A Branched Peptide Mimotope of the Nicotinic Receptor Binding Site Is a Potent Synthetic Antidote against the Snake Neurotoxin α-Bungarotoxin†

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ABSTRACT: We previously produced synthetic peptides mimicking the snake neurotoxin binding site of the nicotinic receptor. These peptide mimotopes bind the snake neurotoxin α-bungarotoxin with higher affinity than peptides reproducing native receptor sequences and inhibit toxin binding to nicotinic receptors in vitro; yet their efficiency in vivo is low. Here we synthesized one of the peptide mimotopes in a tetrabranched MAP form. The MAP peptide binds α-bungarotoxin in solution and inhibits its binding to the receptor with a K_A and an IC_{50} similar to the monomeric peptide. Nonetheless, it is at least 100 times more active in vivo. The MAP completely neutralizes toxin lethality when injected in mice at a dose compatible with its use as a synthetic antidote in humans. The in vivo efficacy of the tetrameric peptide cannot be ascribed to a kinetic and thermodynamic effect and is probably related to different pharmacokinetic behavior of the tetrameric molecule, with respect to the monomer. Our findings bring new perspectives to the therapeutic use of multimeric peptides.

Snakes of the families Elapidae and Hydrophidae have typical paralysing venoms with a high content of curare-mimetic neurotoxins. These postsynaptic neurotoxins mimic the action of curare and prevent the depolarizing action of acetylcholine by binding to the nicotinic acetylcholine receptor (nAchR) at muscle endplates.

Nicotinic acetylcholine receptors are ligand gated ion channels made by the association of five homologous membrane-spanning subunits. nAchRs are located at muscle endplates and in the central nervous system, where different acetylcholine-binding α subunits (α2 to α9) can be assembled in a number of combinations with structural β subunits (β2 to β4), giving rise to nicotinic receptors with different functional and pharmacological properties. The muscle nAchR is composed of two α subunits and one each of the structural β, γ (or ϵ), and δ subunits. Gating of the channel is induced by acetylcholine binding to the ligand sites, located on the two receptor α subunits at their interfaces with γ and δ subunits respectively (see refs *1* and *2* for reviews).

The postsynaptic α-neurotoxins of Elapidae and Hydrophidae snake venom bind with very high affinity to the nicotinic receptor ligand sites and compete with acetylcholine, thus exerting their potent receptor functional blockade at neuromuscular junctions. Snake neurotoxins can be divided into two subfamilies: short (60−62 residues) and long (64−74 residues) neurotoxins, which have a significant sequence homology and share the same three-fingered structure, as determined by X-ray crystallography and NMR (see refs *3* and *4* for reviews). The long neurotoxin α-bungarotoxin (α-bgt) from the snake *Bungarus multicinctus* binds with an affinity in the picomolar range to muscle nicotinic receptors, and it also selectively binds with a similar affinity to central nervous system nicotinic receptors containing the α7 subunit (*5*−*7*).

The three-dimensional structure of nicotinic receptors has not yet been solved. Nonetheless, a sequence of the α subunit amino-terminal domain, which contains the highly conserved cysteine residues 192 and 193, has been determined as containing at least part of the nAchR ligand-binding site (reviewed in *8*). Moreover, the recently solved crystal structure of the molluscan acetylcholine binding protein (AChBP) provided useful information on the location and three-dimensional organization of the nicotinic receptor ligand-binding sites (*9*−*10*). AChBP is structurally and functionally related to the amino-terminal domain of nAchR α-subunit and can bind several nicotinic specific ligands, including α-bgt.

Synthetic peptides reproducing the sequences around cysteines 192 and 193 of muscle and neuronal α7 nAchR retain receptor ability to bind α-bgt, though with much lower affinity (*8*, *11*−*14*).

