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Comparative insights using the molecular homology model of BDNF (Brain derived neurotrophic factor) of *Varanus komodoensis* and the known NGF (Nerve growth factor) structure of *Naja atra*

Ankit Verma, Dhirendra Kumar Sharma*, Rituparna Sarma, Hasnahana Chetia & Juri Saikia

Bioinformatics Infrastructure Facility, Gauhati University, Guwahati - 781014, Assam, India; Dhirendra Kumar Sharma - Email: dksgu@yahoo.co.uk

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Abstract:
BDNF (Brain derived neurotrophic factor) is a secretion protein and a member of the neurotrophin family of growth factors. Structural and functional characterization of BDNF *Varanus komodoensis* is of interest while its structure remains unknown. Thus, a homology molecular model of BDNF was constructed for gleaning possible structural insights. The model was compared with the structure of the homologous NGF (Nerve growth factor, another member of neuro-trophin family) from *Naja atra*. Comparative structural analysis of the models showed structural similarities with their predicted cavities for the interpretation of potential functional analogy.

Background:
Brain Derived Neurotrophic Factor (BDNF) function is with development. It accelerates the differentiation of selected neuronal populations of the peripheral and central nervous systems. BDNF participates in axonal growth, path finding and in the modulation of dendritic growth and morphology in many regions of the Central Nervous Systems (CNS). The versatility of BDNF has been proved for its contribution to a range of adaptive neuronal responses including long-term potentiation (LTP), long-term depression (LTD), certain forms of short-term synaptic plasticity, as well as homeostatic regulation of intrinsic neuronal excitability **[1].** The Nerve growth factor (NGF) is a protein which stimulates the differentiation and maintenance of sympathetic and embryonic sensory neurons. It is known that snake venoms are a rich source of NGF.

NGF acts as a survival factor in nerve cells and it has metal co-ordination sites, primarily limited to Zn (II) and Cu (II). It has been found in the brain with highest concentration of metal ions to modulate the function of the nerve cells by efficiently inhibiting the biological activities of NGF. NGF and BDNF are two members of a family of neuro-trophic factors with overlapping molecular function **[2].** Three neuro-trophic factors NGF, BDNF, NT3 are highly conserved being the member of the NGF family in vertebrates reflecting molecular conservation during evolution and speciation. It is shown that NT-4protein from Xenopus and Viper has 50-60% amino acid identity with NGF, BDNF, and NT-3 with an extended evolutionary relationship **[3].** The study shows that BDNF interacts with TrkB. The involvement of BDNF in glucose metabolism in diabetic and obese mice with sensitivity to the peripheral neurons is shown **[4, 5].**

Active sites of proteins are characterized with evolving side-chains known as hot spots for protein interactions **[6].** BDNF has been considered as an interesting molecule due to its possible association with obsessive compulsive disorder **[7],** Alzheimer disease **[8],** and dementia **[9].** It should be noted that *Varanus*

and the *Naja atra* belong to the same family. BDNF is common and it acts as NGF in *Varanus komodoensis*. However, the structure of BDNF from *V. komodoensis* is unknown. Therefore, it is of interest to develop its homology model to compare with NGF from *Naja atra* for establishing similar structural features.

Methodology:

Sequence data

The sequences of BDNF from *Varanus komodoensis* was downloaded NCBI and that of NGF from *Naja atra* downloaded from UniPROT (comprehensive, high-quality resource for protein function related information) for this study. The UniPROT database documents predicted function for BDNF from *Varanus komodoensis*. Hence, it is of inertest to report the homology model **[10]** for inferring molecular function.

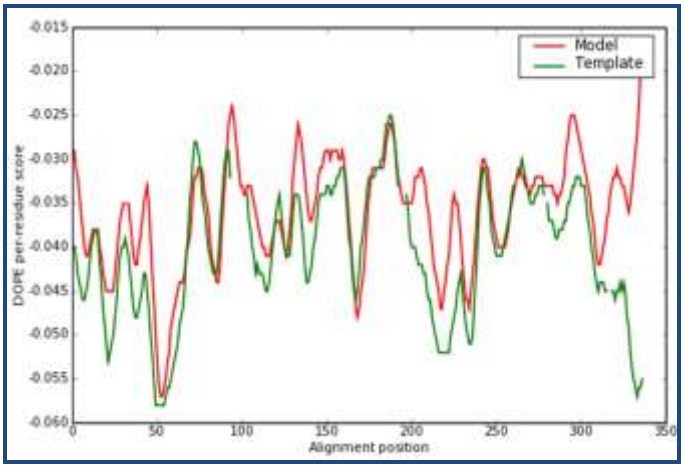

Figure 1: DOPE profile of the model with the template is shown as a function of residue position number.

