Biostable analogs of insect kinin and insectatachykinin neuropeptides: A review of novel classes of antifeedants and aphicides

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Abstract: Neuropeptides are regulators of critical life processes in insects, but are subject to rapid degradation by peptidases in the hemolymph (blood), tissues and gut. This limitation can be overcome via replacement of peptidase susceptible portions of the insect neuropeptides with non-natural residues or moieties to create analogs with enhanced biostability. Two neuropeptide families, the insect kinins and insectatachykinins, stimulate gut motility and Malpighian tubule fluid secretion in certain insects but unmodified members demonstrate little or no effect when fed to pea aphids (Acyrthosiphon pisum) in an artificial diet. Nonetheless, biostable analogs developed via the strategic introduction of either bulky Aib residues and/or β-amino acids demonstrate potent antifeedant and aphidical effects when administered orally; whereas other biostable analogs are inactive. Although the precise mechanism of action has not been delineated, the activity may be associated with disruption of the physiological processes that these neuropeptides regulate in insects. The most active of the biostable insect kinin and insectatachykinin analogs show LC₅₀ values of 0.063 nmole/μl (LT₅₀ = 1.68 days) and 0.0085 nmole/μl (LT₅₀ = 1.1 days), respectively; matching or exceeding the potency of some commercially available aphicides. The biostable analogs represent important leads in the development of alternative, environmentally sound aphid control agents.

Keywords: myotropic, fluid secretion, peptidase resistance, insecticide, A. pisum
INTRODUCTION

About 250 out of a total of approximately 4,000 aphid species that have been identified represent serious pests to various crops around the world, causing both direct damage to plants via the process of ingestion and indirect damage by transmitting viruses that can devastate agricultural crops [1]. The pea aphid (*Acyrthosiphon pisum*) is of particular significance and causes hundreds of millions of dollars of crop damage every year. Many populations of this organism have already acquired resistance towards a number of traditional and modern insecticides, making a search for alternative strategies imperative [2]. In addition, aphids are not sensitive to the toxins produced by the bacterium *Bacillus thuringiensis* (*Bt*) [3]. However, the genome of *A. pisum* has recently been sequenced by the International Aphid Genomic Consortium providing a resource for the discovery of new targets for control (AphidBase; http://www.aphidbase.com; [4]). The sequences of members of several neuropeptide classes native to the pea aphid have been recently reported, including one from the insect kinins (ASDKHGRPKNFFSWG-NH$_2$) [5] and three insectatachyrhinin (also known as tachykinin-related [TRP]) peptides (VPSADAFYGR-NH$_2$, ASMGFMGMR-NH$_2$, and DYYSNKGSAGFFGMR-NH$_2$) [6]. Neuropeptides regulate numerous processes that are critical for insect survival. Due to their specificity and their high activity at extremely low concentrations, regulatory neuropeptides have been studied as potential leads for the development of new environmentally friendly pest control agents. However, the natural peptides are generally not useful as control agents in their native state, as they are susceptible to degradation by endogenous peptidases present in the insect digestive system, hemolymph (blood), and tissues [7-9]. To overcome the limitations inherent in the physicochemical characteristics of peptides, the development of mimic analogs has been used as a strategy to enhance their biological effects. It has been proposed that blocking or overstimulating the receptors of insect neuropeptides could lead to reduction of pest fitness or even increased mortality [7, 10]. Generally, the mimetics are derived by the structural modification of the lead peptide sequence to overcome a number of metabolic limitations, such as proteolytic degradation that restrict the use of peptides as agents capable of modulating aspects of insect physiology [7, 11]. One mimetic approach that was employed in this research is the incorporation of unnatural moieties that impart steric-hindrance such as $\alpha,\alpha$-disubstituted amino acids as well as $\beta$-amino acids adjacent to peptidase hydrolysis-susceptible amide linkages within the neuropeptides [5, 6].

In this manuscript, we review recent research undertaken to evaluate the oral antifeedant and aphicidal activity of unmodified neuropeptides and/or core
fragments along with mimetic analogs featuring enhanced biostability from two distinct insect neuropeptide classes – the insect kinins and tachykinin–related peptides. In each case, the unmodified neuropeptides and core fragments elicit little or no activity, whereas biostable analogs exhibit significant, and in some cases, potent aphicidal properties.

