

Aus der Klinik für Anästhesiologie mit Schwerpunkt operative  
Intensivmedizin der Medizinischen Fakultät Charité – Universitätsmedizin  
Berlin

DISSERTATION

Leukocyte opioid receptors mediate analgesia via Ca<sup>2+</sup>-regulated  
release of opioid peptides

zur Erlangung des akademischen Grades  
Doctor of Philosophy (PhD)

vorgelegt der Medizinischen Fakultät  
Charité – Universitätsmedizin Berlin

von

Melih Özgür Celik

aus Istanbul / Türkei

Datum der Promotion: 10.03.2017



## Zusammenfassung

Qrkqkfg"ukpf"fgt" I qnfuvpcfctf" |wt"Dgjcfnwpi"xqp" o kvvgnvctmgrp"dku"uvctmgrp"Uej ogt|gp<sup>0</sup> I go@E" fgt" mncuukuejgp" Ukejv ygkug" dgyktmgrp" ukp" gkpg" Cpcnigukg" Adgt" fkg" Tgiwncvkqp" rt@/" wpf" rquvu{pcrvkuejgt" Pgwtpqgp" fwtej" fkg" Dnqemc fg" fgu" Ec<sup>4-</sup>/Gkpuvtq ou." wpf" uq okv" fkg" Htgkugv| wpi" gz|kvcvqtuejgt" Pgwtpvtcpu okvgt" \*|0D0" Inwvc o cv+." uqykg" fwtej" J {rgtrqctkukgtwpi" fgt" u{pcrvkuejgp" Og o dtcp" Adgt" fkg" Jgtcdugv| wpi" fgt"kpvtc| gmnwn@tgp" M<sup>-</sup>/Mqp|gpvtcvkqp<sup>0</sup> Fkg" Cp|cjin" fgt"Xgtuejtgkdwpi gp"xqp"Qrkqkfgp" kuv" kppgtj cnd" fgu"ngv| vgp" Lcjt|gjpvu"uvctm"cpiguvgk igp." qdyqjn" fkg" Cpygpfwpi" xqp" Qrkqkfgp" uej ygt ykg igpfg." Adgt" fcu" |gpvtcng" Pgtxgpu{uvgo" xgt okvgnvg" Pgdgpyktmwpi gp" ykg" Cvg o fg rtguukqp" wpf" Cdj@pikimgkv" |gkiv<sup>0</sup> Fkgug" Pgdgpyktmwpi gp" m<sup>3/4</sup>ppgp" o<sup>3/4</sup>inkejgt ykug" fwtej" fkg" rgtkrjgtg" Xgtcdtgejwpi" xqp" Qrkqkfgp" wo icpigp" ygtfgp<sup>0</sup> Ko o wp|gmgp." ygnejg" ukej" cp" Xgtngv| wpi gp" wpf" Gpv|Apfwpiujgtfgp" cptgkejgtp." gzrtk okgtgp" Qrkqkftg|grvqtgp" wpf" Qrkqkfrgrvkfg<sup>0</sup> kp" fkgugt" Uvwfkg" |gkigp" ykt." fcuu" fkg" Cmvkxkgtwpi" xqp" Qrkqkftg|grvqtgp" cwh" Ko o wp|gmgp" fkgug" |wt" Ugmtgvkqp" fgt" gpfqigppg" Qrkqkfrgrvkfg" Og v/ Gpmgrjcnk." /Gpfqtrjkp" wpf" F{pqtrjkp" C"xgtcpncuu." ygnejg" ykgfgtw o "nqmcn" Qrkqkftg|grvqtgp" cwh" rgtkrjgtgp" ugpuqtuejgp" Pgwtpqgp" dkpfgp" wpf" fctAdgt" gkpg" Cpcnigukg" dgyktmgrp<sup>0</sup> Cnu" Oqfgm" hAt" pgwtqrcvjuejgp" Uej ogt|" ywtf" gkpg" ej