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Review

Herpesviruses, autoimmunity and epilepsy: Peptide sharing and potential cross-reactivity with human synaptic proteins

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ABSTRACT

Aggregation of immuno-proteomic data reveals that *i)* herpesviruses and synaptic proteins –in particular Synapsin-1 and Bassoon - share a large number of hexapeptides that also recur in hundreds of epitopes experimentally validated as immunopositive in the human host, and *ii)* the shared peptides are also spread among human epilepsy-related proteins. The data indicate that cross-reactive processes may be associated with pathogenetic mechanisms in epilepsy, thus suggesting a role of autoimmunity in etiopathology of epilepsies after herpesvirus-infections.

1. Introduction

Epilepsies are a group of different clinical conditions manifesting with seizures and characterized by abnormal firing of neurons. Genetic factors [1], brain tumors [2], head trauma [3], stroke [4,5], and infections of the central nervous system (CNS) [6–10] are all frequently occurring recognized risk factors for epilepsy that can explain its high morbidity rate (~ 50 million people worldwide) [11]. Following infections, epileptic seizures can occur within the first two weeks after infection and are then defined as early seizures, or months and years after it, therefore fulfilling the criteria for diagnosing epilepsy. The distinction between the two phenomena is relevant because the pathogenetic mechanisms behind early seizures and late-onset ones are thought to differ, although they have not been fully understood. Understanding the pathogenesis of epilepsy after infections might be relevant for two main reasons. On the one hand it could help improve preventing epilepsy by treating the underlying infection(s) [8,9]. On the other hand it might contribute to shed light on epileptogenesis. In classical views on epileptogenesis, imbalance between inhibitory and excitatory circuits has been proposed to underpin epilepsies [10–15]. However, both decrease and enhancement of inhibition and excitation have been observed in animal models [16–18] and overall the molecular mechanisms behind epileptogenesis are still poorly understood. Recent research has shown how epilepsy can be considered a synaptopathy with disruption of the complex pre- and post-synaptic mechanisms responsible for regulating neurotransmission [19–21].

Acute inflammatory response and cytokine release (TNF-alpha, IL-6) in the context of innate immunity might play a central role in the genesis of early seizures whereas structural and/or functional mechanisms leading to persistent neuronal hyper-excitability seem to underpin delayed unprovoked seizures after CNS-infections [7,8,22]. Recent views suggest long-term immuno-mediated mechanisms also for late-onset epileptic seizures after infections, with a possible involvement of the adaptive immune systems [8,23].

Herpesviruses, among the neurotropic pathogens that have been associated with a high risk of epilepsy - i.e. late unprovoked seizures after infection - are also able to induce CNS-targeting autoimmunity and autoantibody formation [8,24–35]. Indeed, during immune responses following herpesviral infections, peptide commonalities might result in autoimmune cross-reactivity targeting pre- and post-synaptic proteins thus triggering epileptogenesis.

This paper reviews data currently available from immuno-proteomic databases searching for herpesviral immunoreactive sequences common to synaptic proteins. Data indicate a high degree of peptide overlap between herpesviral and human synaptic proteins mainly involving two pre-synaptic proteins that - when altered, mutated or improperly functioning - have been linked to epilepsy, ie, Synapsin-1 (SYN1) [36–42] and Bassoon (BSN) [39–43].

2. Peptide sharing between herpesviruses and synaptic proteins

Eight herpesviral proteomes and two non-neurotropic viruses, ie,

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Table 1
Tabulation of the number of hexapeptides shared between herpesviruses and synaptic proteins.