INSECT KININS

The insect kinins are multifunctional neuropeptides found in several insect and invertebrate groups [12, 13]. The first members were isolated from the cockroach, *Leucophaea maderae*, according to their myostimulatory activity on hindgut contraction [14, 15]. Following their discovery, insect kinins were also shown to stimulate fluid secretion in isolated Malpighian tubules of the cricket *Acheta domestica* and yellow fever mosquito *Aedes aegypti* [12]. Insect kinins, and/or analogs, have subsequently been reported to modulate digestive enzyme release [16, 17] and interestingly they can also inhibit weight gain in larvae of the tobacco budworm (*Heliothis virescens*) and corn earworm (*Helicoverpa zea*), both significant agricultural pests [18, 19].

The insect kinins share the evolutionarily conserved C-terminal pentapeptide Phe-X¹-X²-Trp-Gly-NH₂, where X¹ = His, Asn, Ser or Tyr, and X² = Ser, Pro or Ala [13]. The C-terminal pentapeptide kinin core is the minimum sequence required for full cockroach myotropic and cricket diuretic activity in *in vitro* assays [15] and for activation of kinin receptors expressed in CHO-K1 cells [20]. Within the C-terminal pentapeptide core, the side chains of Phe¹ and Trp⁴ have been deemed critical, whereas the variable position 2 tolerates a wide range of chemical characteristics, from acid to basic residues and from hydrophilic to hydrophobic [13, 20, 21]. The significant activity elicited by restricted-conformation analogs incorporating β-turn mimetic motifs in both myotropic, diuretic and expressed insect kinin receptor assays provide evidence for the importance of a core β-turn conformation for receptor interaction [22].

Due to kinin peptide susceptibility to both exo- and endopeptidases in the insect hemolymph and gut, these insect peptides cannot be directly used as pest control agents. Members of the insect kinin family are hydrolyzed, and therefore inactivated, by tissue-bound peptidases of insects [8, 23, 24]. Two susceptible hydrolysis sites in insect kinins have been reported in the active core sequence Phe¹-Tyr²-Pro³-Trp⁴-Gly⁵-NH₂. The primary site is between Pro³ and the Trp⁴ residue, with a secondary site N-terminal to the Phe¹ residue in natural extended insect kinin sequences [24, 25]. It has been demonstrated experimentally that
the primary hydrolysis site is susceptible to cleavage by angiotensin converting enzyme (ACE) from the housefly and both the primary and secondary hydrolysis sites are cleaved by neprilysin (NEP) [8].

To enhance resistance to peptidase hydrolysis, biostable analogs were developed via incorporation of either bulky Aib or β-amino acid residues to non-critical residue positions adjacent to the primary and secondary hydrolysis susceptible peptide bonds. The Aib residue has been shown to be compatible with the insect kinin turn conformation which is important for receptor interaction [26]. Among those that have been evaluated are the analogs K-Aib-1 (Aib-Phe-Phe-Aib-Trp-Gly-NH$_2$), K-βA-2 (Ac-Arg-β$^3$Phe-Phe-Phe-β$^3$Pro-Trp-Gly-NH$_2$), and the hybrid analog K-Aib-4 (Ac-Arg-β$^3$Phe-Phe-Phe-Aib-Trp-Gly-NH$_2$). The analogs K-Aib-1 and K-Aib-4 demonstrate a highly significant increase in resistance to hydrolysis by peptidases ACE, neprilysin, and Leucine aminopeptidase (aminopeptidase M) as compared with a standard kinin [27]. The analog K-Aib-4, capped with an acetyl group on the N-terminus, was 95-fold less susceptible to hydrolysis by aminopeptidase. Analog K-Aib-1 features a sterically hindered α,α-disubstituted residue at the N-terminus and also demonstrates resistance to hydrolysis by the aminopeptidase, with a rate of hydrolysis being 32-fold lower, than the standard insect kinin [27]. Challenged with NEP, analogs K-Aib-1 and K-Aib-4 were 17 and 10-fold less susceptible to hydrolysis than the standard kinin, respectively. And, analogs K-Aib-1 and K-Aib-4 were 24 and 45-fold less susceptible to hydrolysis by ANCE than the standard kinin, respectively [27].