tqpkuejg" Mqpvvutkmvkqpun@ukqp" fgu" Kuejkcupgtxgu" cp" O@wugp" fwtejighAjtv." ygnejg" |w" ogejcpkuejgt" J {rgtugpukvkv@v" kp" fgt" Rhqvg" hAjtv<sup>0</sup> Fkg" nqmcng" Xgtcdtgejwpi" gzqigpgt" Ciqpkuvgp" fgt" /." U/" wpf" /Qrkqkftg|grvqtgp" pcjg" fgt" Xgtngv| wpi" wpf" kp" fgt" I g igpyctv" Qrkqkfrgrvkf/gzrtk okgtgpfgt" Ko o wp|gmgp" hAjtv" |w" gkpgt" Uej ogt| okpfgtwpi<sup>0</sup> Gkpg" u{uvgo kuejg" Gpvhtgpwpi" xqp" Ko o wp|gmgp" uqykg" gkpg" rjct o cmqnikuejg" kpcmvkxkgtwpi" xqp" Qrkqkfrgrvkfgp" hAjtv" |wt" Cwhjgdwpi" fkgugu" cpcnigkuejgp" Ghhgmvu<sup>0</sup> kp" Qrkqkfrgrvkf/Mpqemqvw" O@wugp" yct" |wfgo" fkg" Uej ogt|nkpfgtwpi" fwtej" nqmcn" cr rnk|kgtvg" Qrkqkftg|grvqt/Ciqpkuvgp" xgttkpigtv<sup>0</sup> kp" Ko o wp|gmn/fg rnvkgtvgp" O@wugp" hAjtv" gk" Vtcpuhgt" xqp" Ko o wp|gmgp" cwu" Yknfv{r." pkejv" cdgt" cwu" Qrkqkftg|grvqt/Mpqemqvw" O@wugp" |wt" Ykgfgtjgtuvgnwpi" fgt" Qrkqkfkpfw|kgtvgp" Cpcnigukg" *in vivo*<sup>0</sup> *Ex vivo* dgyktmgrp" Ciqpkuvgp" fgt" Qrkqkftg|grvqtgp" gkpg" xgtuv@tmvg" Ugmtgvkqp" xqp" Qrkqkfrgrvkfgp" fwtej" |wxqt" cwu" iguej@fkivgp" Pgtxgp" kuqkgtvg" Ko o wp|gmgp<sup>0</sup> Fkg" Rgrvkfugmtgvkqp" yct" cdj@piki" xqp" kpvtc|gmnwn@tgo" Ec<sup>4-0</sup> Gkpg" Dnqemc fg" fgt" Icklq" wpf" Idi" Wpvgtgkpgjgkvgp" jgvgtqtk o gtgt" I/Rtqvkgpg." fgt" RNE" wpf" fgu" KR<sub>5</sub>/Tg|grvqtu" hAjtv" |w" gkpgt" cwh" dcucng" Ygtvg" tgf w|kgtvgp" Rgrvkfugmtgvkqp." y@jtgpf" gkpg" kpjkdvkqp" fgt" RME" gkpgp" pwt" vgn ykug" okpfgtfgp" Ghhgmv" cwh" fkg" Ugmtgvkqp" |gkiv<sup>0</sup> Cpcnqi" fc|w" mppvg" fgt" cpcnigkuejg" Ghhgmv" nqmcn" cr rnk|kgtvgt" Qrkqkfg" kp" Ko o wp|gmn/fg rnvkgtvgp" O@wugp" fwtej" fgp" Vtcpuhgt" xqp" Ko o wp|gmgp" ykgfgtjgti guvgnv" ygtfgp." ygpp" fkg" Ko o wp|gmgp" *ex vivo* okv" gkpg o" Ejgncvt" hAt

gzvte|gmnwn@tgu" Ec<sup>4-</sup>" dgjcpfgnv" ywtfgp." pkejv" cdgt" pcej" Dgjcfnwpi" fgt" Ko owp|gmgp" okv"  
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Gtigdpkuug" |gkigp." fcuu" Qrkqkftg|grvqtgp" cwh" Ko owp|gmgp" Ãdgt" fgp" Ukipcnygi" I klqóI "  
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## Abstract