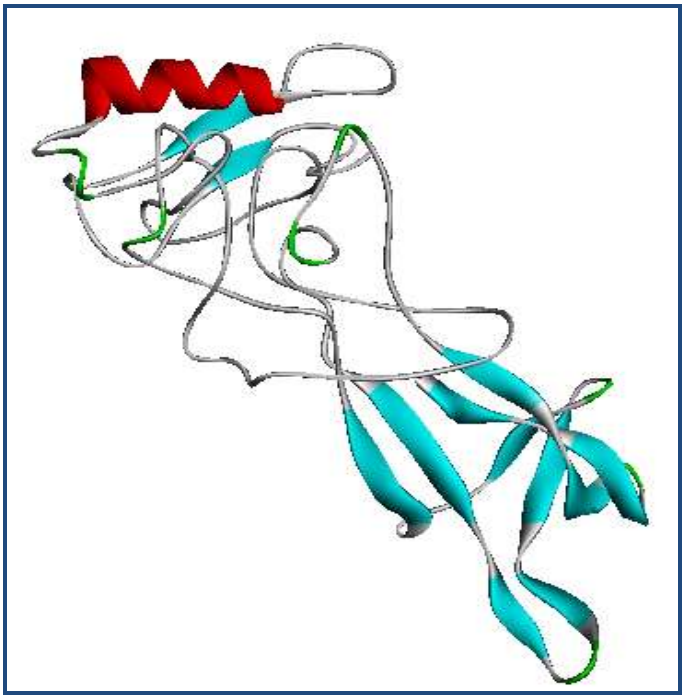

Figure 2: A homology model of BDNF *Varanus komodoensis* is shown. The homology model **[10]** was developed using modeler version 9.0 **[11].**

Template selection

A suitable template (PDB ID: 1BND_A with resolution 2.3 Å) was selected using BlastP (Protein Blast) against the PDB (Protein databank) database for the BDNF query sequence with calculated DOPE Score and molePDF Score **(Figure 1).**

Homology model

The homology model of BDNF **(Figure 2)** was developed using Modeller **[11]** and the model was further analysed for validation using RAMPAGE **[12].**

Cavity prediction and characterization

The active site prediction server **[13]** was used for the calculation of cavities. The server outputs data with cavities for PDB (protein databank) input files. The analysis shows 33 cavities in the BDNF homology model and NGF structure **Table 1 (see supplementary material).** The cavity residue stretch and volume in both BDNF and NGF is shown in **(Table 1)**. The number of residues in the cavity is similar in both BDNF and NGF. However, they differ in their volume. This explains sequence **(Figure 3)** and structure **(Figure 4)** level similarity between BDNF and NGF.

Discussion:

The active site prediction server helped to identify the cavities present in the BDNF protein. 33 cavities are found in the structure with the residue sequence stretch, cavity point and volume cavity to locate the active sites in BDNF for potential ligand binding characterization **(Table 1).** Cavities in protein surface create physiochemical properties which are required for molecular functions. The sequence alignment between BDNF of NGF is shown in **Figure 3** for inferring potential homology **[14]. Table 2 (see supplementary material)** presents the protein features of BDNF and NGF. Further, analysis shows that BDNF and NGF have 51% sequence level similarity level. The similarity level of BDNF for various vertebrates' species is at 93% and 77% in nucleotide and amino acid sequence, respectively **[15].** Reports in Xenopus suggest that leu90 is replaced by a phenylalanine as a result of the transversion of C to T **[16].** It has been reported that all isolated sequences contained an extra amino acid residue at position 96 compared to that of NGF **[17].**

BDNF show three anti parallel B sheets connected to form loops **(Figure 4b**). BDNF and NGF activate the TrkA and TrkB receptors, respectively and the TrkB receptors have high degree of sequence similarity between them **[18].** The interaction of the TrkB receptor with that of BDNF is mediated by multiple contacts. The BDNF structure model demonstrates the presence of lysine 96, arginine 97 and glutamine 84 on its B sheet. This is important for BDNF/ TrkB activity as shown elsewhere **[15].** Active sites in enzyme are usually determined by their hydrophobic patches with the involvement of side chains. **[16]** Active site prediction by its size shows that there are 33 cavities in descending order from 1252 to 162 for BDNF and 1520 to 176 for NGF **(Table 1).** These predictions have extended the identity of the locations for ligand binding to evaluate the volumetric extent of ligands **[17].** It should be noted that the identification and size characterization of some free cavities and the hidden cavities are the initial step for ligand design **[18].**

Figure 3: Sequence alignment of *Varanus komodoensis* BDNF and *Naja atra* NGF is shown.

