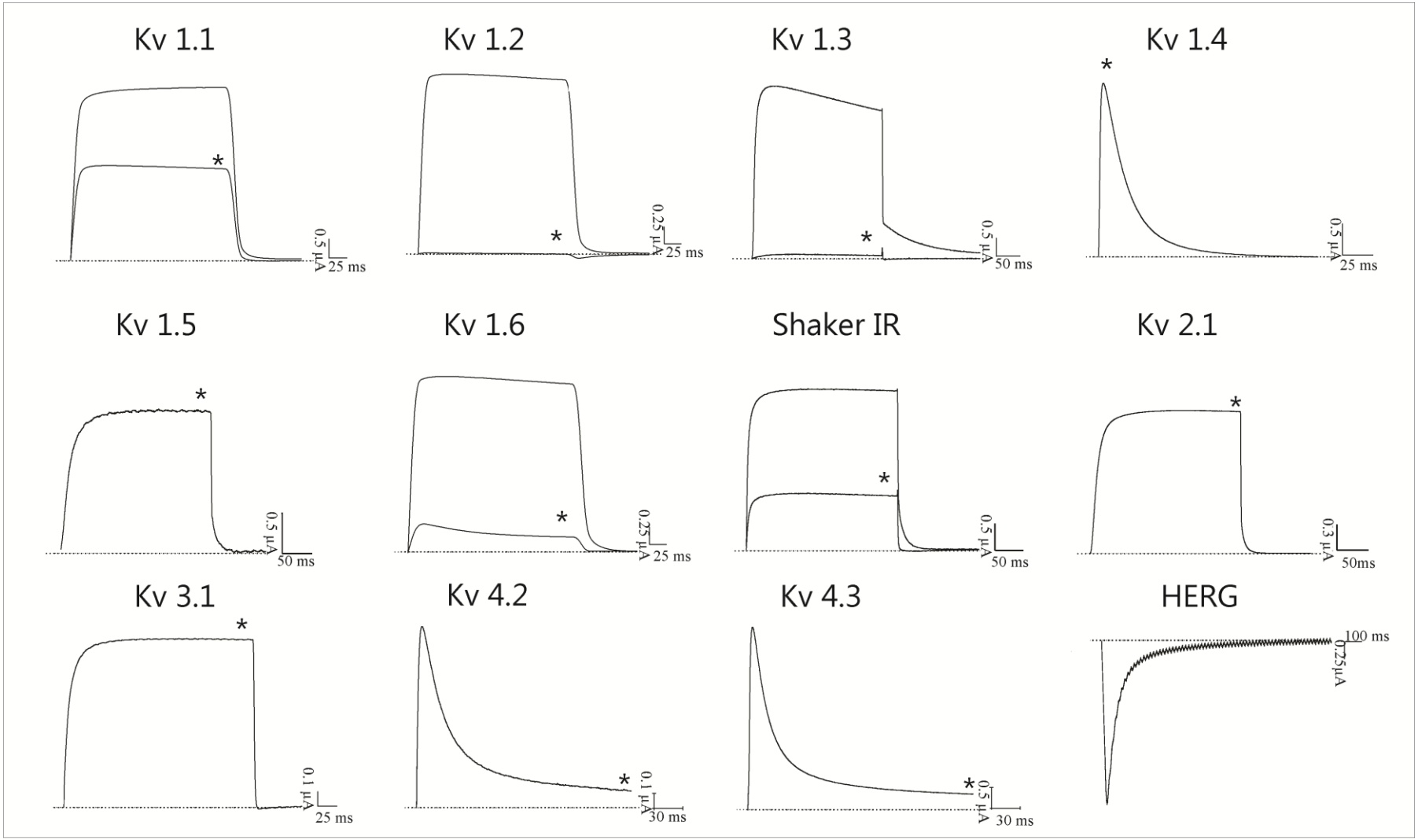
Kv 1.1
0.5 µA
25 ms
Kv 1.2
0.25 µA
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Kv 1.3
0.5 µA
50 ms
Kv 1.4
0.5 µA
25 ms
Kv 1.5
0.5 µA
50 ms
Kv 1.6
0.25 µA
25 ms
Shaker IR
0.5 µA
50 ms
Kv 2.1
0.3 µA
50ms
Kv 3.1
0.1 µA
25 ms
Kv 4.2
0.1 µA
30 ms
Kv 4.3
0.5 µA
30 ms
HERG
100 ms
0.25µA