Qrkqkf" ctg" vjg" iqnf" uvcpfctf" hqt" vtgecv o gpv" qh" o qfgtcvg" vq" ugxtg" rckp<sup>0</sup> Vtcfkvkqpcmn{." qrkqkf" rtqfweg" cpcnigukc" d{" tgiwncvki" dqvj" rtg/" cpf" rquv/u{pcrvke" pgwtqpu" xkc" dnqemkpi" Ec<sup>4-</sup>" kphnwz." eqpugswgpvn{" kpjkdvkpi" vjg" tngcug" qh" gzekvcvt{" pgwtqvtcpu o kvvgtu" \*g0i0." inwvc o cvg+ " cpf" d{" j{rgtrqntk|kpi" vjg" u{pcrvke" o g o dtcpg" xkc" fgetgcukpi" kpvtcegnnwct" M<sup>-</sup>" eqpegpvtcvkqpu<sup>0</sup> Gxgp" vjqwi j"vjg"pw o dgt"qh" rtguetkrvkqpu" hqt" qrkqkf" jcu" i tgecvn{" kpetgcugf" kp" vjg" ncu" fgecf. " vjgtg" ctg" o clqt" rtqdnq o u" ykvj" qrkqkf" fwg" vq" vjgk" egpytcn" ukfg" chhgevu." uwej" cu" tgurktcvqt{" fgtrtguukq" cpf" cf fkevqkq." yjkej" okijv" dg" cxqkfgf" d{" rgtrjgtcn" cf o kpkuvtcvkq" qh" vjg" qrkqkf" Ektewncvki" ngwmqe{vgu" cnuq" rtqfweg" qrkqkf" rgrvkfg" cpf" qrkqkf" tgegrvqtu" fwtkpi" kplwt{" cpf" vjg{" ceew o wncvg" cv" vjg" kphnc o o cvkq" ukvg<sup>0</sup> Jgtg" yg" ujqy" vjcv" vjg" cevxcvkq" qh" qrkqkf" tgegrvqtu" qp" ngwmqe{vgu" ngcfu" vq" vjg" ugetgvkq" qh" ngwmqe{vg" fgtxgf" gpfqigpqu" qrkqkf" rgrvkfg" Og/gpmgrjcnk." β/ gpfqtrjkp" cpf" f{pqtrjkp" C." yjkej" dkpf" vq" vjg" nqecn" qrkqkf" tgegrvqtu" qp" rgtrjgtcn" ugpuqt{" pgwtqpu" vq" ecwug" cpcnigukc<sup>0</sup> Cu" c" o qfgn" qh" pgwtqrcvj {" ej tqke" eqpuvtkevq" kplwt{" qh" vjg" uekcvke" pgtxg" ycu" rgthq o gf" qp" o keg." yjkej" ecwugf" o gejcpekn" j{ rgtugpukvkv{<sup>0</sup> Rckp" ycu" cvvgpwcvgf" d{" vjg" crnkcevqkq" qh" gziqgpqu" ciqpkuvu" qh" vjg" δ/. μ/. " cpf" κ/qrkqkf" tgegrvqtu" cv" vjg" kplwt{" ukvg." yjkej" ycu" kphkvtcvgf" d{" qrkqkf" rgrvkfg" eqpvckkpi" ngwmqe{vgu<sup>0</sup> Vjg" cpcniguke" ghhgev" ycu" cdqnujgf" d{" u{uvg o ke" ngwmqe{vg" fgrngvkq" cpf" rjct o ceqni