Protein[a,b,c]	Virus[c,d]										
	Ade 12	HPV16	EBV	HCMV	HHV1	HHV2	HHV3	HHV6b	HHV7	HHV8	Total
FRAS1	0	2	12	12	5	7	2	6	5	4	55
DYH7	2	2	9	8	8	6	4	10	3	6	58
SYN1	2	0	16	12	16	15	0	3	0	4	68
SYPH	0	0	3	2	2	2	2	2	0	0	13
BSN	3	2	49	47	34	36	9	3	0	12	195
VGLU1	0	0	1	4	5	3	0	1	0	4	18
VGLU2	0	0	0	2	3	3	1	1	3	3	16
DLG4	0	0	6	1	2	5	0	0	1	1	16
MPP2	3	0	3	2	3	4	1	1	1	1	19
GRIA2	0	1	3	0	3	1	4	0	4	1	17
NMDZ1	0	0	2	5	3	1	3	0	1	3	18
NMDE1	1	1	1	2	1	3	4	2	0	4	19
NMDE2	0	1	8	4	4	3	5	4	2	4	35
DCE1	1	0	4	1	1	0	0	2	0	0	9
VIAAT	0	0	3	1	1	2	0	0	1	2	10
GEPH	0	0	9	7	4	3	0	3	1	1	28
GBRA1	1	0	1	1	1	0	0	1	2	2	9
Total	13	9	130	111	96	94	35	39	24	52	603

[a] Fifteen synaptic proteins selected according to Micheva [50] plus 2 controls were analyzed for viral matches: Synapsin-1 (SYN1); Synaptophysin (SYPH); Protein bassoon (BSN); Vesicular glutamate transporter 1 (VGLU1); Vesicular glutamate transporter 2 (VGLU2); Disks large homolog 4 (DLG4); Protein MPP2 (MPP2); Glutamate receptor 2 (GRIA2); Glutamate receptor ionotropic (NMDZ1); Glutamate receptor ionotropic (NMDE1); Glutamate receptor ionotropic (NMDE2); Glutamate decarboxylase 1 (DCE1); Vesicular inhibitory amino acid transporter (VIAAT); Gephyrin (GEPH); Gamma-aminobutyric acid receptor subunit alpha-1 (GBRA1). Control proteins: Extracellular matrix protein FRAS1 (FRAS1) andDynein heavy chain 7, axonemal (DYH7). Proteins given by UniProtKB entry (UniProtKB, http://www.uniprot.org/) [51].

[b] The fifteen protein sequences were dissected into hexapeptides with one-residue-offset: (ie, MGNEVS, GNEVSL, NEVSLE, EVSLEG, and so on). Hexapeptides were used as probes, since 5–6 amino acids (aa) are sufficient minimal determinants in humoral/cellular immunoreactivity as well as in antigen-antibody recognition [52–56]. Hexapeptides were analyzed for occurrences within the viral proteomes using PIR Peptide Match program (http://research.bioinformatics.udel.edu/peptidematch/) [57] as already described [58].

[c] Further details and references at http://www.uniprot.org/ [51].

[d] Proteomes of the following herpesviruses were analyzed: Epstein-Barr virus, strain GD1 (EBV), human cytomegalovirus, strain Merlin (HCMV); human herpesvirus 1, strain 17 (HHV1); human herpesvirus 2, strain HG52 (HHV2); human herpesvirus 3 (HHV3); human herpesvirus 6b, strain Z29 (HHV6b); human herpesvirus 7, strain JI (HHV7); and human herpesvirus 8, strain GK18 (HHV8). Two non-neurotropic viruses, ie, human adenovirus 12 (Ade12) and human papillomavirus type 16 (HPV16), were used as controls.

human adenovirus 12 (Ade12) and human papillomavirus type 16 (HPV16), were examined for hexapeptide matching with 15 human pre−/post-synaptic proteins and 2 control proteins, ie, extracellular matrix protein FRAS1 (FRAS1) and dynein heavy chain 7 (DYH7) (Table 1).

The numerical description of the peptide sharing between viruses and human proteins in Table 1 shows that:

1) herpesviral and synaptic proteins share 581 hexapeptides, including multiple occurrences;

Table 2
Description of herpesviral peptides shared with Synapsin-1 and Bassoon.

