Supporting Information for

The Active Site of Melanopsin: The Biological Clock Photoreceptor

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I. Full sequence alignment of squid rhodopsin and mouse melanopsin.

FASTA sequences of squid rhodopsin (P31356) and mouse melanopsin (Q9QXZ9) were aligned using CLUSTALW2 *(ref-1)* as shown below. Alignments of the transmembrane portions of squid rhodopsin (2Z73 at 2.8 Å), and that of melanopsin, according to the TMHMM prediction *(ref-2)* using the TMHMM v2 server, were performed using CLUSTALW2 and are displayed below. The transmembrane region alignments were found to be in agreement with the full FASTA sequence alignment with only one exception in Helix II. In GPCRs, the extracellular domain, intracellular domain, and interhelical loops are structures that are directly responsible for the function of the protein; consequently, these regions will have great diversity in their primary sequence and may not show strong sequence alignments to other GPCRs. On the other hand, the transmembrane domain serves mostly the same function in GPCRs, which is to span and stabilize the protein in the cell membrane. In order to maintain the functionality of these regions, the hydrophobicity and overall dipole moment of the helix must be preserved, so it is expected that the transmembrane helices between GPCRs will show greater conservation than the other regions. Since the alignment for Helix II contained no gaps, it was adopted into the main sequence alignment. The modified alignment used for determining correspondence between rhodopsin and melanopsin residues is shown below. Residues marked in blue indicate the 163 out of 373 residues in squid rhodopsin are mutated using Schrödinger's Maestro version 9.3 *(ref-3)* to construct the mouse melanopsin homology model. The following mutations resulted in the loss of negative (D27V, D194T, E231G, E233A, E245R, E290H, D340S, D341G) and positive (K109E, K145G, R193F, K239E, K244L) charge. Similarly, the following mutations resulted in the gain of negative (Q28D, F105E, K109E, N229E, A235E, K239E) and positive charge (K61R, K63R, Q66R, K146R, H149K, M225R, S228R, K232R, E245R, K248R, G252R, R258K). The residues at 94, 240, and 241 in squid rhodopsin were used to fill the corresponding positions in the homology model. Within the 4.5Å of the active site, marked by the red boxes in the alignment, 18 out of 38 residues were mutated. Although this alignment contains some large gaps, they occur before and after the seven transmembrane regions, indicating that the gaps are found only in the extracellular domain and intracellular domain respectively. Since these domains are outside of the

4.5Å radius of retinal, residues in these regions are not expected to impact the calculations. For the homology model, residues 1-25 and 342-373 of squid rhodopsin were used for the extracellular and intracellular domain respectively.

>Squid Rhodopsin (P31356) FASTA Sequence from www.uniprot.org
MGRDLRDNETWWYNPSIVVHPHWREFDQVPDAVYYSLGIFIGICGIIGCGGNGIVIYLFTKTKSLQ
TPANMFIINLAFSDFTFSLVNGFPLMTISCFLKKWIFGFAACKVYGFIGGIFGFMSIMTMAMISIDRY
NVIGRPMAASKKMSHRRAFIMIIFVWLWSVLWAIGPIFGWGAYTLEGVLCNCSFDYISRDSTTRSN
ILCMFILGFFGPILIIFFCYFNIVMSVSNHEKEMAAMAKRLNAKELRKAQAGANAEMRLAKISIVIV
SQFLLSWSPYAVVALLAQFGPLEWVTPYAAQLPVMFAKASAIHNPMIYSVSHPKFREAISQTFPWV
LTCCQFDDKETEDDKDAETEIPAGESSDAAPSADAAQMKEMMAMMQKMQQQQAAYPPQGYAP
PPQGYPPQGYPPQGYPPQGYPPQGYPPPPQGAPPQGAPPAAPPQGVDNQAYQA