Figure 32 – Electrophysiological screening of BcsTx1 (0.5 µM) on several cloned voltage–gated potassium channel isoforms belonging to different subfamilies. Representative traces under control and after application of 0.5 µM of BcsTx1 are shown. The asterisk indicates steady-state current traces after toxin application. The dotted line indicates the zero-current level. This screening shows that BcsTx1 selectively blocks K_V1.x channels at a concentration of 0.5 µM.

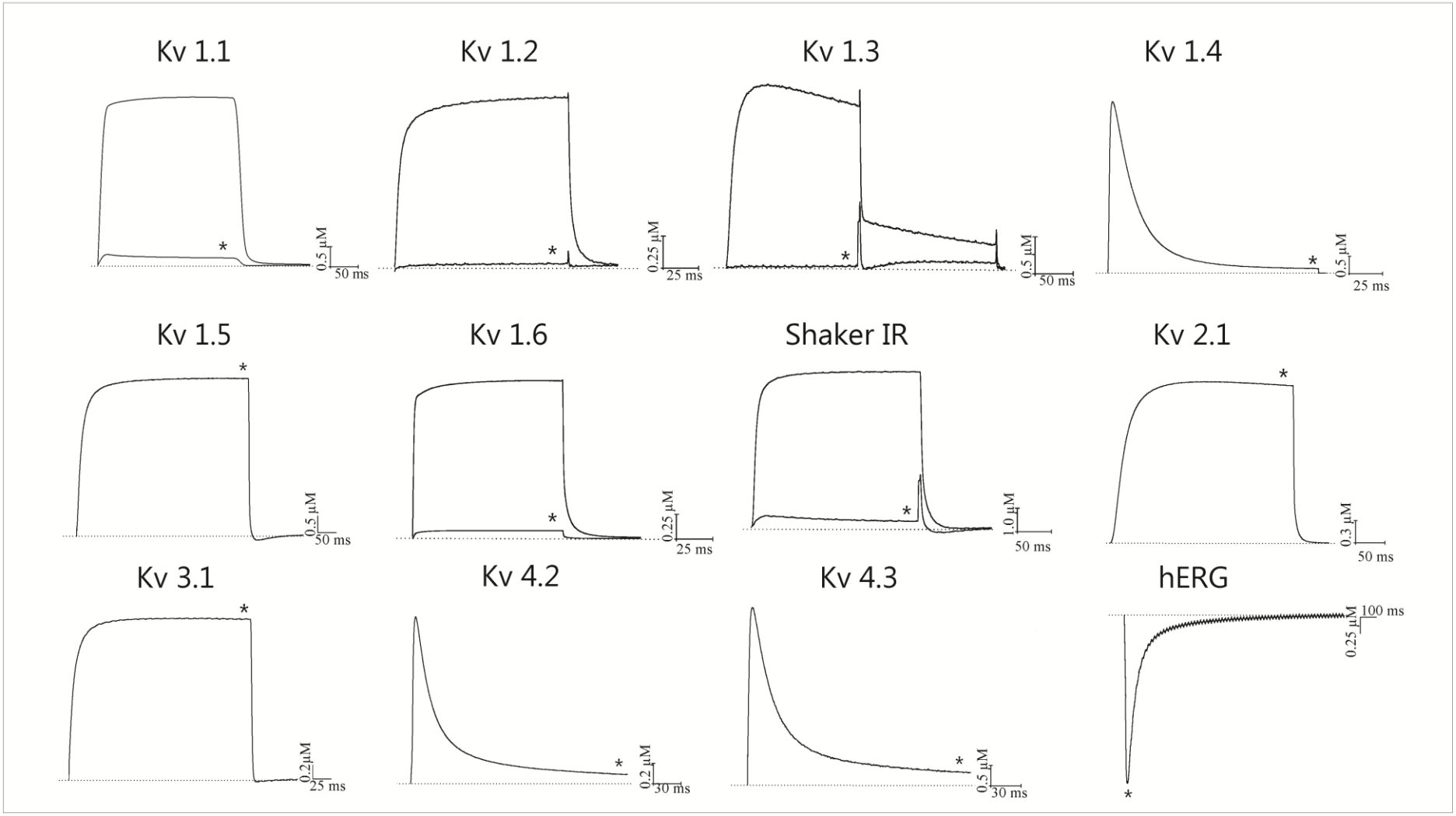
Kv 1.1
0.5 µM
50 ms
Kv 1.2
0.25 µM
25 ms
Kv 1.3
0.5 µM
50 ms
Kv 1.4
0.5 µM
25 ms
Kv 1.5
0.5 µM
50 ms
Kv 1.6
0.25 µM
25 ms
Shaker IR
1.0 µM
50 ms
Kv 2.1
0.3 µM
50 ms
Kv 3.1
0.2µM
25 ms
Kv 4.2
0.2 µM
30 ms
Kv 4.3
0.5 µM
30 ms
hERG
0.25 µM
100 ms