kecn" kpcevxcvkq" qh" qrkqkf" rgrvkfgu<sup>0</sup> kp" cffkvkq." ciqpkuv" kpfwegf" rckp" tgnkgh" ycu" cvvgpwcvgf" qp" qrkqkf" rgrvkfg" mpqem/qwv" o keg<sup>0</sup> Cfqrvkxg" vtcpuhgt" qh" ngwmqe{vgu" htq o " yknf/v{rg" kpq" ngwmqe{vg" fgrngvgf" o keg" tgeqpuvkvwvgf" ciqpkuv" kpfwegf" cpcnigukc" *in vivo*. Cpcnigukc" eqwnf" pqv" dg" tgeqpuvkvwvgf" yjgp" ngwmqe{vgu" ygtg" vtcpuhgtgf" htq o " qrkqkf" tgegrvqt" mpqem/qwv" o keg<sup>0</sup> *Ex vivo*." qrkqkf" tgegrvqt" ciqpkuvu" ukiphkcepvn {" gngxcvgf" vjg" ugetgvkq" qh" qrkqkf" rgrvkfgu" htq o " ngwmqe{vgu" kuqncvgf" htq o " fc o cigf" pgtxgu<sup>0</sup> Vjku" ugetgvkq" ycu" fgrgpfgpv" qp" kpvtcegnnwct" Ec<sup>4-</sup>" cpf" dnqemkpi" I αklq" cpf" I βγ" uwdwpkvu." RNE" cpf" KR<sub>5</sub>- tgegrvqt- fgetgcugf" vjg" qrkqkf" rgrvkfg" ugetgvkq" dcem" vq" vjg" dcucn" ngxgnu" yjknq" RME" kpjkdvkq" qp{ " jcf" c" rctvkn" ghhgev. Uk o knctn {" ngwmqe{vg" fgrngvkq" tguwnvgf" kp" vjg" fgetgcug" qh" gziqgpqu" qrkqkf" cpcnigukc" *in vivo*<sup>0</sup> Vjg" cpcniguke" ghhgevu" eqwnf" dg" tg/guvcdnkujgf" d{" vtcpuhgt" qh" ngwmqe{vgu" *ex vivo* rtgvtgcvgf" ykvj" gzvtcegnnwct" Ec<sup>4-</sup>" ejgncvt." dwv" ycu" wpcnvtgf" yjgp" ngwmqe{vgu" ygtg" rtgvtgcvgf" ykvj" dnqemgtu" qh" I klq." I " rtqvgkpu" qt" kpvtcegnnwct" Ec<sup>4-</sup>" ejgncvt<sup>0</sup> Vjgug" hkpfkpiu" fg o qpuvtcvg" vjcv" dqvj" *in vivo* cpcnigukc" cpf" *ex vivo* qrkqkf" rgrvkfg" tngcug" ygtg" o gfkcvgf" d{" qrkqkf" tgegrvqtu" qp" ngwmqe{vgu" eqwrngf" vq" vjg" I klq<sup>0</sup> I " rtqvgk<sup>0</sup> RNE<sup>0</sup> KR<sub>5</sub>" tgegrvqtu" rcvjyc {" cpf" fgrgpfgpv" qp" kpvtcegnnwct" Ec<sup>4-</sup>" yjkej" ecp" dg" kfgpvkhkgf" cu" cp" wpeqpxgpvkqpcn" o gejcpeku o " qh" rcvjqnqikecn" rckp" eqpvtqn<sup>0</sup>