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[1] Abbreviations: α-bgt, α-bungarotoxin; BSA, bovine serum albumin; ELISA, enzyme-linked immunosorbent assay; Fmoc, fluorenylmethoxycarbonyl; HAPeP, phage library-derived peptide with sequence WRYYESSLKPYPD; HBS, Hepes buffer saline; HPLC, high-performance liquid chromatography; IC_{50}, half-maximal inhibition constant; k_{on}, association kinetic rate; k_{off}, dissociation kinetic rate; K_A, equilibrium association constant; LLPeP, phage library-derived peptide with the sequence MRYYESSLKSYPD; MAP, multiple antigen peptide; NMR, nuclear magnetic resonance; nAchR, nicotinic acetylcholine receptor; p6.7, 14-mer peptide with sequence HRYYESSLEPWYPD; PBS, phosphate buffer saline; SPR, surface plasmon resonance; RIA, radioimmunoassay; RU, resonance units.

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With the aim of obtaining peptides reproducing the nAchr binding site with higher ligand affinity, peptide mimotopes have been produced through different approaches.

A nAchR binding site-mimicking peptide (LLPep), which binds α-bgt and competes with the native receptor for binding, was selected from a random phage-epitope library. The sequence of this peptide is very similar to that of peptides reproducing the regions close to cysteines 192 and 193 of muscle and α7 neuronal nAchR (*15*). A similar sequence is also present in the ligand site of AChBP.

In a previous paper (*16*), we used a combinatorial library approach to produce synthetic peptides mimicking the snake neurotoxin binding site of nicotinic receptors, and we obtained peptides with higher binding capacity than those reproducing native receptor sequences. One of the peptides we identified (p6.7, with the sequence HRYYESSLEPWYPD) has a greater α-bgt binding affinity constant (K_A) by a factor of 20−1000 than peptides reproducing native receptor sequences from different species. Moreover, p6.7 inhibits α-bgt binding to muscle and neuronal receptors with an IC_{50} at least 50 times lower than that of peptides reproducing native sequences.

The structural basis of p6.7 affinity was obtained by the NMR solution structure of the complex (*17*, *18*).

The in vivo effect on α-bgt lethality of receptor-mimicking peptides has been tested in different cases. A cyclic peptide derived from the previously described phage library peptide LLPep has been reported to neutralize α-bgt lethality in mice, albeit at a rather high dose (*19*). Another peptide, HAPep, very similar to our peptide p6.7, with a higher affinity for α-bgt than LLPep and the cyclic peptide (*20*−*22*), had a similar effect in mice when tested in vivo, despite an IC_{50} one-tenth that of the cyclic peptide (*20*). In both cases the amount of peptide that induced protection in mice was very high (1−10 mg/mouse) and therefore hardly suitable for use as antidotes.

With the aim of increasing peptide efficiency and possibly its activity in vivo, we synthesized p6.7 in multiple antigen peptide (MAP) form. MAPs are branched peptides which can be synthesized on a polylisine core (*23*, *24*). We synthesized a tetrabranched MAP (MAP4) of peptide p6.7 and compared its binding to α-bgt with that of the corresponding monomeric peptide. We also tested its ability to neutralize α-bgt lethality when injected in mice, comparing its efficiency with that of the monomeric peptide p6.7. The results indicate that MAPs can considerably increase peptide ability to neutralize α-bgt lethality, thus allowing peptide mimotope of receptor binding sites to be used as efficient synthetic antidotes against snake venom neurotoxins.

EXPERIMENTAL METHODS

Peptide and MAP synthesis. Solid-phase synthesis was carried out on a MultiSynTech Syro automated multiple peptide synthesizer (Witten, Germany), employing 9-fluorenylmethoxycarbonyl (Fmoc) chemistry with 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU)/*N*,*N*-diisopropylethylamine (DIPEA) activation.

Side chain protecting groups were trityl for Hys, 2,2,4,6,7-pentamethyldihydro-benzofuran-5-sulfonyl for Arg, *tert*-butyl ether for Ser and Tyr, *tert*-butyl ester for Asp and Glu, and *tert*-butyloxycarbonyl for Trp.