SYN1. Synapsin-1 (Brain protein 4.1)	
EBV	APPAAR, GAGRGG, GAPPAA, GGAGRG, GGGSGG, GGSGGA, GSGGAG, PAGPPA, PAPPRP, PGPAGP, PGPGPQ, PPPPPP, PQPPPP, QPPPPP, RPSGPG, TAAAAA
HCMV	AAAAAT, GGGSGG, GSSGGG, HLSGLG, PAPPRP, PPPPPG, PPPPPP, QPPPPP, SPQRQA, SSGGGG, TAAAAA, TTAAAA
HHV1	AGRGGA, EPAPPR, GGGSGG, GGPGAP, GRGGAA, GSGGAG, PASPSP, PPASPS, PPPPGA, PPPPPP, QPPPPP, RLPSPT, SGGAGR, SGPGPA, SSGGGG, TAAAAA
HHV2	AAAAAT, AERSSG, APAASP, APPGGQ, GPVPRT, PAASPA, PAPPRP, PPPPPG, PPPPPP, RPPASP, RRRLSD, SPTSAP, TAAAAA, TPSPGA, TTAAAA
HHV3	–
HHV6b	ATPGPG, TPGPGT, VEQAEF
HHV7	–
HHV8	PAPPKA, PPPGAH, TAAAGG, VGGGSG
BSN. Bassoon (Zinc finger protein 231)	
EBV	AAPGGG, AGARGP, AGPGPG, APAPAP, APGGGS, APGPGP, DSGSDS, EADTQG, ESDLAS, FKTIEL, FYGPRD, GAGDGP, GARPGG, GGGGPD, GGGSGA, GLGLQP, GLGQPS, GPRGDA, GPRGRP, GSGALS, GSGGGG, LARRDV, LSPHRL, LSPSSP, MPKPPP, PATTAV, PDPLEI, PEADTQ, PEPPGP, PGGGSG, PGPSTA, PHGGPS, PLARRD, PMPTTQ, PPEPPG, PPGGAG, PQAPSG, PTPLPP, RGPGGP, RPSTPR, RRRRSR, SDSSGG, SGALSR, SGGGGP, SPASPS, SPLPPQ, SPTSLS, SRGPGG, TPATTA
HCMV	APAPAP, ASASTS, ASSSSA, ATAAAP, ATASSS, AVSSSS, DDEDGE, DFMRRQ, DSDEEL, EDSDSS, EEDEDS, EEEELL, GAGGPS, GEEESE, GPQPGS, GQSSSP, GSGGGG, GVVGPG, KSLAPA, LEEDED, LGASLL, PAPLAG, PTTVPA, RGPGGP, RPSTPR, RRRARR, RRRRAR, SEAEAL, SGLAAA, SLAPAA, SSPSRR, SSSAAA, SSSPPL, TAAAPA, TADSAL, TASSSS, TLFPVP, TQQQQQ, VSSSLV, YGGRHG
HHV1	AAGARG, AGQASP, APAPAP, ASSSSA, DSEAEA, EAAGAP, EAEALD, GGAGDG, GPGALP, LGAAVY, LQQQLQ, LRRFKT, PALSPA, PASPAG, PASTPS, PGPGPA, PLRASE, PLSPTA, PPGPPG, PPLSPS, PRPAGG, PVRRRR, QASATT, RDLAFA, RPAGGP, SEAEAL, SGGGGP, SGPAAL, SRMCAA, STAEPR, TGPHPP, TLPAST, TPSGPT, VRRRRS
HHV2	AAGARG, AELRSH, AGLGAT, APGAGG, ASSSSA, EDSDSS, EPAGAL, EPPGPP, GAPAPA, GGPRPR, GKPAAA, GLGATE, GLYRYP, HGPLLP, LGAAVY, LPGGAA, LRHPTD, LRRFKT, LSDSEL, PASPSS, PEPPGP, PPADAA, PPEPPG, PRPAGG, PRVPSA, PSPPPE, RDLAFA, RHPTDL, RPAGGP, RRRRSR, RVPSAG, SAPAAS, SAPEKT, SPSSPS, TLPAST, TPIAAT
HHV3	APTPSP, EAEALD, EEESEE, PASPAG, PPSPSE, PSPSEI, RDLAFA, SEITGV, TPTPAT
HHV6b	AVSSGY, TPKVKS, TQTPSP
HHV7	–
HHV8	AALQSK, DTATSG, GSQVSA, PPSAPA, PQGLPG, PQPGPS, PSPAPA, QQEERQ, SATAVP, SPSVSP, SSSAAA, TPLPPP