## Affidavit

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## Detailed Declaration of Contribution

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Rwdnkecvkqp< Ognkj" " 0" Egnkm." Fqokpkmc" Ncdw|. " Mctgp" Jgppkpi." Ognepkg" Dwuej/Fkgpuvhgtvki." Encktg" Icxgtkwz/Twhh." Dtkikvvg" N0" Mkgghgt." Cpftgcu" \k o ogt." Jcnkpc" Ocejgnumc." Ngwmqe{vg" qrkqkf"tgegrvqtu" o gfkcvg"cpnci gukc"xc"Ec<sup>4</sup> /tgi wncvfg"tgngcug"qh"qrkqkf" rgrvkfgu."Dtckp"Dgjcxkqt" cpf"Ko o wpvk{."4238"fqk<"3203238110ddk04238026023:"

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Page 1 of 13

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Mark	Rank	Abbreviated Journal Title (linked to journal information)	ISSN	JCR Data <sup>i</sup>						Eigenfactor® Metrics <sup>i</sup>	
				Total Cites	Impact Factor	5-Year Impact Factor	Immediacy Index	Articles	Cited Half-life	Eigenfactor® Score	Article Influence® Score
<input type="checkbox"/>	1	<a href="#">NAT REV NEUROSCI</a>	1471-003X	33792	29.298	35.142	5.603	58	8.0	0.07267	16.210
<input type="checkbox"/>	2	<a href="#">BEHAV BRAIN SCI</a>	0140-525X	7873	20.415	23.842	1.700	10	>10.0	0.01290	11.205
<input type="checkbox"/>	3	<a href="#">TRENDS COGN SCI</a>	1364-6613	21382	17.850	23.872	2.444	72	8.6	0.04734	10.525
<input type="checkbox"/>	4	<a href="#">NAT NEUROSCI</a>	1097-6256	51112	16.724	16.874	4.100	221	7.8	0.15525	9.161
<input type="checkbox"/>	5	<a href="#">ANNU REV NEUROSCI</a>	0147-006X	13125	14.265	22.563	3.000	21	>10.0	0.02076	11.517
<input type="checkbox"/>	6	<a href="#">NEURON</a>	0896-6273	78507	13.974	16.092	2.927	385	8.3	0.22300	8.439
<input type="checkbox"/>	7	<a href="#">MOL PSYCHIATR</a>	1359-4184	15797	13.314	13.274	2.892	167	5.6	0.04455	4.886
<input type="checkbox"/>	8	<a href="#">PROG NEUROBIOL</a>	0301-0082	11877	13.177	11.181	1.318	44	9.7	0.02039	3.739
<input type="checkbox"/>	9	<a href="#">TRENDS NEUROSCI</a>	0166-2236	18656	12.504	13.470	2.464	69	>10.0	0.03023	5.941
<input type="checkbox"/>	10	<a href="#">ACTA NEUROPATHOL</a>	0001-6322	14701	11.360	10.616	2.743	109	6.7	0.03705	4.070
<input type="checkbox"/>	11	<a href="#">BIOL PSYCHIAT</a>	0006-3223	42289	11.212	10.799	3.653	190	8.1	0.07406	3.719
<input type="checkbox"/>	12	<a href="#">BRAIN</a>	0006-8950	46207	10.103	10.545	2.320	259	8.9	0.08391	4.110
<input type="checkbox"/>	13	<a href="#">ANN NEUROL</a>	0364-5134	32995	9.638	10.880	2.277	177	>10.0	0.05956	4.360
<input type="checkbox"/>	14	<a href="#">J PINEAL RES</a>	0742-3098	6914	9.314	7.140	2.391	87	6.1	0.00780	1.142
<input type="checkbox"/>	15	<a href="#">FRONT NEUROENDOCRIN</a>	0091-3022	3407	8.852	9.045	1.297	37	6.5	0.00728	3.062
<input type="checkbox"/>	16	<a href="#">NEUROSCI BIOBEHAV R</a>	0149-7634	18522	8.580	10.504	1.498	233	6.2	0.04536	3.622
<input type="checkbox"/>	17	<a href="#">CEREB CORTEX</a>	1047-3211	26911	8.285	7.881	1.423	409	7.1	0.06829	3.383
<input type="checkbox"/>	18	<a href="#">SLEEP MED REV</a>	1087-0792	4392	7.341	9.636	2.375	48	6.6	0.01038	3.463
<input type="checkbox"/>	19	<a href="#">NEUROSCIENTIST</a>	1073-8584	4096	7.295	7.609	1.977	44	6.9	0.01011	2.903
<input type="checkbox"/>	20	<a href="#">MOL NEURODEGENER</a>	1750-1326	2312	6.510	5.599	0.523	65	4.1	0.00936	1.968



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Page 2 of 13



Ranking is based on your journal and sort selections.