Figure 33 – Inhibitory effects of BcsTx2 (3 µM) on 12 voltage-gated potassium channels isoforms expressed in *X. laevis* oocytes. Representative whole-cell current traces in the absence and in the presence of 3 µM BcsTx2 are shown for each channel. The dotted line indicates the zero-current level. The * indicates steady state current traces after application of 3 µM BcsTx2. This screening carried out on a large number of K_V channel isoforms belonging to different subfamilies shows that BcsTx2 selectively blocks Shaker channels subfamily.

In order to characterize the potency and selectivity profile, concentration-response curves were constructed for BcsTx1. IC_{50} values yielded 405 ± 20.56 nanomolar (nM) for rKv1.1, 0.03 ± 0.006 nM for rKv1.2, 74.11 ± 20.24 nM for hKv1.3, 1.31 ± 0.20 nM for rKv1.6 and 247.69 ± 95.97 nM for *Shaker* IR (Figure 34A and Table 7). A concentration–response curve was also constructed to determine the concentration at which BcsTx2 blocked half of the channels. The IC_{50} values calculated are 14.42 ± 2.61 nM for rK_V1.1, 80.40 ± 1.44 nM for rK_V1.2, 13.12 ± 3.29 nM for hK_V1.3, 7.76 ± 1.90 nM for rK_V1.6, and 49.14 ± 3.44 nM for *Shaker* IR (Figure 34B and Table 7). Similarly to BgK, the BcsTx1 and 2 potencies are within the nanomolar range and, are more potent when compared to type 2 sea anemone toxins, such as Kalicludines (AsKC1-3), which blocks K_V1.2 channels with IC_{50} values around 1 µM (Schweitz et al, 1995). In general, previous work has shown that type 1 sea anemone toxins are more potent than type 2 and, it has been proposed in the literature that toxins with a *'functional dyad'* are more potent, because it provides a secondary anchoring point, contributing to a higher toxin affinity (Sabatier et al, 2004a; Sabatier et al, 2008). However, APEKTx1, a type 2 toxin from *A. elegantissima*, is a selective blocker of K_V1.1, with an IC_{50} value of 1 nM and the existence of a *'functional dyad'* has not been shown (Peigneur et al, 2011). Moreover, the electrophysiological characterization of the scorpion toxins Pi1 and Tc32 (from *Pandinus imperator* and *Tityus cambridgei*, respectively), which are known to potently inhibit K_V1 channels, suggested that other amino acids, rather than those of the '*functional dyad*' are also involved in both potency and selectivity of the K_V channel isoforms (Batista et al, 2002; Sabatier et al, 2004b). Although, it is worth noting

that the '*functional dyad*' of α-KTx family of scorpion toxins is very important for high affinity block and selectivity (Rodriguez de la Vega & Possani, 2004). For instance, toxin Pi2 (α-KTx7.1), from the venom of *P. imperator*, has a '*functional dyad*' formed by Lys27 and Trp8 and, is able to block $K_V1.2$ current with an IC_{50} value (0.032 nM) comparable to BcsTx1 (Rogowski et al, 1996). Also, MgTX (α-KTx2.2) toxin, from *Centruroides margaritatus*, binds with very high affinity to $K_V1.6$ (IC_{50} value of 5 nM) and, it was proposed the role of the side chain of the dyad lysine (Lys27) as a critical residue to the binding of the toxin to the ion conduction pathway of the channel (Garcia-Calvo et al, 1993).