The analog K-βA-2 is capped by an acetyl group to enhance resistance to aminopeptidases, and none is hydrolyzed by NEP in the period of time that is required to degrade 100% of the natural insect kinin LK-1 [28]. During a period of time in which 82% of LK-1 is degraded, only 4% of analog K-βA-2 is hydrolyzed by ANCE [28].

All three of the biostable analogs have demonstrated agonist responses that match the potency range of native insect kinins in an in vitro Malpighian tubule fluid secretion assay of the cricket Acheta domesticus, as well as on a receptor expressing system of the mosquito Aedes aegypti [20, 24, 27]. Of particular note, K-Aib-1 matches or exceeds the potency of native insect kinins in both an in vitro Malpighian tubule fluid secretion assay and a receptor expressing system of the mosquito Aedes aegypti [27].

The three biostable analogs were fed to aphids [5] dissolved in an artificial diet containing sugar and the resulting effects compared with that of the unmodified core insect kinin sequence FFSWG-NH$_2$ and the native aphid kinin (ASDKHGRPKNTFFSWG-NH$_2$). The core kinin C-terminal pentapeptide
sequence proved inactive [5] and the aphid kinin demonstrated only weak activity at the highest concentration of 0.2 nmol/µl (Smagghe and Nachman, unpublished data) (Table 1). In contrast, the biostable analogs K-Aib-1 and K-βA-2 demonstrated antifeedant and aphicidal effects. K-Aib-1 was particularly potent with an LC$_{50}$ of 0.063 nmol/µl (0.046 µg/µl) and an LT$_{50}$ of about 1.68 days. Analog K-βA-2 was less potent, with an LC$_{50}$ of 0.119 nmol/µl (0.122 µg/µl) (Table 1) [5]. In contrast, the hybrid analog K-Aib-4 proved to be inactive, with only 22% mortality at the highest concentration tested (0.1 nmol/µl). It is interesting to note that the absolute order of activity of the two active biostable insect kinin analogs in the aphid assay correlates with that of the potency of interaction with expressed tick and mosquito IK receptors [5], which provides indirect evidence that the mode of action, although not identified, may be via interaction with insect kinin receptors.

Table 1. Aphid mortality LC$_{50}$ values, expressed as µg/µl and nmol/µl (= mM), in the artificial diet for three biostable insect kinin analogs and two natural insect kinins against the pea aphid Acyrthosiphon pisum [5]

<table>
<thead>
<tr>
<th>Name</th>
<th>Sequence</th>
<th>LC$_{50}$ in diet [5]</th>
<th>LC$_{50}$ in diet [5]</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>µg/µl</td>
<td>nmol/µl (= mM)</td>
</tr>
<tr>
<td>K-Aib-1</td>
<td>[Aib]FF[Aib]WG-NH$_2$</td>
<td>0.046</td>
<td>0.063</td>
</tr>
<tr>
<td>K-Aib-4</td>
<td>Ac-R[β3Phe]FF[Aib]WG-NH$_2$</td>
<td>Inactive</td>
<td>Inactive (22%/0.1 mM)*</td>
</tr>
<tr>
<td>K-βA-2</td>
<td>Ac-R[β3Phe]FF[β3Pro]WG-NH$_2$</td>
<td>0.122</td>
<td>0.119</td>
</tr>
<tr>
<td>Insect kinin fragment</td>
<td>FFFSWG-NH$_2$</td>
<td>Inactive</td>
<td>Inactive (0%/0.2 mM)*</td>
</tr>
<tr>
<td>Aphid kinin</td>
<td>ASDKHGRPKNTFSSWG-NH$_2$</td>
<td>Inactive</td>
<td>Inactive (29%/0.2 mM)*</td>
</tr>
</tbody>
</table>

* % toxicity with highest concentration tested (given between brackets)