> Mouse Melanopsin (Q9QXZ9) FASTA Sequence from www.uniprot.org
MDSPSGPRVLSSLTQDPSFTTSPALQGIWNGTQNVSVRAQLLSVSPTTSAHQAAAWVPFPTVDVPD
HAHYTLGTVILLVGLTGMLGNLTVIYTFCRNRGLRTPANMFIINLAVSDFLMSVTQAPVFFASSLY
KKWLFGETGCEFYAFCGAVFGITSMITLTAIAMDRYLVITRPLATIGRGSKRRTALVLLGVWLYAL
AWSLPPFFGWSAYVPEGLLTSCSWDYMTFTPQVRAYTMLLFCFVFFLPLLIIIFCYIFIFRAIRETGR
ACEGCGESPLRQRRQWQRLQSEWKMAKVALIVILLFVLSWAPYSTVALVAFAGYSHILTPYMSSV
PAVIAKASAIHNPIIYAITHPKYRVAIAQHLPCLGVLLGVSGQRSHPSLSYRSTHRSTLSSQSSDLSWI
SGRKRQESLGSESEVGWTDTETTAAWGAAQQASGQSFCSQNLEDGELKASSSPQVQRSKTPKVPG
PSTCRPMKGQGARPS SLRGDQKGRLAVCTGLSECPHPHTSQFPLAFLEDDVTLRHL

Full alignment between Rhodopsin and Melanopsin

```
Squid          --MGRDLRDNETWWYNPSIVVHPHWR--------------------------------E 25
Mouse          MDSPSGPRVLSSLTQDPSFTTSPALQGIWNGTQNVSVRAQLLSVSPTTSAHQAAAWVPFP 60

Squid          FDQVPDAVYYSLGIFIGICGIIGCGGNGIVIYLFTKTKSLQTPANMFIINLAFSDFTFSL 85
Mouse          TVDVPDHAHYTLGTVILLVGLTGMLGNLTVIYTFCRNRGLRTPANMFIINLAVSDFLMSV 120

Squid          VNGFPLMTISCFLKKWIFGFAACKVYGFIGGIFGFMSIMTMAMISIDRYNVIGRPMAASK 145
Mouse          T-QAPVFFASSLYKKWLFGETGCEFYAFCGAVFGITSMITLTAIAMDRYLVITRPLATIG 179

Squid          KMSHRRAFIMIIFVWLWSVLWAIGPIFGWGAYTLEGVLCNCSFDYISRDSTTRSNILCMF 205
Mouse          RGSKRRTALVLLGVWLYALAWSLPPFFGWSAYVPEGLLTSCSWDYMTFTPQVRAYTMLLF 239

Squid          ILGFFGPILIIFFCYFNIVMSVSNHEKEMAAMAKRLNAKELRKAQAGANAEMRLAKISIV 265
Mouse          CFVFFLPLLIIIFCYIFIFRAIRETGRACEGCGE--SPLRQRRQWQRLQSEWKMAKVALI 297

Squid          IVSQFLLSWSPYAVVALLAQFGPLEWVTPYAAQLPVMFAKASAIHNPMIYSVSHPKFREA 325
Mouse          VILLFVLSWAPYSTVALVAFAGYSHILTPYMSSVPAVIAKASAIHNPIIYAITHPKYRVA 357

Squid          ISQTFPWVLTCCQFDD----------------------------KETEDDKDAETEIPA 356
Mouse          IAQHLPCLGVLLGVSGQRSHPSLSYRSTHRSTLSSQSSDLSWISGRKRQESLGSESEVGW 417

Squid          GESSDAAPSADAAQMKEMMAMMQKMQQ---QQAAYPPQGYAPPPQGYPPQGYPPQGYPPQ 413
Mouse          TDTETTAAWGAAQQASGQSFCSQNLEDGELKASSSPQVQRSKTPKVPGPSTCRP--MKGQ 475

Squid          GYPPQGYPPPPQGAPPQGAPPAAPPQGVDNQAYQA---------- 448
Mouse          GARPSSLRGDQKGRLAVCTGLSECPHPHTSQFPLAFLEDDVTLRHL 521
```