Peptide p6.7 (HRYYESSLEPWYPD) was synthesized on a 4-(2′,4′-dimethoxyphenyl-Fmoc-aminomethyl)-phenoxy-acetamido-norleucyl 4-methylbenzhydrylamine (RINK Amide MBHA) resin. MAP4p.6.7 was synthesized on $Fmoc_4$−Lys_2−Lys−βAla Wang resin. The Lys_2−Lys−βAla building block allows four-peptide scaffolding: the Lys directly linked to β-Ala bears two Lys linked through their C-terminus; then four NH_2 groups are available for the peptide.

Peptides were cleaved from the resins and deprotected by treatment with trifluoroacetic acid containing water and triisopropylsilane (95/2.5/2.5).

After precipitation with diethyl ether, peptide purity was assessed by high-performance liquid chromatography (HPLC) and by ETTAN MALDI TOF mass spectrometry (Amersham Biosciences, Uppsala, Sweden).

BIACORE. For kinetic experiments MAP4p6.7 was immobilized on the carboxymethylated dextran matrix of a CM5 sensor chip (BIACORE AB, Uppsala, Sweden) using standard amine coupling chemistry. Typically, a response of 500 resonance units (RU) was obtained. α-bgt (SIGMA) diluted in Hepes buffer saline pH 7.4 (HBS) was then injected over the immobilized MAP4p6.7 with a flow rate of 30 μL/min at concentrations ranging from 0.1 to 10 μg/mL. At the end of each cycle, regeneration of the matrix was obtained with a pulse of 25 mM NaOH.

The kinetics of p6.7 binding to α-bgt was analyzed as already described (*16*) by testing the peptide in solution on biotinylated-α-bgt (Molecular Probes, Oregon, USA) immobilized on a streptavidin-coated dextran matrix (SA-sensor chip, BIACORE AB).

To compare p6.7 and MAP4p6.7 binding, we immobilized biotinylated-α-bgt over a SA-sensor chip. Peptides in HBS were injected over the immobilized α-bgt with a flow rate of 30 μL/min at concentrations ranging from 0.1 to 1 μg/mL.

Competition RIA. Microtiter plates (Falcon 3912, Becton Dickinson, Oxnan, CA) were coated overnight at 4 °C with affinity purified nAchR from Torpedo electric organs (*16*) (5 μg/mL in 0.05M carbonate buffer pH 9.6) and then blocked with 3% BSA in phosphate buffer saline (PBS) pH 7.4 for 1h at room temperature. Peptides at concentrations ranging from 10 to 100 pg/mL or from 54 μM to 5.4 pM were incubated together with 10^5 cpm (0.45 nM) of ^{125}I−α-bungarotoxin (Amersham Italia srl) for 1 h at room temperature.

After washing with PBS, α-bgt binding to nAchR was detected by a γ-counter. The half-maximal inhibition constant IC_{50} of different peptides was evaluated by nonlinear regression analysis of curves using GraphPad Prism 3.02 software.

In vivo experiments. For in vivo experiments, 15 g Swiss mice were inoculated subcutaneously (s.c.) with 10 μg α-bgt (SIGMA) in 100 μL PBS pH 7.4, and after 5 min, they were inoculated s.c. with different amounts of p6.7 or MAP4p6.7 in 250 μL PBS pH7.4. Mice treated with peptide antidotes were followed for 10 days.

RESULTS

Synthesis of the tetrabranched peptide MAP4p6.7. The peptide p6.7, which has the sequence HRYYESSLEPWYPD (Table 1), was selected in a previous study as an effective