Clearly, the aphicidal activity of the insect kinin analogs is associated with the presence of components that enhance the resistance of the C-terminal core region to peptidases, as the unmodified insect kinin core peptide demonstrates no activity. The presence of structural components that protect both susceptible regions is not in itself sufficient for activity, as analog K-Aib-4 demonstrates little or no aphicidal effects even though its sterically-hindered Aib residue is also present at the same position of the active analog K-Aib-1, and its β3Pro residue is similarly present in the same position of active analog K-βA-2.
While honeydew formation is depressed in the aphids exposed to the active analogs, the observations of normal piercing behavior and the presence of at least some honeydew suggest that ingestion is nonetheless taking place. Impairment of normal physiological patterns in the aphids ingesting the active analogs may lead to a reduction in subsequent feeding and, in turn, to the observed reduction in levels of honeydew formation. Furthermore, the unmodified peptide is readily ingested by the aphids, as is the essentially inactive analog K-Aib-4 which also contains the same unnatural α,α-disubstituted and β-amino acids found in the active analogs. Thus, the fact that these three insect kinin analogs do not trigger avoidance of diet ingestion would seem to suggest that some ingestion of the three active biostable analogs may also be taking place.

Two aphicides that are currently used in the marketplace for selective IPM control against aphids in agriculture are pymetrozine and fonicamid, and these can serve as references. Both compounds act specifically against aphids as feeding inhibitors, although their exact mechanism(s) remain unidentified. Fonicamid [N-(cyanomethyl)-4-(trifluoromethyl)-3-pyridinecarboxamide] is a novel insecticide; its LC₅₀ as determined in an experimental setup similar to that used for the insect kinin analogs was 0.144 nmol/μl with a typical loss of honeydew formation followed by death, and its LT₅₀ was 1.1 days to kill 50% of aphids feeding on diet containing 0.44 nmol/μl [5]. For pymetrozine [(E)-4,5-dihydro-6-methyl-4-[(3-pyridylmethyleneamino)-1,2,4-triazin-3(2H)-one], Sadeghi and co-workers calculated with use of a similar feeding apparatus with a diet sachet an LC₅₀ of 0.01 μg/ml [29].

INSECTATACHYKININS

Like the insect kinins, the insectatachykinins (also designated ‘tachykinin-related peptides’; TRPs) demonstrate an activity profile that includes both myostimulatory activity on gut tissues as well as Malpighian tubule secretion. The multifunctional TRP neuropeptides have been found in several invertebrate groups [14, 30]. They were first isolated from the locust, Locusta migratoria, according to their myostimulatory activity on the isolated hindgut of the cockroach Leucophaea maderae. Following their discovery, TRPs were also shown to have myostimulatory activity on Locusta foregut and oviduct preparations [30]. TRPs have been shown to be present in endocrine cells of the cockroach [30], locust and Drosophila midgut [30], and evidence suggests that the midgut serves as a hormonal release site for the TRPs [31]. Malpighian tubules are located in proximity to the midgut, and it is of interest to note that TRPs have been shown
to stimulate Malpighian tubule writhing in the locust *L. migratoria*, and stimulate diuretic activity in tubules of the locusts *L. migratoria* and *Schistocerca gregaria* [32], as well as in tubules of the moth *Manduca sexta* [33].

Most TRPs share the conserved C-terminal pentapeptide motif Phe-X¹-Gly-X²-Arg-NH₂, a consensus sequence that has not been reported in vertebrates [30]. They do, however, share limited sequence similarity (approx. 30%) to the vertebrate tachykinin family, appearing more similar to fish and amphibian tachykinins (up to 45%) than to mammalian members [30, 34]. Nonetheless, receptor data indicate major pharmacological differences between TRPs from invertebrates and vertebrates that are mainly attributable to differences in the C-terminal amino acid (Arg vs Met) likely resulting from ligand-receptor coevolution [30]. These differences could be explored for design of insect-specific ligands.

