SUPPLEMENTARY INFORMATION

SUPPLEMENTARY FIGURE LEGENDS

Supplementary Fig. 1: Peptide coverage and semi-tryptic peptides proof the origin of soluble ectodomains from true ectodomain shedding (a) The amino acid sequence of selected membrane proteins (Sez6, Sez6L1, Latrophilin 1, APP, APLP1, L1 and CHL1) is depicted with tryptic peptides marked yellow, semi-tryptic peptides marked green and the transmembrane domain marked red. Putative BACE1 cleavage sites are depicted in pink while identified cleavage sites are underlined yellow. Only ectodomain-derived peptides even of the polytopic membrane protein Latrophilin 1 can be detected. **(b)** Semi-tryptic peptides of APP, APLP1 and Sez6L1 and their reduction upon C3 treatment proof the origin of these peptides from BACE1 cleavage. The closer the semi-tryptic peptide is to the original cleavage site, the stronger is the reduction.

SUPLEMENTARY TABLES

Supplementary Table 1: HEK293T secretome list of filtered identified protein IDs.

This table contains the identified proteins of the HEK293T secretome which fulfill following criteria: at least three-fold enriched, annotated as glycoprotein in SWISS-PROT, identified with at least two unique peptides and not part of the MaxQuant contaminant protein list.

Supplementary Table 2: HEK293T secretome peptides of filtered identified protein IDs.

This table contains the corresponding peptides of the proteins in suppl table 1.

Supplementary Table 3: HEK293T protein groups raw data.

This table includes all identified proteins including contaminants and cytosolic proteins of the HEK293T experiment. This file is the unprocessed protein data output file of the MaxQuant suite.

Supplementary Table 4: HEK293T peptides raw data.

This table contains all identified peptides of the HEK293T experiment. This file is the unprocessed peptide data output file of the MaxQuant suite.

Supplementary Table 5: Neuronal secretome list of filtered identified protein IDs including quantified ratio between BACE1 inhibition and control (C3/DMSO).

This table contains the identified proteins of the neuronal secretome which fulfill following criteria: annotated as glycoprotein in SWISS-PROT, identified in at least four out of five biological replicates, identified with at least two unique peptides and not part of the MaxQuant contaminant protein list. It is the whole filtered data set while table 1 contains the significantly changed proteins under BACE1 inhibition.

Supplementary Table 6: Neuronal secretome list of filtered peptides of identified protein IDs.

This table contains the corresponding peptides of the proteins in suppl table 5.

Supplementary Table 7: Neuronal secretome protein groups raw data.

This table contains all identified proteins including contaminants and cytosolic proteins of the neuronal secretome of five biological replicates. This file is the unprocessed protein data output file of the MaxQuant suite.

Supplementary Table 8: Neuronal secretome peptides raw data

This table contains the corresponding peptides of all identified proteins of suppl table 7. This file is the unprocessed peptide data output file of the MaxQuant suite.

A

Seizure protein 6

MRPAALLLLPSLLALLAHGLSS EAPITGEGHATGIRETDGELTAAPTPEQSDRGVHFVTTAPTLKLLNHHPLLEEFLQEGLEREEAPQPALPFQPDSPTHFTPSPLPRLTNQDNRPVFTSPTPAVAAAPTQPHSREKPWNLESKPPELSITSSLPPGPSMAVPTLLPEDRPSTTPPSQAWTPTQEGPGDMDRPWVPEVMSKTTGLGVEGTIATSTASGDDEETTTTIITTTVTTVQPPGPCSWNFSGPEGSLDSPTAPSSPSDVGLDCFYYISVYPGYGVEIKVENISLQEGETITVEGLGGPDPLPLANQSFLLRGQVIRSPTHQAALRFQSLPLPAGPGTFHFRYQAYLLSCHFPRRPAYGDVTVTSLHPGGSAHFHCATGYQLKGARFLTCLNATQPFWDSQEPVCIAACGGVIRNATTGRIVSPGFPGNYSNNLTCHWLLEAPESQRLHLHFEKVSLAEDDDRLIIRNGNNVEAPPVYDSYEVEYLPIEGLLSSGRHFFVEFSTDSSGAAAGMALRYEAFQQGHCYEPFVKYGNFSSSAPSYPVGTTVEFSCDPGYTLEQGSIIIECVDLHDPQWNETEPACRAVCSGEITDSAGVVLSPNWPEPYGRGQDCIWGVHVEEDKRIMLDIRVLRIGSGDVLTFYDGDDLTARVLGQYSGPRGHFKLFTSMADVTIQFQSDPGTSALGYQQGFVIHFFEVPRNDTCPELPEIPNGWKNPSQPELVHGTVVTYQCYPGYQVVGSSILMCQWDLSWSEDLPSCQRVTSCHDPGDVEHSRRLISSPKFPVGATVQYVCDQGFVLTGSAILTCHDRQAGSPKWSDRAPKCLLEQFKPCHGLSAPENGARSPEKRLHPAGATIHFSCAPGYVLKGQASIKCVPGHPSHWSDPPPICRAASLDGFYNGR***SLDV***AKAPAASSALDAAH**LAAAIFLPLVAMVLLVGGVYL**YFSRFQGKSPLQLPRTHPRPYNRITVESAFDNPTYETGSLSFAGDERI