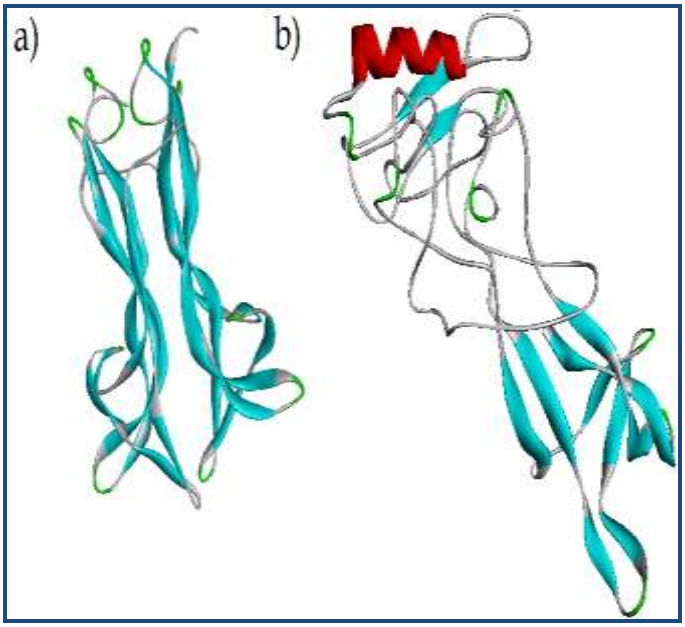

Figure 4: A qualitative visual comparison of NGF from Naja atra and BDNF from *Varanus komodoensis* is presented.

The BDNF and NGF **(Figure 4a & 4b)** show a domain characterised by six conserved cysteine residues **[19].** The sequence similarity between BDNF and NGF is shown in **Figure 3** at 51%. It has been stated that vertebrate BDNF reached an optimally functional structure very early in the vertebrate evolution **[20].** It is observed that BDNF evolution is fragmentary in nature **[21, 22]** except for Zebra Fish. Thus, the reported homology model of BDNF finds application in understanding its function in relation to its evolutionary molecular conservation.

Conclusion:

It is of interest to characterize the structure of BDNF from *Varanus komodoensis*. Hence, a structural model of the protein was reported with its 33 cavities identified using prediction methods. Comparison of the BDNF homology model with the known NGF structure from *Naja atra* show structural similarity inferring functional analogy. The model data presented with the predicted cavities finds useful for further in-depth analysis of BDNF from *Varanus komodoensis*.

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Supplementary material:

Table 1: Predicted cavities in BDNF from *Varanus komodoensis* and NGF from *Naja atra*