Members of the TRP family are hydrolyzed, and therefore inactivated, by tissue-bound peptidases of insects. Two susceptible hydrolysis sites in TRPs have been reported in the C-terminal active core region sequence Gly¹-Phe²-Tyr³-Gly⁴-Val⁵-Arg⁶-NH₂. The primary site is between Gly⁴ and the Val⁵ residue, with a secondary site between the Gly¹ and Phe² residues. It has been demonstrated experimentally that the primary hydrolysis site is susceptible to cleavage by angiotensin converting enzyme (ANCE) from the housefly and both the primary and secondary hydrolysis sites can be cleaved by neprilysin (NEP) [35]. The N-terminal region of TRPs are susceptible to degradation not only by aminopeptidases but by the enzyme dipeptidyl peptidase IV (DPP IV); the latter has been shown to hydrolyze the bond between Pro and Ser of the locust TRP sequence Lom-TK-1 (or Locma-TRP-1)(GPSGFYGVRamide) and Leuma-TRPs [35].

To enhance resistance to peptidase hydrolysis, biostable analogs were developed via incorporation of bulky Aib residues to non-critical amino acid positions adjacent to the primary and secondary hydrolysis susceptible peptide bonds [36]. The following two multi-Aib TRP analogs were synthesized, Leuma-TRP-Aib-1 (pEA[Aib]SGFL[Aib]VR-NH₂) and Leuma-TRP-Aib-2 (pEA[Aib]S[Aib]FL[Aib]VR-NH₂). Both biostable Aib TRP analogs showed complete resistance to *Drosophila* ACE (ANCE) and enhanced resistance to NEP over a 2 h period, whereas natural Leuma-TRP-1 degraded to the extent of 98-99%. Nonetheless, the virtually complete protection afforded to Leuma-TRP-Aib-2 (0.0% hydrolysis) was much greater than that to Leuma-TRP-Aib-1 (47% hydrolysis) during exposure to NEP [6]. This difference is likely due to the presence in Leuma-TRP-Aib-2 of the extra Aib residue which protects the secondary NEP hydrolysis site between the Gly¹ and Phe² residues of the TRP C-terminal hexapeptide core sequence.
Although data on the activity of natural and/or modified TRP analogs have not been previously collected on in vitro bioassays of the pea aphid, data on the evaluations of the natural and biostable TRP analogs used in this study have been obtained for the isolated cockroach hindgut myotropic bioassay to determine and compare the extent of retention of biological activity. Both TRP Aib analogs retained significant myostimulatory activity in the hindgut bioassay, although the extent of this activity retention was different. The hindgut myostimulatory activity of analog Leuma-TRP-Aib-2 was much greater than that of Leuma-TRP-Aib-1. The EC\textsubscript{50} of Leuma-TRP-Aib-1 for stimulation of hindgut contractility was 10.5 nM (6.9-16.0) as compared with an EC\textsubscript{50} of 7.2 nM (5.1-10.3) for the parent natural cockroach TRP, Leuma-TRP-1 [6]. The difference in activity is not statistically significant, so the two are essentially equivalent in myostimulatory activity, and both achieve a maximal response. Leuma-TRP-Aib-2 was considerably less potent, but did demonstrate significant activity at 1 μM, achieving 48 ± 21% of the maximal response of the parent natural TRP. While the additional Aib residue in Leuma-TRP-Aib-1 confers an advantage over Leuma-TRP-Aib-2 in resistance to the enzyme NEP, it also leads to a considerable drop in activity in the hindgut myotropic assay [6].

The biostability afforded the two Aib analogs would also appear to greatly enhance the physiological effects of TRP peptides when fed to the pea aphid A. pisum. While the natural TRP peptides, including two that are native to the aphid, showed little or no aphicidal activity, high mortality appeared within the first 24 h for those treatment groups that received the two biostable analogs. The observation of high mortality within the first 24 h after exposure to the sugar water solutions containing the biostable TRP analogs strongly suggests that feeding is taking place, as death due only to starvation would be expected to require a longer time frame. After feeding for 3 days, an LC\textsubscript{50} value of 0.0085 (0.0037-0.0196) nmol/μl and an LT\textsubscript{50} of 1.1 days (at 0.5 nmole/μl) was calculated for Leuma-TRP-Aib-1 (Table 2) [6], matching or exceeding the potency of commercially available aphicides. By comparison, the LC\textsubscript{50} of commercial aphicides flonicamid and pymetrozine introduced in the first section above were determined to be 0.144 nmole/μl and 0.01 μg/μl, respectively. For the other biostable Leuma-TRP-Aib-2, activity was also observed but was lower than Leuma-TRP-Aib-1; its LC\textsubscript{50} was calculated at 0.165 (0.081-0.337) nmol/μl (Table 2) [5, 29]. It is of interest to note that the absolute order of activity of the two active biostable TRP analogs in the aphid assay correlates with that of the order of activity in the myotropic hindgut bioassay [6], which provides evidence that the mode of action, although not identified, may be via interaction with TRP receptors.
Table 2. Aphid mortality LC$_{50}$ values, expressed as µg/µl and nmol/µl (= mM), in the artificial diet for two biostable TRP analogs and two natural insect TRP against the pea aphid *Acyrthosiphon pisum* [6].