Table 7 – BcsTx1 and BcsTx2 IC_{50} values in nanomolar (nM)

Isoforms	BcsTx1	BcsTx2
$K_V1.1$	405 ± 20.56	14.42 ± 2.61
$K_V1.2$	0.03 ± 0.006	80.40 ± 1.44
$K_V1.3$	74.11 ± 20.24	13.12 ± 3.29
$K_V1.6$	1.31 ± 0.20	7.76 ± 1.90
***Shaker* IR**	247.69 ± 95.97	49.14 ± 3.44

In order to elucidate whether BcsTx1 and 2 blocks the current through a physical obstruction of the *Shaker* IR channel pore or act as a gating modifier, current-voltage (I-V) experiments were performed. The currents were inhibited at the test potentials from − 90 to 100 mV, and the inhibition was not associated with a change of the shape of the I-V relationship. The control curve and the curve in the presence of BcsTx1 (500 nM) were characterized by a $V_{1/2}$ values of 20.85 ± 0.69 mV and 22.62 ± 0.73 mV, respectively. Moreover, the control curve and the curve in the presence of BcsTx2 (50 nM) were characterized by a $V_{1/2}$ values of 18.49 ± 1.49 mV and 23.88 ± 1.57 mV, respectively. The $V_{1/2}$ of activation was not significantly shifted ($p < 0.05$) and thus, channel gating was not altered by BcsTx1 and BcsTx2 binding (Figure 34C and 34D). Additionally, BcsTx1 and 2 shows a non-dependence of voltage for the blockage on a wide range from –10 mV to 50 mV (Figure 34E and 34F), and the blockage effect was reversible and a completely recovery was observed after washout, suggesting an extracellular site of action (Figure 34G and 34H). To date, type 1

sea anemone toxins have been described to act solely through a K_V channel pore-blocking mechanism (Castaneda & Harvey, 2009) .

