic activity in many invertebrate and vertebrate animals, reveals the JH-like effects, as shown already, in insect development and reproduction (Nemec et al. 1993). I recently discovered that RA (like juvenoids) could induce juvenilization of Haller's organ regenerates both in prostrate (Belozero 2003b) and metastriate ticks (Belozero 2004a). In contrast to JH-mimics (methoprene and pyriproxyfen), but similarly with antijuvenoid precocene, this retin-

oid exerts its morphogenetic effect in sensillar sets of Haller's organ on the intact right foreleg too. It is of interest, that RA (as well as precocene) does affect the sensillar structures in Haller's organ of the intact right tarsus, but do not affect its cuticular structures and its external shape. It is quite possible that RA has some relation to the phenomenon of the so called "regenerative induction" (Belozero 2001a), inasmuch as the exogenous RA induces some structural changes in sensillar sets of Haller's organ of the intact foreleg (Fig. 3), similar to regenerative changes in this organ at the amputated contralateral limb. Action of RA in morphogenetic processes in ticks is confirmed also by its specific teratogenic effects through axial duplication of the precapsular (anterior-pit) and capsular compartments in Haller's organ regenerates (Belozero 2002b, 2003b), and by involvement of nuclear retinoid receptors, RAR and RXR, in cellular and molecular mechanisms of developmental control in ticks (Palmer et al. 1999).

CONCLUSION

The results of experiments on effects of insect JH-agonists and antagonists, as well as retinoids, on Haller's organ regeneration in ixodid ticks pro-

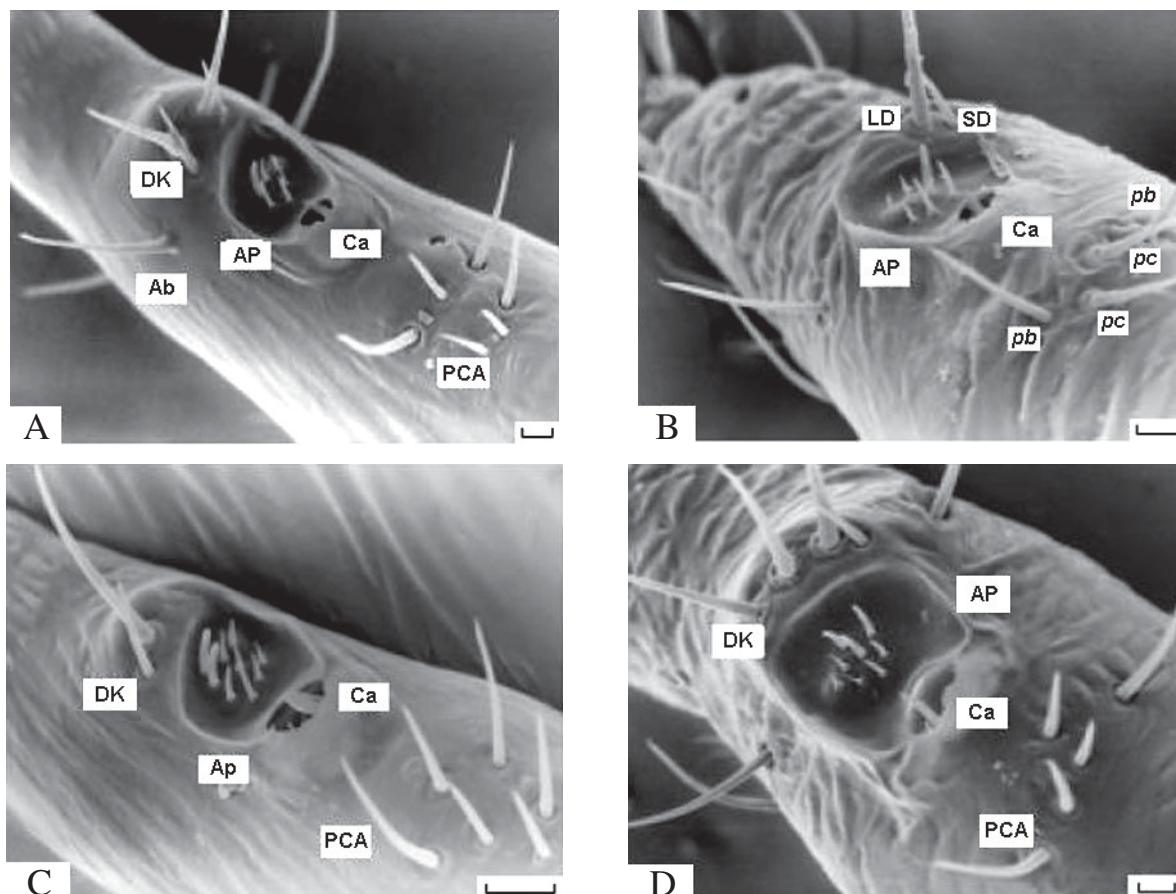


Fig. 3. External compartments of Haller's organ in *Ixodes ricinus* nymphs (A–C) and an adult tick (D). DK — the distal knoll, Ca — the capsule, AP — the anterior pit (precapsular) and PCA — the postcapsular area. A — nymphal Haller's organ of the right (control, nonamputated) foreleg with normal sensillar sets in DK (2 LD + 2 SD), in AP (1 p + 2 g + 2 t + 1 c) and in PCA (2 pb + 4 pc), as well as with normal shape of the tarsus and unchanged structure of its integument; B — the nymphal regenerate of the left foreleg (effect of methoprene) with the larval set of sensilla in DK (1 LD + 1 SD), with nymphal set in AP (1 p + 2 g + 2 t + 1 c) and with larval set in PCA (2 pb + 2 pc), as well as with regenerative deformation of tarsus and its integument; C — the inductive changes in nymphal Haller's organ of the right (nonamputated) foreleg (1 LD + 1 SD in DK, and multiplication of AP-sensilla), similar to those in the regenerates of the contralateral foreleg, amputated at larval or nymphal stage (no changes of the tarsal shape and of structure in its integument in the right, nonamputated foreleg); D — an adult regenerate of the left foreleg (effect of pyriproxyfen): multiplication of sensilla in DK (3 LD + 1 SD) and AP (3 p + 2 g + 2 t + 1 c), but retention of nymphal set in PCA (2 pb + 4 pc), the tarsus shape and structure of its integument express typical regenerative changes (from: Belozero 2003a).

duce reliable evidence of similarity between chelicerate and mandibulate arthropods in regard to the role of JHs as “*status quo*” factors controlling their developmental morphogenetic events. This idea presents a positive perspective for further investigations in tick endocrinology, inasmuch as the use of Haller's organ regeneration as a specific and sensitive test can be of real significance in bioassaying compounds with JH-activity for chelicerate arthropods, and in studying the structure and origin of real JHs that are peculiar for ixodoid ticks and likely relate (Laufer 1988) to terpenoid compounds.

ACKNOWLEDGEMENTS

The work was supported by the Russian Foundation of Basic Research (grant 01–04–49778) and

by Federal Program for Leading Scientific Schools (project HIII–7130.2006.4). The author thanks Prof. G. Weigmann for his generous help for the author's attendance at the 5th EURAAC Symposium in Berlin. The author is grateful also to Prof. D.E. Sonenshine (USA), Prof. W.R. Kaufman (Canada) and Dr. A.V. Bochkov (Russia-USA) for supplying some important bibliographic information, as well as to Dr. P.B. Klimov (Russia-USA) for correction of the English style of the paper.

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