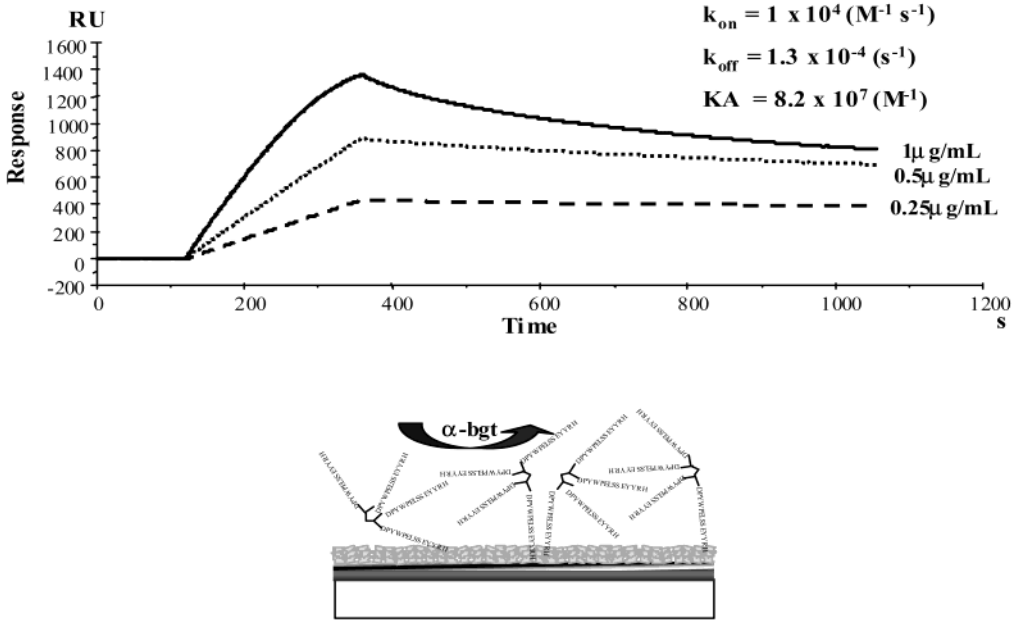

FIGURE 1: BIACORE kinetic analysis of α-bgt binding to immobilized MAP4p6.7. α-bgt, from 0.25 to 1 μg/mL, was injected with a flow of 30 μL/min onto a CM5 sensor chip where MAP4p6.7 had been covalently bound by standard amine coupling. Association and dissociation kinetic rates were calculated by the BIAevaluation 3.0 program. A schematic representation of the experiment is shown under the sensorgram: α-bgt was injected on a CM5 sensor chip prepared with covalently bound MAP4p6.7.

Table 1: Sequence Alignment of Peptide Mimotopes of nAchR Binding Sites Compared with Native Sequences

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
p6.7 (*16*)	H	R	Y	Y	E	S	S	L	E	P	W	Y	P	D
LLPeP (*15*)	M	R	Y	Y	E	S	S	L	K	S		Y	P	D
HAPeP (20)	W	R	Y	Y	E	S	S	L	E	P		Y	P	D
human alpha1	S	V	T	Y	S	C	C	P	D	T	P	Y	L	D
human alpha7	E	R	F	Y	E	C	C	K	E	P		Y	P	D
Torpedo alpha1	W	V	Y	Y	T	C	C	P	D	T	P	Y	L	D
AChBP[a]	S	V	T	Y	S	C	C	P	E	A		Y	E	D

[a] Acetylcholine-binding protein (*9*).

mimotope of the nicotinic receptor binding site. Peptide p6.7 binds α-bungarotoxin with a K_A of 5.8 × 10^7 (M^{-1}) and inhibits α-bgt binding to both muscle and neuronal nAchR in vitro with an IC_{50} of (1−2) × 10^{-7} (M) (*16*). The solution structure of the complex between p6.7 and α-bgt has been solved (*17*), and p6.7 affinity in relation to similar peptide mimotopes has been discussed in the light of conformational and kinetic features (*18*). Despite its efficiency in vitro, p6.7 resulted as a poor inhibitor in vivo. A 5 mg sample of p6.7 was not enough to completely neutralize α-bgt toxicity when injected in mice, which excludes any possible use of this peptide as an antidote against snake toxins in humans. To increase p6.7 efficiency in α-bgt binding, we synthesized a tetrabranched form of the peptide (MAP4p6.7) on a core of three lysine residues by using the Multiple Antigen Peptide (MAP) strategy (*23*, *24*). MAP4p6.7 purity was confirmed by HPLC and mass spectrometry.