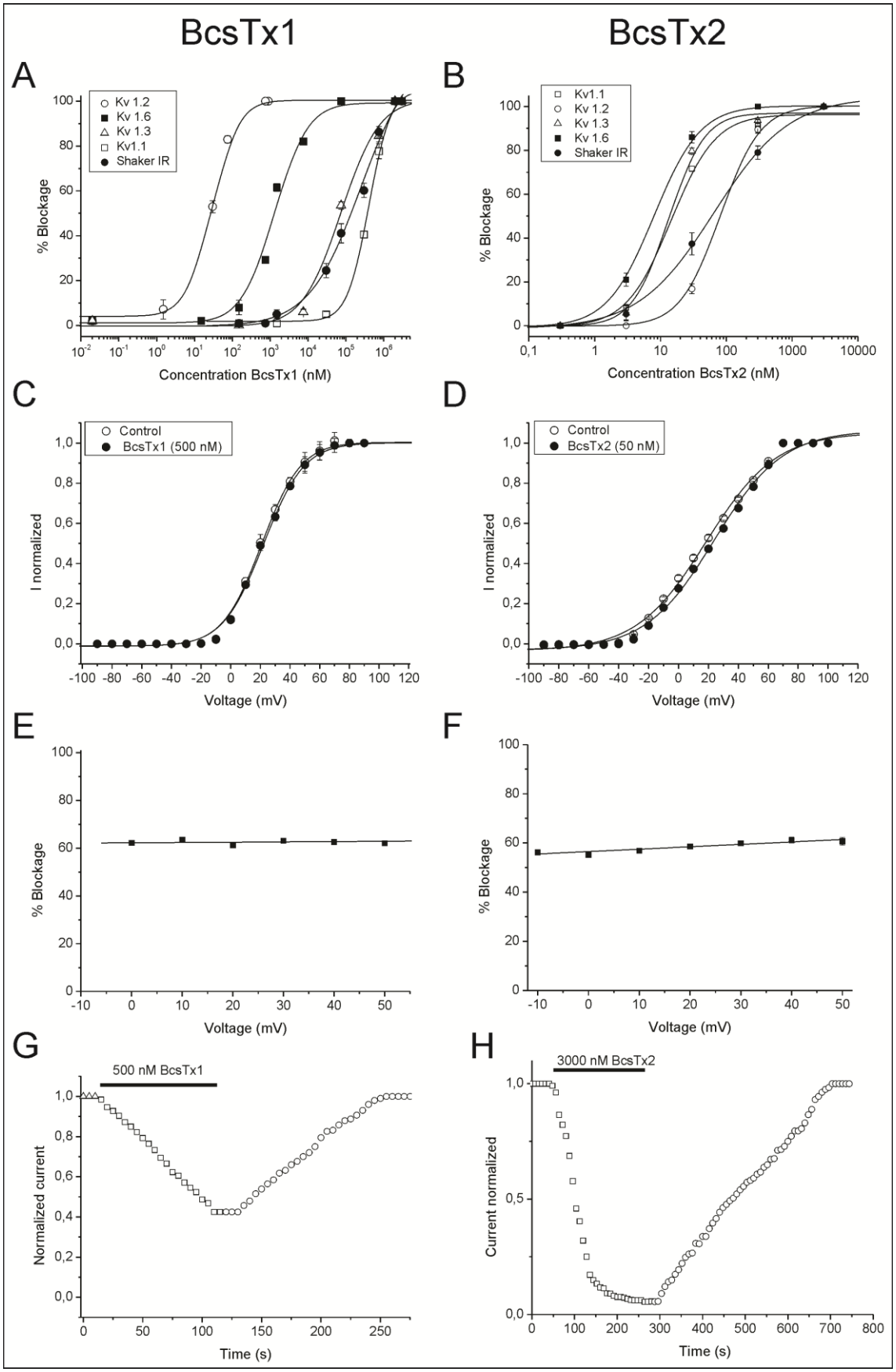

Figura 34 – Functional features of BcsTx1 and BcsTx2 on K_V channels. (A – B) Dose-response curves of BcsTx1 and BcsTx2 on $rK_V1.1$, $rK_V1.2$, $hK_V1.3$, $rK_V1.6$ and *Shaker* IR channels. The curves were obtained by plotting the percentage blocked current as a function of increasing toxin concentrations. All data are presented as mean ± standard error of at least 3 experiments (n ≥ 3). (C – D) Current-voltage relationship for *Shaker* IR isoform in control condition and in the presence of BcsTx1 (500 nM) and BcsTx2 (50 nM). Current traces were evoked by 10 mV depolarization steps from a holding potential of -90 mV. Open circles indicates the $V_{1/2}$ in control; closed circles, indicates the addition of toxins. (E – F) Percentage of currents left after application of BcsTx1 (500 nM) and BcsTx2 (50 nM) on *Shaker* IR channel. In a range of test potentials from -10 mV to +50 mV, no difference was observed in the degree of BcsTx1- and BcsTx2-induced blockage. (G – H) Representative experiment of the time course of *Shaker* IR current inhibition with BcsTx1 (500 nM) and BcsTx2 (3000 nM) and the reversibility hereof. Control (open square), washout (open circles). Blockage occurred rapidly and binding was reversible upon washout. Plots shown are a representative of at least 3 individual experiments.

3.4. Bioinformatics Analysis

3.4.1. Molecular models of BcsTx1 and 2.

Venomous animals produce a wide variety of neurotoxins with different types of amino acid sequences, secondary structures and disulfide bridge frameworks; and none of them is definitively associated with a particular animal species or ion channel selectivity (Sabatier et al, 2008). Type 1 sea anemone toxins are associated with the αα type of family fold. BgK toxin has an *'helical cross-like'* motif, in which one α-helix is disposed perpendicular to the others (Dauplais et al, 1997) (Figure 35A), and ShK has an *'helical capping'* motif (3_{10}αα), since one α-helix (formed by three amino acid residues) caps the other two helical structures (Tudor et al, 1996). The molecular models of the BcsTx1 and 2 (Figure 35B and 35C) were constructed using BgK as template, and the quality of the models were analyzed using PROCHECK (Laskowski et al, 1993).