Alignment within the transmembrane regions

```
Squid|TM1        PDAVYYSLGIFIGICGIIGCGGNGIVIYLFTKT 33  (30-62)
Mouse|TM1        -------LGTVILLVGLTGMLGNLTVIYTF--- 23  (72-94)

Squid|TM2        ANMFIINLAFSDFTFSLVNGFPLMTISCFL 30  (69-98)
Mouse|TM2        --MFIINLAVSDFLMSVTQAPVFFA----- 23  (106-128)

Squid|TM3        FGFAACKVYGFIGGIFGFMSIMTMAMISIDRYNVI 35  (103-137)
Mouse|TM3        ------EFYAFCGAVFGITSMITLTAIAM------ 23  (143-165)

Squid|TM4        SHRRAFIMIIFVWLWSVLWAIGPIFG- 26  (148-173)
Mouse|TM4        ----TALVLLGVWLYALAWSLPPFFGW 23  (186-208)

Squid|TM5        DSTTRSNILCMFILGFFGPILIIFFCYFNIVMSVSNHEKEMAAMAK 46 (194-239)
Mouse|TM5        -------TMLLFCFVFFLPLLIIIFCYIFI---------------- 23 (235-257)

Squid|TM6        ELRKAQAGANAEMRLAKISIVIVSQFLLSWSPYAVVALLAQFG 43 (245-287)
Mouse|TM6        ------------------LIVILLFVLSWAPYSTVALVAFA- 23  (296-318)

Squid|TM7        --TPYAAQLPVMFAKASAIHNPMIYSVSH 27  (293-319)
Mouse|TM7        ILTPYMSSVPAVIAKASAIHNPIIYAIT- 28  (319-521)
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Modified alignment (Helix II alignment incorporated)

```
Squid            --MGRDLRDNETWWYNPSIVVHPHWR--------------------------------E 25
Mouse            MDSPSGPRVLSSLTQDPSFTTSPALQGIWNGTQNVSVRAQLLSVSPTTSAHQAAAWVPFP 60

Squid            FDQVPDAVYYSLGIFIGICGIIGCGGNGIVIYLFTKTKSLQTPANMFIINLAFSDFTFSL 85
Mouse            TVDVPDHAHYTLGTVILLVGLTGMLGNLTVIYTFCRNRGLRTPANMFIINLAVSDFLMSV 120

Squid            VNGFPLMTISCFLKKWIFGFAACKVYGFIGGIFGFMSIMTMAMISIDRYNVIGRPMAASK 145
Mouse            TQAPVFFAISSLYKKWLFGETGCEFYAFCGAVFGITSMITLTAIAMDRYLVITRPLATIG 179

Squid            KMSHRRAFIMIIFVWLWSVLWAIGPIFGWGAYTLEGVLCNCSFDYISRDSTTRSNILCMF 205
Mouse            RGSKRRTALVLLGVWLYALAWSLPPFFGWSAYVPEGLLTSCSWDYMTFTPQVRAYTMLLF 239

Squid            ILGFFGPILIIFFCYFNIVMSVSNHEKEMAAMAKRLNAKELRKAQAGANAEMRLAKISIV 265
Mouse            CFVFFLPLLIIIFCYIFIFRAIRETGRACEGCGERLSPLRQRRQWQRLQSEWKMAKVALI 297

Squid            IVSQFLLSWSPYAVVALLAQFGPLEWVTPYAAQLPVMFAKASAIHNPMIYSVSHPKFREA 325
Mouse            VILIFVLSWAPYSTVALVAFAGYSHILTPYMSSVPAVIAKASAIHNPIIYAITHPKYRVA 357

Squid            ISQTFPWVLTCCQFDD----------------------------KETEDDKDAETEIPA 356
Mouse            IAQHLPCLGVLLGVSGQRSHPSLSYRSTHRSTLSSQSSDLSWISGRKRQESLGSESEVGW 417

Squid            GESSDAAPSADAAQMKEMMAMMQKMQQ---QQAAYPPQGYAPPPQGYPPQGYPPQGYPPQ 413
Mouse            TDTETTAAWGAAQQASGQSFCSQNLEDGELKASSSPQVQRSKTPKVPGPSTCRP--MKGQ 475

Squid            GYPPQGYPPPPQGAPPQGAPPAAPPQGVDNQAYQA----------- 448
Mouse            GARPSSLRGDQKGRLAVCTGLSECPHPHTSQFPLAFLEDDVTLRHL 521
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II. Distance of the Schiff-base nitrogen to key amino acid residues in the squid rhodopsin and mouse rhodopsin.