2) the extent of the sharing is unexpected considered that the probability for two proteins to share a hexapeptide is equal to 20^{-6} (that is 1 in 64,000,000 or 0,000000015625);
3) the herpesviruses most involved in the sharing are EBV, HCMV, HHV1, and HHV2 (Table 1, last line), whilst the two non-neurotropic viruses, ie, Ade12 and HPV16, show a low level of peptide sharing;
4) the peptide matching is highly imbalanced toward two synaptic proteins, ie, Synapsin-1 (SYN1) and Bassoon (BSN), with Synapsin-1 showing 66 matches and Bassoon alone hosting 190 out of 581 herpesviral matches, that is 33% of the total herpesviral peptide matching (Table 1, last column). Such an anomalous concentration of herpesviral matches in the two synaptic proteins does not appear to depend on their amino acid (aa) length (705 aa and 3026 aa, respectively) since the two longer control proteins FRAS1 (4008 aa) and DYH7 (4024 aa) show a comparatively lower number of herpesviral peptide occurrences (53 and 54 herpesviral matches, respectively).

3. Predominant involvement of Synapsin-1 and Bassoon in herpesviral peptide sharing

The magnitude of the peptide sharing reported in Table 2 prevents detailed analyses protein-by-protein. Hence, this study focussed on the main players of the sharing, that is Synapsin-1 and Bassoon, the herpeviral peptide commonalities of which are described in Table 2.

4. Immmunologic potential of the peptide sharing between herpesviruses and Synapsin-1 and Bassoon

The peptides shared between the eight herpesviruses and Synapsin-1 and Bassoon were investigated for their immunologic properties by exploring the Immune Epitope DataBase resource (IEDB, www.iedb.org) [59]. Almost all peptide matches described in Table 2 recur in hundreds of epitopes experimentally validated as immunopositive in the human host. Tables 3 and 4 show a synopsis of the data for Synapsin-1 and Bassoon, respectively.

Table 3

Epitopes containing peptide sequences common to Synapsin-1 and herpeviruses.