BcsTx1 and 2 shares 55.3% and 62% of sequence identity with BgK, respectively. BcsTx1 and BcsTx2 analyzes revealed that 87.1% and 90.0% of residues are located in the most favored regions, 12.9% and 6.7% are located in additionally allowed regions and, 0% and 3.3% are located in generously allowed regions of the Ramachandran diagram, respectively (Ramachandran et al, 1963). The secondary structure of both toxins consists of three α-helical segments; the first α-helix comprises the amino acids 8–17, the second comprises the residues 24–29, and the amino acids 31–34 consists the third α-helix. Despite of the overall moderately identity between these three toxins, the residues of the second and third α-helices are highly identical. BgK second α-helix shares 83.3% and 100% of identity to BcsTx1 and 2, respectively, and the third is 100% identical within the three toxins.

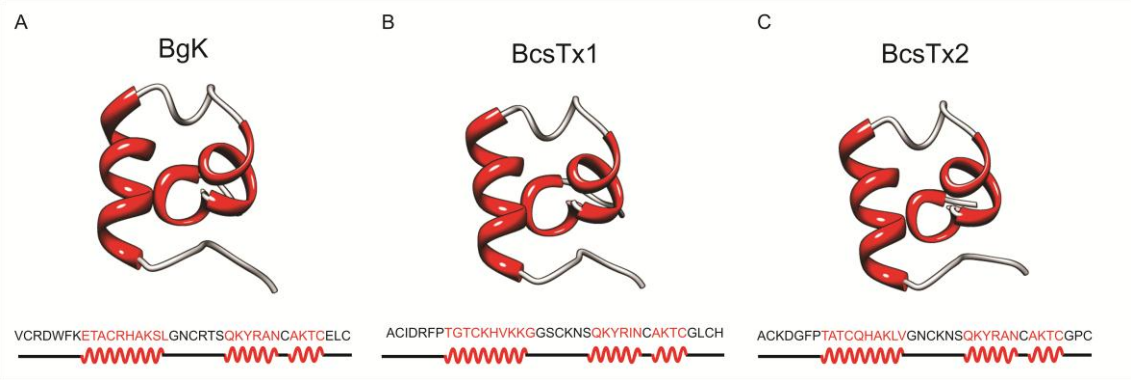

Figure 35 – 3-D model representation of BcsTx1 and BcsTx2. Models were constructed using BgK toxin as template (PDB code 1BGK). (A) Ribbon representation of NMR structure of BgK. Amino acid sequence and secondary structure: α-helix (red) and loops (gray). (B) Stereoscopic 3-D model of BcsTx1. (C) BcsTx2 molecular model.

4. Conclusions

In summary, we demonstrate for the first time, a venom composition and biological activity comparison between two geographically distant populations of sea anemones. Moreover, this is the first electrophysiological characterization of a sea anemone type 1 toxin on cloned *Shaker* IR insect channel, allowing us

to suggest that the role of these toxins in the physiology of the sea anemone would be related with predation and defense against predator and, highlights the possible application of these peptides as tools for research in neuroscience, as well as in the development of novel insecticides.

5. Considerações Finais

Na presente dissertação de Mestrado, quatro neurotoxinas de duas espécies de anêmonas do mar foram descritas e caracterizadas. No primeiro capítulo, nós investigamos dois peptídeos (AbeTx1 e BcsTx4) das anêmonas do mar *A. bermudensis* e *B. caissarum*. A caracterização eletrofisiológica mostrou que ambas são capazes de modular a cinética de *ativação* do $K_V1.1$, ao passo que o bloqueio dos outros subtipos não está relacionada à alterações em suas cinéticas de *ativação*/*inativação*. Mutantes da AbeTx1 permitiram inferir como esta se liga aos diferentes subtipos de K_V e a importância que um conjunto de aminoácidos básicos têm para sua funcionalidade. Interessantemente, estas duas neurotoxinas possuem um motivo estrutural semelhante ao das "*kappa-toxinas*", nunca antes descrito para toxinas de anêmonas do mar.