Latrophilin 1

MARLAAALWSLCVTTVLVTSATQGLSRAGLPFGLMRRELACEGYPIELRCPGSDVIMVENANYGRTDDKICDADPFQMENVQCYLPDAFKIMSQRCNNRTQCVVVAGSDAFPDPCPGTYKYLEVQYDCVPYIFVCPGTLQKVLEPTSTHESEHQSGAWCKDPLQAGDRIYVMPWIPYRTDTLTEYASWEDYVAARHTTTYRLPNRVDGTGFVVYDGAVFYNKERTRNIVKYDLRTRIKSGETVINTANYHDTSPYRWGGKTDIDLAVDENGLWVIYATEGNNGRLVVSQLNPYTLRFEGTWETGYDKRSASNAFMVCGVLYVLRSVYVDDDSEAAGNRVDYAFNTNANREEPVSLAFPNPYQFVSSVDYNPRDNQLYVWNNYFVVRYSLEFGPPDPSAGPATSPPLSTTTTARPTPLTSTASPAATTPLRRAPLTTHPVGAINQLGPDLPPATAPAPSTRRPPAPNLHVSPELFCEPREVRRVQWPATQQGMLVERPCPKGTRGIASFQCLPALGLWNPRGPDLSNCTSPWVNQVAQKIKSGENAANIASELARHTRGSIYAGDVSSSVKLMEQLLDILDAQLQALRPIERESAGKNYNKMHKRERTCKDYIKAVVETVDNLLRPEALESWKDMNATEQVHTATMLLDVLEEGAFLLADNVREPARFLAAKQNVVLEVTVLNTEGQVQELVFPQEYPSENSIQLSANTIKQNSRNGVVKVVFILYNNLGLFLSTENATVKLAGEAGTGGPGGASLVVNSQVIAASINKESSRVFLMDPVIFTVAHLEAKNHFNANCSFWNYSERSMLGYWSTQGCRLVESNKTHTTCACSHLTNFAVLMAHREIYQGRINELLLSVITWVGIVISLVCLAICISTFCFLRGLQTDRNTIHKNLCINLFLAELLFLVGIDKTQYEVACPIFAGLLHYFFLAAFSWLCLEGVHLYLLLVEVFESEYSRTKYYYLGGYCFPALVVGIAAAIDYRSYGTEKACWLRVDNYFIWSFIGPVSFVIVVNLVFLMVTLHKMIRSSSVLKPDSSRLDNIKSWALGAIALLFLLGLTWAFGLLFINKESVVMAYLFTTFNAFQGVFIFVFHCALQKKVHKEYSKCLRHSYCCIRSPPGGTHGSLKTSAMRSNTRYYTGTQSRIRRMWNDTVRKQTESSFMAGDINSTPTLNRGTMGNHLLTNPVLQPRGGTSPYNTLIAESVGFNPSSPPVFNSPGSYREPKHPLGGREACGMDTLPLNGNFNNSYSLRSGDFPPGDGGPEPPRGRNLADAAAFEKMIISELVHNNLRGASGGAKGPPPEPPVPPVPGVSEDEAGGPGSADRAEIELLYKALEEPLLLPRAQSVLYQSDLDESESCTAEDGATSRPLSSPPGRDSLYASGANLRDSPSYPDSSPEGPNEALPPPPPAPPGPPEIYYTSRPPALVARNPLQGYYQVRRPSHEGYLAAPSLEGPGPDGDGQMQLVTSL