1	2	1	2	1	2
3579	aPGPGPQpgplresivcyfm	469,657	QPPPPPPpl	596,654	ilRPSGPGaaslw
18,529	gaaTAAAGGyka	471,128	sprsplPAPPRPfl	600,271	pprPPPPPP
55,339	RPSGPGpel	474,484	AAAAATmal	600,272	ppvPPPPPP
66,417	tssdSPTSAPektplpvsat	474,785	aeaPPPPPP	617,452	hggyGGGSGGgssy
106,447	gePGPAGPqgapgpa	475,813	APAASPAsl	633,628	laPPPPPGl
119,736	aePPPPPPepari	477,192	eaPPPPPPp	634,300	lplPPPPPP
133,664	PPPPPPPPPP	477,608	egTAAAAAa	634,351	lPPPPPPhl
143,034	rkrrsasTAAAGGgg	477,858	eqVGGGSGGAG	635,601	pgspgsPGPAGPa
143,060	sasTAAAGGggstdnl	478,876	gTAAAAAar	635,926	QPPPPPlwi
161,584	aavlfaaTAAAAAav	478,877	gTAAAAATgr	637,390	srfsSSGGGGgggrfsss
162,616	keaPAPPKA	485,382	seaTPSPGA	638,372	vkPPPPPPp
196,337	aPPPPPPGh	507,551	PPPPPGkpq	642,962	fqhGGPGAPpsssay
196,887	vPPPPPPPP	508,279	sPAPPRPsl	682,961	syGGGSGGgf
224,924	paPPPPPPP	510,092	qaAAAAATv	691,821	ppmPPPPPP
227,041	aPGPGPQpgplresi	510,136	SGPGPAaal	694,312	ePGPAGPlsvqarle
230,030	nyTPGPGTrf	516,567	gGGGSGGiaeagsghm	694,589	ggaGSGGAGgts
236,939	gggygsGGGSGGygsrrf	532,144	hSGPGPAgfpvpnqpvy	694,672	gmaPGPGPQpgplre
239,351	aeTAAAAAavaa	532,792	lPPPPPGsf	695,337	lqrpptqhePGPAGP
239,460	aprpAAAAATal	538,982	TPGPGTrfpl	696,125	qynsSSGGGG
240,498	spRPSGPGpssf	541,821	epstpGGGSGGggavaaa	696,495	SSGGGGggg
240,519	spygggygsGGGSGGygsr	541,886	evlpTAAAAA	697,400	aaAAAAATaar
241,986	pggganiPPPPPPPGgigga	544,035	lvVGGGSGGla	698,193	aeQPPPPPlw
419,512	aPAPPKAea	544,466	ppsPPPPPP	699,685	aTAAAAAay
434,248	sGGGSGGygsrrf	544,474	PQPPPPPPp	704,647	evvrylGGSGGAGgr
437,706	gPPPPPGkpq	544,507	pvPPPPPPP	705,985	fPGPAGPsf
440,520	shrPPPPPGkpe	552,614	hyevlvlGGGSGGitm	715,912	lhqTTAAAA
440,782	sSSGGGGgggrfssssgy	553,579	ldqsGGPGAPttprklps	724,519	sdanraSSGGGGggl
445,795	kprPPPPPP	554,486	nhyevlvlGGGSGGi	725,044	SGPGPAsnl
448,938	sSSGGGGgggrf	555,294	qplPPPPPPpppppyy	727,327	TAAAAAsir
452,749	aPPPPGAav	556,448	sSSGGGGgggrfsss	730,069	vaTAAAAAl
457,321	pAAAAATal	563,779	hhqqqqQPPPPPipan	734,113	avsaAAAAATr
457,387	phPPPPPPp	564,434	legegSSGGGGrgggsf	778,609	SSGGGGgggrfs
457,472	psPPPPPPp	570,502	APPAARgll	780,424	aaatvrSPTSAP
457,858	QPPPPPPpf	573,898	keaPAPPKAea	784,973	asTPGPGTanaa
458,445	rpprPPPPPP	576,739	rpaaAAAAAT	792,450	ggnqpqrPPPPPGkpq
458,490	RPSGPGaasl	576,860	rPPPPPPsl	794,111	gpgfvPPPPPPpy
458,491	RPSGPGgem	584,203	iPPPPPPms	794,358	gPPPPPGkp
459,294	sPAPPRPwl	587,144	PPPPPPism	797,891	hcalqelyqAERSSGe
459,544	sprpGAPPAAi	587,624	pvrpAAAAATal	806,252	lrwgglpqlGGPGAPe
460,030	tPAPPKAvl	588,452	rhPAGPPAr	809,328	pgpqvsyppppaghSGPGPA
463,435	apmspgSSGGGGqpl	588,842	rprPPPPPP	814,391	rPPPPPGkpq
466,565	ilfPPPPPPni	590,387	tpRPSGPGpssf	829,091	vrylGGSGGAGgrl
467,984	lPAASPAallp	591,126	vwgPPPPGAp	837,999	mppaPPPPPPqn
468,163	lppppgPPPPPPl	594,059	AGRGGAArpngp	838,125	pppwmQPPPPP
469,335	pwmQPPPPPm	595,649	ghPPPPPP	838,916	wgPPPPGAp

Column 1: Epitopes listed according to the IEDB ID number. Epitope details and references at www.iedb.org [69]. Column 2: Sequences common to Synapsin-1 and herpeviruses are in capital letters.

Table 4
Epitopes containing peptide sequences common to Bassoon and herpeviruses.