No segundo capítulo, as toxinas BcsTx1 e BcsTx2, da anêmona *B. caissarum*, foram também caracterizadas funcionalmente. Pela primeira vez demonstrou-se que toxinas do tipo 1 de anêmonas atuam em canais de *Drosophila melanogaster*, aventando a possibilidade da utilização destas neurotoxinas como modelos para o desenvolvimento de inseticidas. Neste trabalho também se demonstrou pela primeira vez, uma comparação do perfil cromatográfico da "*fração neurotóxica*" entre duas populações de anêmonas que estão geograficamente distantes e, interessantemente, uma variação no padrão de expressão de neurotoxinas foi observado.

Contudo, o raciocínio lógico da utilização de neurotoxinas de anêmonas do mar para a caracterização funcional e estrutural dos canais voltagem – dependentes de K^+ se mostrou eficiente, e os resultados obtidos servirão de base para formular novas hipóteses e delinear novos experimentos que serão realizados ao longo do meu doutoramento.

6. Conclusões

- ✓ A metodologia empregada para obtenção da peçonha das anêmonas *A. bermudensis* e *B. caissarum* e o isolamento e purificação das frações (FrIII) contendo os peptídeos neurotóxicos mostraram-se muito eficazes, permitindo a caracterização de quatro neurotoxinas que atuam em canais voltagem – dependentes de K^+.

- ✓ As neurotoxinas AbeTx1, BcsTx1, BcsTx2 e BcsTx4 são seletivas para os subtipos de K_V da subfamília *Shaker*. Seus mecanismos de ação são específicos para os diferentes subtipos, podendo bloquear a corrente dos íons K^+ através da modulação da cinética de *ativação* ou então pela simples obstrução física da passagem dos íons K^+ através do poro.

- ✓ A expressão dos peptídeos BcsTx1 e BcsTx2, pela anêmona do mar *B. caissarum*, está relacionada com a predação e/ou defesa contra predadores.

- ✓ As toxinas BcsTx1 e BcsTx2 são os novos membros do tipo 1 (subtipo 1b) de neurotoxinas de anêmonas do mar que atuam em K_V. Análises sugerem uma divergência evolutiva, uma vez que peptídeos com este motivo estrutural estão presentes em animais de diferentes Filos.

- ✓ A sequência de aminoácidos e o padrão de pontes dissulfeto da AbeTx1 e BcsTx4 nos permitem inferir que estes possuem um motivo estrutural semelhante ao das "*kappa-toxinas*" e, por isso, são os primeiros membros de um novo tipo (tipo 5) de neurotoxinas de anêmonas do mar que atuam em K_V.

- ✓ A utilização de neurotoxinas de anêmonas do mar como ferramentas para o estudo da estrutura e função dos canais voltagem – dependentes de K^+ se mostrou muito eficaz.

7. Financiamentos

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Instituto de Biociências da Universidade de São Paulo

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Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) por intermédio do *Programa de Apoio à Pós-Graduação* (PROAP)

Vigência 2011/2012

- ✓ Compra de peptídeo sintético do Laboratório GenScript (R$ 2.106,00).
- ✓ Compra de serino protease "*Endoproteinase Lys-C*" do Laboratório Sigma (R$ 1.096,00).

Vigência 2012/2013

- ✓ Realização de estágio na Universidade Federal do Rio de Janeiro para medidas de Ressonância Magnética Nuclear (R$ 2.300,00).

Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq)

- ✓ Processo nº 563874/2005-8 - Caracterização bioquímica de neurotoxinas da peçonha da anêmona *Bunodosoma caissarum* e do molusco *Conus ermineus* do Arquipélago de São Pedro e São Paulo. Uma comparação com as neurotoxinas da anêmona *Bunodosoma caissarum* do litoral sudeste do Brasil. Auxílio concedido ao professor Dr. José Carlos de Freitas (coordenador do projeto de pesquisa).