Table S1: Comparison of distances from the PSB nitrogen atom to side chain oxygen atom of N87, Y111 and E180 residues in squid rhodopsin and Q87, Y111 and E180 residues in mouse melanopsin.

Distance (Å)	Squid Rhodopsin	Mouse Melanopsin
OH (Y111)…N (PSBR)	3.41	3.08
OD1 (N87Q)…N (PSBR)	3.93	4.71
OE2 (E180)…N (PSBR)	4.29	4.12

III. Bond lengths, angles and dihedral angles along the retinal polyene chain of the PSB11 chromophore in squid rhodopsin and mouse melanopsin.1.3595

BOND LENGTH (Å)

Bond	Squid Rhodopsin	Mouse Melanopsin
C5=C6	1.361	1.358
C6-C7	1.469	1.472
C7=C8	1.357	1.355
C8-C9	1.444	1.448
C9=C10	1.377	1.373
C10-C11	1.421	1.430
C11=C12	1.379	1.371
C12-C13	1.431	1.435
C13=C14	1.391	1.385
C14-C15	1.397	1.400
C15=N	1.324	1.315
BLA (Å)	0.068	0.078
λ_{max} (nm)	490	447

Note: Increase in BLA contributes to the decrease in λ_{max}.

BOND ANGLE (deg)

Bond	Squid Rhodopsin	Mouse Melanopsin
C5=C6-C7	121.748	123.105
C6-C7=C8	122.567	124.644
C7=C8-C9	127.903	127.113
C8-C9=C10	115.826	116.648

C9=C10-C11	128.475	128.095
C10-C11=C12	126.459	126.314
C11=C12-C13	129.361	128.297
C12-C13=C14	117.101	117.475
C13=C14-C15	123.500	122.806
C14-C15=N	123.102	122.929

DIHEDRAL ANGLE (deg)

Bond	**Squid Rhodopsin**	**Mouse Melanopsin**
C5=C6-C7=C8	-45.47	-42.597
C6-C7=C8-C9	-173.51	-175.141
C7=C8-C9=C10	160.06	172.509
C8-C9=C10-C11	178.90	171.266
C9=C10-C11=C12	168.89	167.832
C10-C11=C12-C13	-17.26	-22.069
C11=C12-C13=C14	165.77	163.759
C12-C13=C14-C15	176.11	172.100
C13=C14-C15=N	163.17	166.761
C14-C15=N-C	179.55	178.601

IV. ONIOM (QM/MM) where QM=B3LYP/6-31G*; MM= AMBER96; optimized Cartesian coordinates (in Å).

Retinal geometry of squid rhodopsin (490 nm)