BDNF cavities with sequence	Volume (Å³)	Cavity point (Å)	NGF	Volume (Å³)	Cavity point (Å)
cavity_1_RAEGLDYPSNKMVQTCIW	1252	3.312 12.045 11.666	cavity_1_YTPNECIGVHKSRDAFW	1520	-1.518 59.015 25.209
cavity_2_SVRLGYTCFIKDQPWNAEM	1207	17.128 5.297 19.198	cavity_2_DWSGYKTEIHCRVPNAF	1244	-2.957 56.001 34.465
cavity_3_WYLETSKFVADQPIRGM	1203	10.257 1.850 41.847	cavity_3_RFITNYKEMWQVLSAD	1224	16.558 58.602 14.455
cavity_4_EAYRLNKPISDMVFTGCQW	1101	8.173 8.131 19.417	cavity_4_HSCETVYPNFADKRWIG	1169	5.377 42.152 30.187
cavity_5_NPREMVQSLGTCIDKAYW	1011	13.839 13.141 11.860	cavity_5_WYTFKEIRMNVLSADQ	1024	16.684 47.879 12.118
cavity_6_EWIAYTSVKDQFLPRG	974	12.669 -7.227 30.801	cavity_6_RNHKDTCGSVEYAFWI	988	-3.099 40.724 23.441
cavity_7_SKYDTVRGCIQAEPLWNM	933	17.775 -1.326 14.186	cavity_7_NKDCHSVETYAFRWIG	935	1.320 45.585 22.315
cavity_8_LYKGAENRISDTQCV	844	5.155 -6.005 14.307	cavity_8_TVEYMIGRNKQFLSWAD	882	17.329 58.793 5.247
cavity_9_YKLENIWSDAFTVCGQRP	811	5.694 -5.491 24.056	cavity_9_VEFWTYKRIGNALSD	862	11.118 42.942 9.130
cavity_10_WYLKTGQEVADPFIRS	775	9.069 -0.727 45.276	cavity_10_TDSARGFVIKENWY	835	9.423 60.721 23.677
cavity_11_LRAESKGYDPNMV	773	-5.352 6.740 12.111	cavity_11_PKNCTEVADWRIGFY	764	-3.468 55.570 12.642
cavity_12_NKLRSDEYVGTCFIQPWA	755	10.872 1.470 16.590	cavity_12_PESNGYTKDCVAR	689	-11.421 53.528 19.900
cavity_13_TGCIKQDRSAYWLNMPE	730	20.105 3.510 11.608	cavity_13_YWFEIKNVLARTSDQM	682	17.911 44.095 8.560
cavity_14_ELARDPSNHQMVGT	704	3.527 16.403 1.182	cavity_14_SVCTDPAENKFIRWY	669	9.305 53.060 30.795
cavity_15_YKELWNIDSVFTCQRP	675	6.875 3.582 28.544	cavity_15_FKYVWALRTSDENQMG	657	25.300 44.662 12.818
cavity_16_YFSLRDTAQGENKPM	665	12.469 -0.645 -5.727	cavity_16_SKHNDWITGERPV	643	-11.678 53.216 41.898
cavity_17_EQVGTDMRSAINWLYPC	662	16.287 12.483 1.107	cavity_17_TSFEWDRYIKGNAL	622	9.781 42.376 18.573
cavity_18_LREYSAKPGND	601	-1.970 -3.361 7.207	cavity_18_TEDFRKVWIAGYNLM	613	13.763 44.769 26.201
cavity_19_NKSDRTQGAEYLMP	569	11.957 -6.848 7.536	cavity_19_RTGIVNEMKWFQSYLA	568	12.727 63.935 14.625
cavity_20_TYKDLQAEVPFWRMG	530	14.260 -9.835 49.168	cavity_20_TDCSARFVEIKYW	556	8.502 53.290 22.315
cavity_21_KEDSTLVPAQRYFMG	515	19.030 -4.543 32.353	cavity_21_KPSNHEDWGIRY	518	-21.436 45.843 34.299
cavity_22_YQEKFIWTLVARSMGD	508	18.504 -5.734 41.175	cavity_22_DCHSTVEYPAK	502	-3.596 47.979 30.284
cavity_23_YETSFKDCILVRPQM	505	15.293 2.141 34.134	cavity_23_KSHNDEWIGRP	496	-16.458 47.662 39.531
cavity_24_DYHFTRSQGANLP	432	12.969 7.253 -7.892	cavity_24_KNPSEDWIGTRYCVH	446	-17.661 52.692 27.555
cavity_25_AWKTEYLDVQFIRM	422	10.663 -9.156 41.516	cavity_25_KNSHEDWGIRYTCV	375	-13.453 45.557 32.956
cavity_26_WLARVMFTGYKDNS	414	24.416 -5.156 45.805	cavity_26_KTVEFAIRWY	367	18.303 51.374 27.532
cavity_27_KYELWNIDSFTVC	399	1.848 -1.678 29.407	cavity_27_EKDTRAIGFVYMS	336	3.750 58.864 10.118
cavity_28_IEVLHADSYFQTRG	333	2.800 10.564 -6.413	cavity_28_KITNWSGHREPVCY	332	-5.611 40.466 37.682
cavity_29_DEKLVATMGWRFNS	318	19.566 -12.446 44.274	cavity_29_KNCSEVATFWRDI	328	-3.142 46.692 15.358
cavity_30_LSPEGNYKDRFTAQ	311	3.039 -5.109 -0.265	cavity_30_PKNSEGWIDHRTCV	322	-14.292 39.286 27.885
cavity_31_RAQYNDLKCPGMES	286	19.888 3.080 1.529	cavity_31_IKFTWAELVRSYMNQG	321	24.278 48.007 19.287
cavity_32_ERVLIASHPGDY	236	-7.217 4.012 0.661	cavity_32_TAKVEYMINLSW	299	9.566 55.607 3.002
cavity_33_RSLPHAVEYF	162	1.479 4.709 -1.254	cavity_33_IRKGTFNASWEVQM	176	19.236 39.291 18.492

Table 2: Comparative evaluation between NGF and BDNF proteins

Properties	NGF	BDNF
PDB ID	4EC7	Structure unknown
Organism	*Naja atra*	*Varanus komodoensis*
Common Name	Chinese Cobra	Komodo Dragon
Amino Acid Length	116 *2= 232	223
Molecular Weight	13.06 kDa	25.10 kDa
Chain	A & B	-
Chain Break threshold	A=7, B=7	-
No. of Atoms	1763	1755
No of Bonds	1777	1787
No of Helices	0	1
No of Strands	18	13
No of Turns	0	28
Iso-electric Point	6.08	8.46
Groups		
Name	Size	Size
Disulfide Residues	12	4
Backbone	866	893
Side chain	828	862

Properties	NGF	BDNF
Hydrophobic	68	73
Hydrophilic	76	80
Acidic	26	29
Basic	30	34