8. Resumo

ORTS, D.J.B. **Neurotoxinas de anêmonas do mar como ferramentas para o estudo da fisiologia de canais voltagem – dependentes de potássio**. 2013. 92 folhas. Dissertação (Mestrado). Instituto de Biociências da Universidade de São Paulo, Departamento de Fisiologia, São Paulo, 2013.

A peçonha das anêmonas do mar é uma fonte de compostos bioativos, incluindo toxinas peptídicas que são ferramentas para o estudo da estrutura e função dos canais voltagem dependentes de K^+ (K_V). Neste trabalho, quatro neurotoxinas foram purificadas da peçonha das anêmonas do mar *Actinia bermudenesis* e *Bunodosoma caissarum*. AbeTx1 e BcsTx4 possuem um motivo estrutural semelhante à das "*kappa-toxinas*" e análises funcionais e estruturais permitiram concluir que são os primeiros membros de um novo (tipo 5) de neurotoxinas de anêmonas do mar que atuam em canais K_V. Por sua vez, a similaridade estrutural das toxinas BcsTx 1 e BcsTx2 nos permitiu inferir que estas são membros do já descrito tipo 1 (subtipo 1b) de neurotoxinas de anêmona que também atuam em canais K_V. A caracterização funcional foi realizada utilizando-se diferentes subtipos de canais K_V, expressos em ovócitos de *Xenopus laevis* e as medidas eletrofisiológicas foram feitas empregando-se a técnica de "*voltage-clamp*" com dois microelétrodos. AbeTx1, BcsTx1 e BcsTx2 (3 µM) apresentaram uma seletividade de atividade para os subtipos de K_V1.1–K_V1.3, K_V1.6 e *Shaker* IR, ao passo que a BcsTx4 (3 µM) é somente capaz de bloquear a corrente dos subtipos de K_V1.1, K_V1.2 e K_V1.6. Os mecanismos de ação envolvidos na seletividade da atividade e na potência com que estas se ligam aos seus alvos biológicos foram discutidos com base nos resultados obtidos e análises fisiológicas permitiram propor que estas toxinas atuam como "armas" para defesa contra predadores e/ou para captura de presas.

Palavras chave: anêmonas do mar, *A. bermudensis*, *B. caissarum*, peçonha, neurotoxinas, canais voltagem - dependentes de K^+, *Xenopus laevis*, voltage–clamp technique.

9. Abstract

ORTS, D.J.B. **Sea anemones neurotoxins as tools to study the physiology of voltage–gated potassium channels.** 2013. 183 pages. Thesis (Master). Instituto de Biociências da Universidade de São Paulo, Departamento de Fisiologia, São Paulo, 2013.

The sea anemones venom is a rich source of bioactive compounds, including peptide toxins which are tools for studying the structure and function of voltage-dependent channels K^+ (K_V). In this work, four neurotoxins were purified from the venom of the sea anemones *Actinia bermudenesis* and *Bunodosoma caissarum*. AbeTx1 and BcsTx4 have a structural motif similar to that of *kappa-toxins* and functional and structural analysis showed that they are the first members of a new type (type 5) of sea anemone neurotoxins acting on K_V channels. Moreover, the structural analysis of BcsTx1 and BcsTx2 toxins allowed us to conclude that they are members of the previously described type 1 (subtype 1b) of sea anemone neurotoxins. Functional characterization was performed by means of a wide electrophysiological screening on different K_V channels using oocytes of *Xenopus laevis* and electrophysiological measurements were performed employing the voltage-clamp technique. AbeTx1, BcsTx1 and BcsTx2 (3 M) showed a selective activity for K_V1.1-K_V1.3, K_V1.6 and *Shaker* IR, while BcsTx4 (3 µM) only blocks K_V1.1, K_V1.2 and K_V1.6. The mechanisms involved in potency and selectivity were discussed based on the results obtained and physiological analyses have provided new insights on the role of these toxins in the physiology of the sea anemones.

Keywords: sea anemones, *A. bermudensis*, *B. caissarum*,venom, neurotoxins, voltage-gated potassium channels, *Xenopus laevis*, voltage–clamp technique.

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