51 Atoms

N	9.796233	38.054782	57.858373
H	8.874230	38.327781	58.190451
H	9.949860	37.043264	57.784239
C	17.131212	44.828289	61.316098
C	18.532048	44.846576	60.654834
C	18.870817	46.259227	60.126053
H	19.906116	46.277020	59.772084
H	18.779472	47.006821	60.922821
H	18.237644	46.559165	59.284186
C	18.548568	43.860266	59.463264
H	18.399492	42.824057	59.788053
H	19.506550	43.917572	58.932764
H	17.755349	44.100632	58.751135
C	16.912775	44.359680	62.574668
C	15.608993	44.463847	63.332561
H	15.119096	43.483846	63.410627
H	14.902069	45.168229	62.891403
H	15.819203	44.788952	64.362000
C	19.631556	44.455889	61.667449
H	19.860961	45.321078	62.302797
H	20.550740	44.232709	61.115124
C	19.220124	43.289667	62.561279
H	18.961602	42.416279	61.948123
H	20.049083	42.987873	63.210366
C	18.004888	43.701138	63.388020
H	17.572340	42.835050	63.909033
H	18.305715	44.399838	64.183154
C	16.029066	45.291883	60.462118
H	16.203974	46.156939	59.824983
C	14.869973	44.599724	60.325323
H	14.771476	43.680386	60.893245
C	13.772753	44.876468	59.427957
C	13.645232	46.232245	58.791031
H	14.483039	46.425287	58.111967
H	13.676323	47.020597	59.551211
H	12.721317	46.331297	58.215712
C	12.925458	43.821423	59.175028
H	13.167594	42.897372	59.686577
C	11.761487	43.797790	58.360372
H	11.313150	44.752256	58.089777
C	11.061109	42.678445	57.961636
H	10.061518	42.853916	57.567039
C	11.469136	41.306496	57.959251
C	12.906167	40.878555	58.117623
H	13.087954	40.474542	59.121559
H	13.595416	41.701705	57.942621
H	13.152791	40.094901	57.395900
C	10.472504	40.349016	57.793664
H	9.437313	40.675394	57.796475
C	10.729282	38.979201	57.692339
H	11.721453	38.619755	57.440379

Retinal geometry of mouse melanopsin (447 nm)

51 Atoms

N	9.536555	37.770705	58.055030
H	8.652185	38.035166	58.506020
H	9.663435	36.762490	57.921536
C	16.896084	44.580690	61.786132
C	18.358192	44.786896	61.322341
C	18.566113	46.269721	60.935087
H	19.613902	46.434563	60.665674
H	18.320884	46.930397	61.775062
H	17.967183	46.571643	60.072391
C	18.649815	43.881527	60.105541
H	18.701231	42.830259	60.410656
H	19.613400	44.145544	59.657082
H	17.875110	43.969477	59.339211
C	16.574050	44.111854	63.019571
C	15.181455	44.063435	63.598212
H	14.808043	43.033520	63.650082
H	14.455235	44.659683	63.042434
H	15.218442	44.431866	64.634084
C	19.373618	44.450753	62.437242
H	19.473228	45.323616	63.091085
H	20.360131	44.282930	61.990588
C	18.942312	43.256586	63.283238
H	18.805268	42.372106	62.645830
H	19.715611	43.001970	64.013196
C	17.624085	43.588667	63.977149
H	17.212995	42.705492	64.487803
H	17.794607	44.332410	64.774947
C	15.890171	44.909756	60.763936
H	16.105047	45.753516	60.112549
C	14.799379	44.155628	60.485922
H	14.626657	43.273588	61.092688
C	13.831180	44.374326	59.430754
C	13.923933	45.608065	58.575660
H	14.870607	45.602746	58.025708
H	13.913291	46.520925	59.182327
H	13.125844	45.664238	57.833565
C	12.894633	43.389228	59.240190
H	13.011245	42.498232	59.850922
C	11.737365	43.422707	58.400698
H	11.371285	44.396256	58.083790
C	10.954095	42.351096	58.054642
H	9.968790	42.567740	57.651687
C	11.300848	40.958731	58.058937
C	12.738963	40.491129	58.061467
H	12.990353	39.958233	58.987196
H	13.431241	41.323099	57.954979
H	12.917668	39.802974	57.226767
C	10.263723	40.042115	58.003495
H	9.239572	40.390368	58.100933
C	10.473911	38.667940	57.839762
H	11.434242	38.303403	57.485884

Retinal geometry of bovine rhodopsin (495 nm)