Mark	Rank	Abbreviated Journal Title (linked to journal information)	ISSN	JCR Data 						Eigenfactor® Metrics 	
				Total Cites	Impact Factor	5-Year Impact Factor	Immediacy Index	Articles	Cited Half-life	Eigenfactor® Score	Article Influence® Score
<input type="checkbox"/>	21	<a href="#">NEUROPSYCHOPHARMACOL</a>	0893-133X	22869	6.399	7.825	1.794	291	6.7	0.05002	2.647
<input type="checkbox"/>	22	<a href="#">CURR OPIN NEUROBIOL</a>	0959-4388	13090	6.373	6.958	1.671	152	8.5	0.03561	3.510
<input type="checkbox"/>	23	<a href="#">NEUROPSYCHOL REV</a>	1040-7308	2314	6.061	7.594	0.440	25	6.6	0.00478	2.468
<input type="checkbox"/>	24	<a href="#">CEPHALALGIA</a>	0333-1024	7906	6.052	4.363	1.333	132	7.8	0.01180	1.131
<input type="checkbox"/>	25	<a href="#">GLIA</a>	0894-1491	11548	5.997	5.411	1.285	158	7.7	0.02057	1.692
<input type="checkbox"/>	26	<a href="#">J NEUROSCI</a>	0270-6474	172201	5.924	6.780	1.148	1342	8.5	0.35339	2.785
<input checked="" type="checkbox"/>	27	<a href="#">BRAIN BEHAV IMMUN</a>	0889-1591	9464	5.874	6.020	1.462	238	4.9	0.02405	1.795
<input type="checkbox"/>	28	<a href="#">BRAIN STRUCT FUNCT</a>	1863-2653	3534	5.811	6.803	1.307	244	3.0	0.01508	2.514
<input type="checkbox"/>	29	<a href="#">J PSYCHIATR NEUROSCI</a>	1180-4882	2690	5.570	6.207	1.136	44	6.5	0.00551	2.034
<input type="checkbox"/>	30	<a href="#">PAIN</a>	0304-3959	32930	5.557	6.244	1.119	269	>10.0	0.04578	2.019
<input type="checkbox"/>	31	<a href="#">NEUROIMAGE</a>	1053-8119	79475	5.463	6.797	1.160	770	6.7	0.18031	2.325
<input type="checkbox"/>	32	<a href="#">MOL NEUROBIOL</a>	0893-7648	5142	5.397	5.392	1.155	283	3.4	0.01336	1.483
<input type="checkbox"/>	33	<a href="#">BRAIN PATHOL</a>	1015-6305	4403	5.256	4.485	1.026	77	7.5	0.00880	1.550
<input type="checkbox"/>	34	<a href="#">ALZHEIMERS RES THER</a>	1758-9193	1164	5.197	5.126	0.921	76	2.5	0.00538	1.726
<input type="checkbox"/>	35	<a href="#">FRONT MOL NEUROSCI</a>	1662-5099	1592	5.154		0.329	79	3.2	0.00785	
<input type="checkbox"/>	36	<a href="#">NEUROBIOL AGING</a>	0197-4580	19205	5.153	5.193	1.261	429	5.7	0.04583	1.663
<input type="checkbox"/>	37	<a href="#">SOC COGN AFFECT NEUR</a>	1749-5016	4695	5.101	5.532	0.848	210	3.4	0.01840	2.073
<input type="checkbox"/>	38	<a href="#">HUM BRAIN MAPP</a>	1065-9471	17184	4.962	5.638	0.931	378	6.5	0.04047	2.088
<input type="checkbox"/>	39	<a href="#">MOL AUTISM</a>	2040-2392	847	4.961	5.184	0.921	63	2.5	0.00452	1.962
<input type="checkbox"/>	40	<a href="#">NEUROPHARMACOLOGY</a>	0028-3908	17341	4.936	4.709	1.288	365	5.8	0.03944	1.460

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**Curriculum vitae**

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## Complete list of publications

**Celik M. Ö.** " Ncdw| " F0." Jgppkpi " M0." Dwuej/Fkgpuvhtvki " O0." Icxgkewz" Twhh" E0." Mkgthgt" D0N0." \k o ogt" C0." Ocejgnumc" J0" \*4238+" Ngwmqe{vg" qrqkf" tgegrvqtu" ogfkcvg" cpenigukc" xkc" Ec4-/tgiwncvgf" tngcug" qh" qrqkf" rgrvkfgu0" Dtckp" DgjcX" Ko owp0" 79<" 449/640" \*Ko rcev" hcevqt<" 70:3+

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-**Çelik M. Ö.**" O0." Ocejgnumc" J0." 4238." Ngwmqe{vg"qrkqkf"tgegrvqtu" o gfkcvg"cpeni gukc"xc"tgngcug qh"qrkqkf"rgrvkfgu"}Rquvgt."4238"DODH" o ggvkpi "\*Dgtnkpl I gt o cp{+\_"

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## Acknowledgements

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