L1

MVVMLRYVWPLLLCSPCLLIQIPDEYKGHHVLEPPVITEQSPRRLVVFPTDDISLKCEARGRPQVEFRWTKDGIHFKPKEELGVVVHEAPYSGSFTIEGNNSFAQRFQGIYRCYASNKLGTAMSHEIQLVAEGAPKWPKETVKPVEVEEGESVVLPCNPPPSAAPPRIYWMNSKIFDIKQDERVSMGQNGDLYFANVLTSDNHSDYICNAHFPGTRTIIQKEPIDLRVKPTNSMIDRKPRLLFPTNSSSRLVALQGQSLILECIAEGFPTPTIKWLHPSDPMPTDRVIYQNHNKTLQLLNVGEEDDGEYTCLAENSLGSARHAYYVTVEAAPYWLQKPQSHLYGPGETARLDCQVQGRPQPEITWRINGMSMETVNKDQKYRIEQGSLILSNVQPTDTMVTQCEARNQHGLLLANAYIYVVQLPARILTKDNQTYMAVEGSTAYLLCKAFGAPVPSVQWLDEEGTTVLQDERFFPYANGTLSIRDLQANDTGRYFCQAANDQNNVTILANLQVKEATQITQGPRSAIEKKGARVTFTCQASFDPSLQASITWRGDGRDLQERGDSDKYFIEDGKLVIQSLDYSDQGNYSCVASTELDEVESRAQLLVVGSPGPVPHLELSDRHLLKQSQVHLSWSPAEDHNSPIEKYDIEFEDKEMAPEKWFSLGKVPGNQTSTTLKLSPYVHYTFRVTAINKYGPGEPSPVSETVVTPEAAPEKNPVDVRGEGNETNNMVITWKPLRWMDWNAPQIQYRVQWRPQGKQETWRKQTVSDPFLVVSNTSTFVPYEIKVQAVNNQGKGPEPQVTIGYSGEDYPQVSPELEDITIFNSSTVLVRWRPVDLAQVKGHLKGYNVTYWWKGSQRKHSKRHIHKSHIVVPANTTSAILSGLRPYSSYHVEVQAFNGRGLGPASEWTFSTPEGVPGHPEALHLECQSDTSLLLHWQPPLSHNGVLTGYLLSYHPVEGESKEQLFFNLSDPELRTHNLTNLNPDLQYRFQLQATTQQGGPGEAIVREGGTMALFGKPDFGNISATAGENYSVVSWVPRKGQCNFRFHILFKALPEGKVSPDHQPQPQYVSYNQSSYTQWNLQPDTKYEIHLIKEKVLLH***HLDV***KTNGTGPVRVSTTGSFASEGWFIAFVSAIILLLLILLILCFIKRSKGGKYSVKDKEDTQVDSEARPMKDETFGEYRSLESDNEEKAFGSSQPSLNGDIKPLGSDDSLADYGGSVDVQFNEDGSFIGQYSGKKEKEAAGGNDSSGATSPINPAVALE