51 Atoms

N	45.694430	12.502870	16.364385
H	45.807918	13.373397	16.914726
H	46.444345	12.305347	15.688714

C	35.568625	7.669884	17.142234
C	34.995010	6.241890	17.288725
C	33.702505	6.321771	18.128443
H	32.952901	6.975493	17.676432
H	33.929950	6.733959	19.112773
H	33.266081	5.325390	18.272255
C	35.970925	5.283604	18.004033
H	36.198759	5.598337	19.027142
H	36.916052	5.188017	17.461361
H	35.523240	4.284771	18.068614
C	35.223538	8.465664	16.095637
C	35.575557	9.928031	15.962908
H	36.372887	10.073718	15.222171
H	35.894625	10.387829	16.898835
H	34.692141	10.470690	15.602100
C	34.716811	5.663125	15.885088
H	34.261306	4.670450	15.988319
H	35.678087	5.520899	15.369712
C	33.821342	6.567984	15.042812
H	32.824641	6.620010	15.492403
H	33.692457	6.135658	14.042543
C	34.397880	7.983650	14.926069
H	35.031968	8.065493	14.028753
H	33.585097	8.708361	14.775229
C	36.432612	8.157183	18.218899
H	36.147971	7.894226	19.236736
C	37.574754	8.860050	17.991401
H	37.851853	9.007029	16.952494
C	38.486832	9.440215	18.944544
C	38.191727	9.389086	20.419274
H	37.438774	8.633720	20.641006
H	37.808565	10.345121	20.785965
H	39.092373	9.147788	20.990478
C	39.627532	10.034788	18.447995
H	39.795602	9.960811	17.379603
C	40.533658	10.815884	19.212458
H	40.175547	11.114086	20.194388
C	41.752051	11.354073	18.857318
H	42.133455	12.116700	19.526857
C	42.634430	11.026008	17.784490
C	42.379761	9.826035	16.903419
H	41.716662	10.084853	16.067383
H	41.901359	9.025744	17.471605
H	43.297345	9.421118	16.472648
C	43.752532	11.847084	17.616102
H	43.894133	12.691885	18.287052
C	44.715035	11.652702	16.622000
H	44.680531	10.768083	15.991591

Retinal geometry of G89Q mutant in bovine rhodopsin (481 nm)

51 Atoms

N	45.703702	12.547579	16.397008
H	45.798153	13.420060	16.948515
H	46.460402	12.359470	15.726177
C	35.566823	7.663189	17.134140
C	34.976945	6.243572	17.296092
C	33.695275	6.346527	18.149956
H	32.942163	6.992959	17.693294
H	33.936137	6.779354	19.122385
H	33.256346	5.355480	18.320644
C	35.950178	5.278854	18.006785
H	36.188698	5.594798	19.027106
H	36.890095	5.174061	17.456379
H	35.494355	4.284128	18.077921
C	35.227206	8.454329	16.082277
C	35.594714	9.911349	15.935536
H	36.383520	10.043106	15.183150
H	35.930920	10.374018	16.863924
H	34.712749	10.461268	15.582097
C	34.675798	5.657484	15.900328
H	34.207358	4.672519	16.017026
H	35.629399	5.496137	15.376384
C	33.787592	6.569625	15.058211
H	32.796416	6.646288	15.516465
H	33.640448	6.129839	14.063669
C	34.390856	7.971958	14.920526
H	35.024910	8.028786	14.021130
H	33.591870	8.709929	14.760913
C	36.437170	8.148578	18.206283
H	36.149801	7.893908	19.225444
C	37.586181	8.839670	17.976867
H	37.866820	8.979327	16.937929
C	38.498442	9.418106	18.930867
C	38.200856	9.367253	20.405336
H	37.443685	8.615672	20.625373
H	37.822303	10.324330	20.773376
H	39.099456	9.121205	20.977686
C	39.640588	10.012831	18.436786
H	39.811859	9.939519	17.369039
C	40.541124	10.796788	19.204042
H	40.180866	11.087439	20.187307
C	41.755120	11.348514	18.853008
H	42.126322	12.111321	19.528107
C	42.644878	11.034159	17.782820
C	42.404216	9.838480	16.891732
H	41.740890	10.097675	16.055968
H	41.931819	9.029015	17.452104
H	43.326450	9.445797	16.459415
C	43.757917	11.865015	17.626960
H	43.887410	12.707784	18.303102
C	44.731215	11.685132	16.641207
H	44.712851	10.802351	16.007253

V. References for the Supporting Information

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