In vitro activity of MAP4p6.7. MAP4p6.7 binding to α-bgt and its ability to inhibit toxin binding to nAchR in vitro were compared with those of the monomeric peptide.

Kinetic constants and K_A of the monomeric and tetrameric peptides were measured by surface plasmon resonance (SPR) using a BIACORE. Monomeric p6.7 was tested in solution on biotinylated α-bgt, which had previously been captured by matrix-bound streptavidin, as previously described (*16*). Kinetic rates and affinity of toxin-binding sites of MAP4p6.7 were calculated by immobilizing the tetrabranched peptide on the sensor chip and using α-bgt as analyte in solution because immobilized α-bgt gives multivalent analyte binding (Figure 1). Increasing concentrations of α-bgt were injected over the matrix in different cycles, and the k_{on} and k_{off} of the reaction were calculated and compared with those of the monomeric peptide. We found that the affinity of each toxin-binding site of the tetrabranched peptide was practically identical to that of the monomeric peptide. The stoichiometry of α-bgt binding to MAP4p6.7 was also calculated from the BIACORE results. When α-bgt is injected at a concentration allowing saturating matrix-bound peptide binding sites, the number of analyte molecules bound per ligand molecule (S) can be calculated from the following relation: $S = (RU_A/RU_L \times MW_L/MW_A)$, where RU_A is the response (resonance units) of the bound analyte and RU_L is the response of immobilized ligand. The resulting ratio was four molecules of α-bgt per molecule of matrix-bound MAP4p6.7, indicating that all peptides of the tetrameric MAP, including the one or more linked to the matrix via their N-terminus, bind α-bgt.

The tetrabranched form of the peptide was expected to have a lower k_{off} in the case of multivalent analyte binding. MAP4p6.7 was therefore injected in BIACORE over the matrix-bound α-bgt, and the resulting kinetic rates and K_A of MAP4p6.7/α-bgt binding were compared with those of the monomeric peptide (Figure 2). In experiments where the tetrabranched and monomeric peptides were compared on a binding site number basis, the k_{off} of MAP4p6.7 was 10 times lower than that of the monomeric peptide. The k_{on} of MAP4p6.7 was 5 times that of p6.7, and the resulting K_A of MAP4p6.7 was 2 × 10^9 (M^{-1}) compared to 5.8 × 10^7 (M^{-1}) of the monomeric peptide. The stoichiometry of the complex MAP4p6.7/α-bgt in these experiments was 0.25, confirming that MAP4p6.7 binds to α-bgt with all four sites.