<table>
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<th>LC$_{50}$ in diet [6]</th>
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<tbody>
<tr>
<td>Leuma-TRP-Aib-1</td>
<td>pEA[Aib]SGFL[Aib]VR-NH$_2$</td>
<td>0.0087 0.0085</td>
<td></td>
</tr>
<tr>
<td>Leuma-TRP-Aib-2</td>
<td>pEA[Aib]S[Aib]FL[Aib]VR-NH$_2$</td>
<td>0.174 0.165</td>
<td></td>
</tr>
<tr>
<td>Leuma-TRP-1</td>
<td>APSGFLGVR-NH$_2$</td>
<td>Inactive</td>
<td></td>
</tr>
<tr>
<td>Acypi-TRP-1</td>
<td>ASMGFMGMR-NH$_2$</td>
<td>Inactive (32%/0.5 mM)*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inactive (14%/0.5 mM)*</td>
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</tbody>
</table>

* % toxicity with highest concentration tested (given between brackets)

**Other Insect Peptide Classes**

Antifeedant effects and increased mortality have been observed as well for members of two other insect neuropeptide families that have been fed to the pea aphid in artificial diets. A biostable analog of the C-type allatostatin Manse-AS (Manse denotes that the peptide is native to the lepidopteran *Manduca sexta*) containing D-amino acids that was introduced in an artificial diet led to aphid mortality at an LC$_{50}$ of 0.18 µg/µl, at least 4 times more potent than the parent unmodified allatostatin peptide [37], but 20-fold less potent than the biostable insectatachykinin analog Leuma-TRP-Aib-1 [6]. A diet containing Acypi-MS or LMS (at 0.5 µg/µl), unmodified members of the myosuppressins, fed to aphids also led to increased mortality over a longer 10-day period [38]. Two modified myosuppressin analogs proved to be inactive.

**SUMMARY**

While natural and unmodified neuropeptides of the insect kinin and insectatachykinin (TRP) classes demonstrate little or no activity when fed to the pea aphid *A. pisum*, biostable analogs with enhanced resistance to degradation by peptidases demonstrate potent anti-feedant and aphicidal effects that match or exceed the potency of some commercially available aphicides [5, 6]. The mechanism of the aphid antifeedant activity and high induction of mortality demonstrated by these biostable insect neuropeptide analogs cannot
be clearly identified at this point, but it may be associated with disruption of the physiological processes that this important neuropeptide family regulates in insects. The TRPs, like the insect kinins [5, 12, 13, 15], have been shown to stimulate both contractions of the hindgut [30, 34] as well as in vitro Malpighian tubule writhing [39] and fluid secretion in insects [32]. The aphicidal activity of the biostable insect kinin or TRP analogs may therefore result from a disruption of the digestive process by interfering with normal gut motility patterns and/or interference with normal fluid cycling in the gut. The osmotic pressure of plant phloem sap is generally higher than that of insect body fluids [40]. Pea aphids feature no Malpighian tubules. Nonetheless, water cycling along the length of the gut lumen is believed to contribute to the osmoregulation.

The active biostable neuropeptide analogs described in this review and/or 2nd generation analogs, either in isolation or in combination with biostable analogs of other neuropeptide classes that also regulate aspects of diuretic, antidiuretic, digestive, reproductive and/or developmental processes, represent potential leads in the development of selective, environmentally friendly pest aphid control agents capable of disrupting those critical processes.

Acknowledgements

This research was supported by the USDA/DOD DWFP Initiative (#0500-32000-001-01R)(RJN).

REFERENCES

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