Seizure protein 6 like 1

MPVARPQAAGPDRISLFLVAFLLGSPAAAQAEDGGPEGEMHPSTAYLLPSASLESSLEEGVTSAAPGLLPSQEALEAMEESLPPALPDEASVQHTPALRKGLPSLKQLNSARRQLRPLATPTTLQRLGSPASATTKLREPEDPEQPTAPAPLQIAPFTALATTLPHSPQPAQAPDDSSPGSPLDKGDNELTGSASEESQETTTSTIVTTTIITTEQAPALCGVSFSDPEGYIDSSDFPPQPYSSFLECTYNVTVYTGYGVELQVKSVNLSEGELLSIRGVDGPTLTVLANQTLLVEGQVIRSPTNTISVYFRTFQDDGLGTFQLHYQAFMLSCPFPRRPDAGEVTVMDLHSGGVAHFHCHLGYELQGAKTLTCINASKPHWSSQEPVCSAPCGGAVHNATIGRVLSPSFPGTANGSQLCVWTIEAPEGQKLHLHLERLLLHEKDRMIVYSGRTNTSALLYDSLRTESVPFEGLLSEGSSIRIEFTSDQGQAASAFNIRFEAFEKGHCYEPYIQNGNFTTSDPTYNIGTIVEFTCDPGHSLEQGPAVIECVNVRDPYWNDTEPLCRAMCGGELSAVAGVVLSPNWPEPYAEGEDCVWKIHVGEEKRIFLDIQFLNLSNSDILTIYDGDEVVPHVLGQYFGHSSPQKLYSSTPDLTIQFHSDPAGLIFGKGQGFIMNYIEVSRNDSCSDLPEIQNGWKTTSHTELVRGARITYQCDPGYDIVGSDTLTCQWDLSWSSDPPFCEKIMYCTDPGEVEHSTRLISDPVLLVGTTIQYTCSPGFVLEGSSLLTCYSRETGTPIWTSRLPHCVSEESLACDNPGLPENGYQILYKRLYLPGESLTFMCYEGFELMGEVTIRCILGQPSHWSGPLPICKVNQDSFEHAL***EAEA***AAESSLEGGNMA**LAIFIPVLLISLLLGGAYIYV**TRCRQYSSLRLPLMYSHPYSQITVETEFDNPIYETGETREYEVSI

APP

MLPSLALLLLAAWTVRALEVPTDGNAGLLAEPQIAMFCGKLNMHMNVQNGKWESDPSGTKTCIGTKEGILQYCQEVYPELQITNVVEANQPVTIQNWCKRGRKQCKTHTHIVIPYRCLVGEFVSDALLVPDKCKFLHQERMDVCETHLHWHTVAKETCSEKSTNLHDYGMLLPCGIDKFRGVEFVCCPLAEESDSVDSADAEEDDSDVWWGGADTDYADGGEDKVVEVAEEEEVADVEEEEADDDEDVEDGDEVEEEAEEPYEEATERTTSTATTTTTTTESVEEVVREVCSEQAETGPCRAMISRWYFDVTEGKCVPFFYGGCGGNRNNFDTEEYCMAVCGSVSTQSLLKTTSEPLPQDPDKLPTTAASTPDAVDKYLETPGDENEHAHFQKAKERLEAKHRERMSQVMREWEEAERQAKNLPKADKKAVIQHFQEKVESLEQEAANERQQLVETHMARVEAMLNDRRRLALENYITALQAVPPRPHHVFNMLKKYVRAEQKDRQHTLKHFEHVRMVDPKKAAQIRSQVMTHLRVIYERMNQSLSLLYNVPAVAEEIQDEVDELLQKEQNYSDDVLANMISEPRISYGNDALMPSLTETKTTVELLPVNGEFSLDDLQPWHPFGVDSVPANTENEVEPVDARPAADRGLTTRPGSGLTNIKTEEISEV***KMDA***EFGHDSGFEVRHQKLVFFAEDVGSNKGAIIGLMVGGVVIATVIVITLVMLKKKQYTSIHHGVVEVDAAVTPEERHLSKMQQNGYENPTYKFFEQMQN