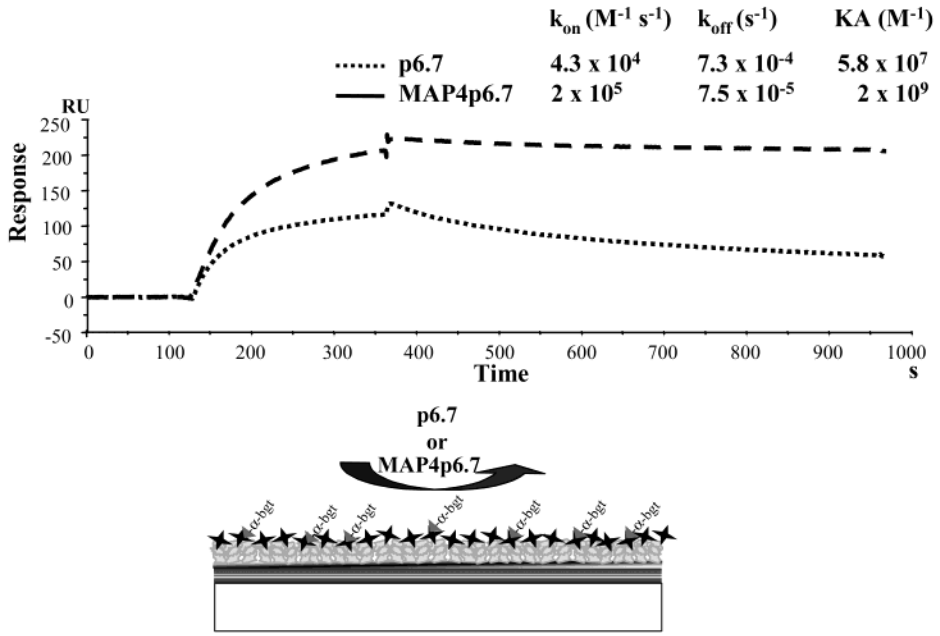

FIGURE 2: BIACORE kinetic analysis of MAP4p6.7 and p6.7 binding to immobilized α-bgt. Peptides were injected at concentrations of 0.25−1 μg/mL with a flow of 30 μL/min onto α-bgt-biotin, immobilized on a streptavidin-coated SA sensor chip. Association and dissociation kinetic rates were calculated by the BIAevaluation 3.0 program. The overlay of sensorgrams obtained with 1 μg/mL of MAP4p6.7 and p6.7 is shown. A schematic representation of the experiments is shown under the sensorgram. MAP4p6.7 or p6.7 was injected on a SA sensor chip containing immobilized α-bgt-biotin.

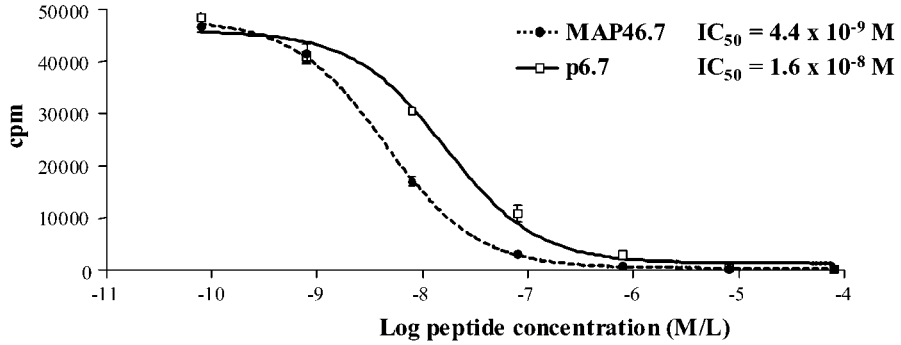

FIGURE 3: Inhibition of ^{125}I-α-bgt binding to nAchR by MAP4p6.7 and p6.7. Peptides at different concentrations, ranging from 54 μM to 5.4 pM, were incubated together with ^{125}I-α-bgt (0.45 nM) on plates coated with affinity-purified nAchR. Assays were performed in triplicate and the half-maximal inhibition IC_{50} was calculated by nonlinear regression analysis using GraphPad Prism 3.02 software.

The half-maximal inhibition constant IC_{50} was calculated for MAP4p6.7 and for the monomeric peptide by a solid-phase radioimmunoassay using ^{125}I-α-bgt and affinity-purified nAchR from Torpedo electric organs. The RIA was more sensitive than the ELISA we previously used to measure the IC_{50} of peptide mimotopes, including p6.7 (*16*). In the RIA all the peptides tested had an IC_{50} about one-tenth that calculated from the ELISA data. This may be due both to the more accurate fitting of the curves, allowed by the higher sensitivity, and to the much lower concentration of α-bgt used in the RIA with respect to the ELISA (0.45 and 125 nM, respectively).

The IC_{50} of MAP4p6.7, expressed as molar concentration of toxin-binding peptides, was 9.3×10^{-9}M, very close to the IC_{50} of the monomeric p6.7 (1.6×10^{-8}M). When the peptides were compared on the basis of their molar concentration, the IC_{50} of the tetrameric MAP4p6.7 was about 4 times lower than that of the monomeric peptide (Figure 3).

In vivo activity of MAP4p6.7. The LD_{100} and LD_{50} of α-bgt in mice were defined by injecting 15 g mice subcutaneously with increasing amounts of the toxin and were 10 and 5 μg, respectively. All mice injected with 10 μg of toxin died in 20−47 min.

To compare the in vivo activity of MAP4p6.7 with that of the monomeric peptide, we injected mice subcutaneously with 10 μg of α-bgt and after 5 min gave them MAP4p6.7 or p6.7 subcutaneously. Results are reported in Figure 4 and Table 2. Injection of 0.5 mg of p6.7 was completely ineffective in protecting mice from the effect of the toxin, whereas injection of 5 mg of p6.7 produced a delay in the lethal effect, since all the mice died in about 5 h. Mice injected with 10 μg of MAP4p6.7 all died in about 2−3 h. The survival time of mice injected with 20 μg of the same peptide was highly variable: eight out of nine mice died in a period comprised between 2.5 and 6 h, and one survived for 22 h (Figure 4). A 50 μg sample of MAP4p6.7 protected about 45% mice from toxin lethality, although all the animals were clearly suffering symptoms. Injection of 100 μg of MAP4p6.7 completely neutralized α-bgt lethality in mice and protected animals from any visible symptom (Table 2).

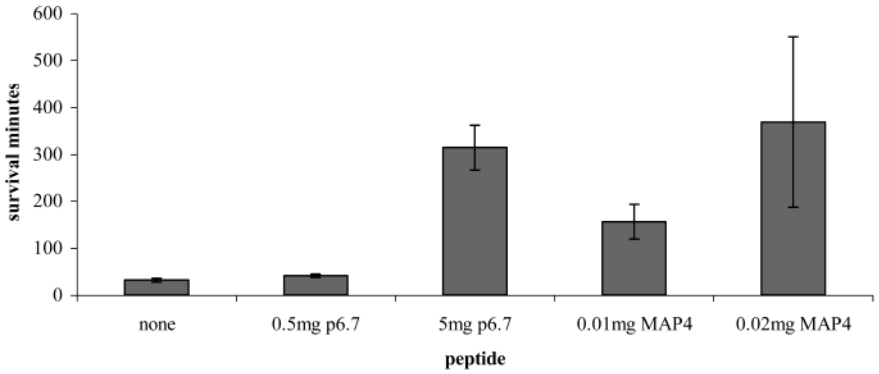

FIGURE 4: In vivo activity of MAP4p6.7 and p6.7. 15 g Swiss mice were injected subcutaneously with 10 μg/100 μL of α-bgt. After 5 min they were injected s.c. with 250 μL of MAP4p6.7 or p6.7. The average survival time after injection of toxin was calculated with one group of 30 mice. Results of mice treated with 20 μg MAP4p6.7 are from nine mice, while the others are from groups of three mice. The results obtained with MAP4p6.7 doses affording protection are reported in Table 2.

Table 2: Neutralization of Toxin Lethality in Mice by MAP4P6.7

no. of mice	amount (μg)[a]		outcome[b]
	α-bgt	MAP4p6.7	
30	10	0	30 dead after 32 min (±4.1[c])
30	10	50	13 alive with symptoms and 17 dead after 311 min (±119[c])
30	10	100	30 alive no symptoms

[a] Subcutaneous injection. [b] Treated mice were followed for 10 days. [c] Standard deviation.

DISCUSSION

The efficiency of polyvalent molecules as specific ligands or inhibitors has been demonstrated in different cases in which multivalent binding produces high avidity interactions, able to compensate for the low affinity of each binding site (for a review, see ref *25*). These include interactions of polyvalent ligands with surfaces displaying multiple receptors (*26*, *27*) or with repetitive antigenic determinants on toxins or pathogens (*28*, *29*) and the binding of multivalent carbohydrates with lectins (*30*). In general, the increase in affinity or the decrease in IC_{50} can be ascribed to the thermodynamic effect of the multivalent interaction between the polyvalent molecules and oligomeric or membrane-anchored targets (*31*). In some cases, the efficiency of polyvalent with respect to monovalent ligands in vitro has been confirmed by their in vivo effect (*32*).