APLP1

MGPTSPAARGQGRRWRPPLPLLLPLSLLLLRAQLAVGNLAVGSPSAAEAPGSAQVAGLCGRLTLHRDLRTGRWEPDPQRSRRCLLDPQRVLEYCRQMYPELHIARVEQAAQAIPMERWCGGTRSGRCAHPHHEVVPFHCLPGEFVSEALLVPEGCRFLHQERMDQCESSTRRHQEAQEACSSQGLILHGSGMLLPCGSDRFRGVEYVCCPPPATPNPSGMAAGDPSTRSWPLGGRAEGGEDEEEVESFPQPVDDYFVEPPQAEEEEEEEEERAPPPSSHTPVMVSRVTPTPRPTDGVDVYFGMPGEIGEHEGFLRAKMDLEERRMRQINEVMREWAMADSQSKNLPKADRQALNEHFQSILQTLEEQVSGERQRLVETHATRVIALINDQRRAALEGFLAALQGDPPQAERVLMALRRYLRAEQKEQRHTLRHYQHVAAVDPEKAQQMRFQVQTHLQVIEERMNQSLGLLDQNPHLAQELRPQIQELLLAEHLGPSELDASVPGSSSEDKGSLQPPESKDDPPVTLPKGSTDQESSSSGREKLTPLEQYEQKVNASAPRGFPFHSSDI***QRDE***LAPSGTGVSREALSGLLIMGAGGGSLIVLSLLLLRKKKPYGTISHGVVEVDPMLTLEEQQLRELQRHGYENPTYRFLEERP

CHL1

MMELPLCGRGLILSLIFLLLKLSAAEIPLSVQQVPTIVKQSYVQVAFPFDEYFQIECEAKGNPEPIFSWTKDDKPFDLSDPRIIAANNSGTFKIPNEGHISHFQGKYRCFASNRLGTAVSEEIEFIVPGVPKFPKEKIEPIDVEEGDSIVLPCNPPKGLPPLHIYWMNIELEHIEQDERVYMSQRGDLYFANVEENDSRNDYCCFAAFPKLRTIVQKMPMKLTVNSSNSIKQRKPKLLLPPAQMGSLSAKTVLKGDTLLLECFAEGLPTPHIQWSKPGSELPEGRATIEVHEKTLKIENISYQDRGNYRCTANNLLGKASHDFHVTVEEPPRWKKKPQSAVYSTGSSGILLCEAEGEPQPTIKWRLNGLPIEKHPFPGDFMFPREISFTNLLPNHTGVYQCEASNIHGTILANANIDVIDVIPLIKTKNEENYATVVGYSAFLHCEYFASPKATVVWEVADETHPLEGDRYHTHENGTLEIYRTTEEDAGSYSCWVDNAMGKAVITANLDIRNATKLRVSPKNPRIPKSHVLELYCESQCDSHLKHSLKLSWSKDGEAFEMNGTEDGRIVIDGAYLTISNITAEDQGVYSCSAQTSLDSTSKKTQVTVLGVGDPPETFTCQKDKNRSVRLLREAGDDHNSKSASTIVEFEGNREEPGKWEELTRVQGEETDVVLSLAPYVRYQFRVTAVNEVGRSHASLPSDHHETPPAAPDKNPQNIRVQASQPKEMIIKWEPLKSMEQNGPGLEYKVSWKPQGAPEEWEEEIVTNHTLRVMTPTVYAPYDVKVQAINQLGSSPDPQPVTLYSGEDYPSTAPVIQRVDVMNSTLVKVTWSSIPKETVHGLLRGYQINWWKTKSLLDGRTHPKEVNILRFSGQRNSGMVPSLDPFSEFHLTVLAYNSKGAGPESEPYIFQTPEGVPEQPSFLKVIKVDKDTATLSWGLPKKLNGNLTGYLLQYQIINDTYELGELNEINVTTPSKSSWHLSNLNSTTKYKFYLRACTSRGCGKPISEEGATLGEGSKGIRKITEGVNVTQKIHPVEVLVPGAEHIVHLMTKNWGDNDSI***FQDV***IETRGREYAGLYDDISTQGWFIGLMCAIALLTLILLTICFVKRNRGGKYSVKEKEDLHPDPEVQSAKDETFGEYSDSDEKPLKGSLRSLNRNMQPTESADSLVEYGEGDQSIFNEDGSFIGAYTGAKEKGSVESNGSSTATFPLRA

B

Protein Name	Peptide Mass	Peptide Sequence	Ratio C3/DMSO
APP	1064.506	TEEISEVKM	0
APLP1	1133.5142	GFPFHSSDIQ	0.029302188
Seizure protein 6 like 1	1629.9031	VNQDSFEHALEA	0.004555976
Seizure protein 6 like 1	1158.5306	VNQDSFEHAL	0.111999769
Seizure protein 6 like 1	974.40937	VNQDSFEH	0.128996595

Supplementary Fig.1