In our studies, we used a tetravalent MAP to inhibit α-bgt binding to the nicotinic receptor. MAP4p6.7 contains four copies of the peptide p6.7, which is a mimotope of the toxin binding site of nAchR and competes with the receptor for toxin binding. We compared the efficiency of the tetrameric peptide with that of the monomeric p6.7, in terms of kinetic rates, affinity constant, and IC_{50}. We also tested its activity in vivo. We found that MAP4p6.7 is much more effective than the monomeric p6.7 in neutralizing α-bgt lethality in mice. The monomeric peptide does not neutralize toxin lethality, even at a dose of 5 mg/mouse. When mice are instead injected with a single 100 μg dose of MAP4p6.7, 5 min after the injection of a lethal dose of α-bgt, they are completely protected from toxin lethality and apparently without symptoms.

The peptide mimotope with the highest affinity for α-bgt described so far, HAPep (*20*−*22*), has a K_A about 10 times higher than that of the monomeric peptide p6.7. Nonetheless, HAPep neutralizes α-bgt lethality at a dose of 5 mg/mouse (*20*), which is at least 50 times higher than that used with MAP4p6.7. In the experiments in vivo described in ref *20*, 5μg α-bgt was used, and the toxin was incubated with the peptide prior to injection in mice, whereas we used 10 μg α-bgt, injecting it in mice 5 min before MAP4p6.7. Thus, our data indicate that tetrameric peptides are much more effective that monomeric peptides in vivo.

Testing MAP4p6.7 efficiency in vitro, we found that when the binding of the tetrameric and monomeric peptide to α-bgt were compared in BIACORE under conditions of monomeric ligand−analyte interaction, the kinetic rates and K_A of each peptide in MAP4p6.7 were similar to those of the monomeric peptide. This indicates that no cooperative effect or steric hindrance modifies the binding of each peptide in the tetrameric structure. When p6.7 and MAP4p6.7 were compared on the basis of binding site numbers, under conditions of multimeric binding of the tetrameric peptide to α-bgt immobilized to the BIACORE sensor chip, the resulting K_A of Map4p6.7 was about 40 times higher than that of p6.7. The increase in K_A of the tetrameric peptide is mainly due to a decrease of 1 order of magnitude in the k_{off} of the complex. This result is in line with general findings about polyvalent interactions but does not reflect the physiological conditions under which our tetrameric inhibitor is expected to act in vivo. Indeed, the peptide is a mimotope of the receptor binding site and acts as a soluble competitor of the receptor in the binding with the soluble, monomeric toxin.

The IC_{50} of MAP4p6.7 was compared with that of the monomeric peptide by a solid-phase RIA, which reflects the physiological mechanism of action of the peptides more closely. In this experiment, the receptor was immobilized on the plastic surface, and the competition between peptides and α-bgt was tested in solution. When the monomeric peptide and MAP4p6.7 were compared on the basis of toxin-binding site numbers, they were found to have very similar IC_{50}, whereas when they were compared on a molar basis, MAP4p6.7 was about 4 times more effective than p6.7, which simply reflects the difference in toxin-binding site numbers.

In summary, in the absence of a multivalent interaction, the in vitro activity of the tetrameric peptide as a soluble competitor is not significantly different from that of the corresponding monomeric peptide. Nonetheless, the MAP is much more effective than the monomeric peptide in

neutralizing toxin lethality in vivo. The in vivo efficacy of the tetrameric peptide cannot therefore be ascribed to a kinetic and thermodynamic effect but is more probably related to different pharmacokinetic behavior of the tetrameric molecule, with respect to the monomer, such as protease susceptibility and clearance.

Our data indicate that MAPs can be efficient synthetic antidotes against snake toxins. We also showed that the general efficacy of polymeric peptides in vivo may not only be related to their avidity in the presence of multivalent interactions, but also to different pharmacological properties with respect to monomeric peptides.

This finding opens several new perspectives in the use of synthetic peptides in therapy.

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