1	2	1	2	1	2
2766	alnargvlllstRDLAFAga	459,602	spSPSPSSl	578,041	SPSSPSvrrql
7888	ddvwtsgsDSDEELv	463,291	APAPAPal	589,473	rSAPAASer
7945	dEDSDSSdgyppnrq	463,292	APAPAPapal	592,863	rPEPPGPyfydltvtsah
10,089	DSDEELvtterktpr	463,293	APAPAPapam	600,552	qSRGPGGPgsfelw
18,961	gdEDSDSSdgyppnrqdprf	463,294	APAPAPasal	602,436	tcapqhgAPGPGPAdask
22,302	gsDSDEELvtterktprvtg	463,372	APGPGPstf	606,522	sDSDEELvtterktprvt
35,973	lfsgdEDSDSSdgyp	463,581	aPSPAPAgl	621,021	lfkPPQPPA
49,756	ptpvnpstAPAPAPt	466,007	gPPGPPGpgtpm	624,154	rqSPLPPQk
49,920	pvnpstAPAPAPtpt	469,689	qPRVPSAkav	625,131	sgkrsAPGGGSkvpq
55,346	RPSTPRaav	473,264	vyPASPSSwli	629,273	aLPGGAAvaav
57,159	sdaessdgedfivEEESEEs	475,502	agATAAAPv	645,276	isPASTPScl
57,997	sgdEDSDSSdgyppn	475,818	APAPAPaaa	649,591	RVPSAGssl
65,790	tptpvnpstAPAPAPtptfa	478,327	gATAAAPvp	651,213	vAPAPAPel
66,417	tssdSPTSAPEKTplpvsat	478,745	gplPGPGPAl	662,660	GSGGGGgghgsy
103,262	hviAGQASPsridgt	487,616	tpASSSSAl	689,903	elaATAAAPAv
108,121	sgfqglpgPPGPPGegggk	492,351	iiPQGLPGsieely	693,972	avdtGSGGGGqphdt
128,303	apsTAAAPAeekkve	495,772	vrfdPASPSSl	694,261	egrhhllvtGAGDGP
136,889	TLPASTlvrllvhay	504,475	APAPAPavtg	694,425	fGSGGGGggtg
142,848	lgmhqlQQEERQka	504,476	APAPAPrppqd	694,672	gmAPGPGPQpgplre
146,216	ekAPAPAPe	504,481	apaqAPAPAP	694,765	GSGGGGqphdtaprg
213,306	klSPSPSSr	507,548	PPGPPGkagp	694,866	hllvtGAGDGPplcs
226,662	rgvlllstRDLAFAg	507,993	RVPSAGsslv	695,164	latggGPRGDAtset
239,759	gsgggsyGSGGGGgghgsy	509,963	lpYSPSPSl	695,231	lgqTPASPArysp
240,412	slfgplPGPGPAlv	510,102	qgvlllstRDLAFAg	695,531	natsPQAPSGqktav
240,601	tqdsvgPPGPPGp	516,990	gpapsTAAAPAeekk	695,795	PQAPSGqktavptvt
240,691	vPRPAGGefgydkdtsl	525,694	sddEEESEEakrl	695,960	qapPTPLPPvspgdq
244,807	aaappakTAAAPAka	527,797	tpdsiASSSSAahpp	696,037	qllpapgPDPLEIqp
246,310	aappakTAAAPAkaa	531,786	gAPGPGPAdaskvvak	696,192	rktPHGGPShsstvm
389,989	TAAAPAkaaapakaa	540,854	aasnGSGGGGggisag	696,314	saaaavdtGSGGGGq
432,057	qTQQQQQpalvny	541,162	APAPAParsl	696,658	tppknatsPQAPSGq
433,856	EEDEDSlad	541,821	epstPGGGSGGGGavaaa	696,982	wngsGSGGGGg
437,231	fekAAGARGlstes	543,879	lPGGGSGppedv	699,025	APAPAPaer
441,481	vPRPAGGef	551,970	ggapsTAAAPAeekkv	699,055	apfPSPAPA
441,811	yGSGGGGgggrgsy	552,912	itappgTAAAPAkpa	700,933	dRPAGGPsa
442,481	APGGGSkkrdsl	554,914	PPGPPGprgypgipg	701,534	EAAGAPdrgr
443,487	epRGPGGPl	556,330	SPSPSSrvtv	702,964	eihgGAGGPSgr
451,565	aaAPAPAPa	556,479	sTAAAPAeekkve	718,870	nRPAGGPsa
451,601	aAPAPAPaa	570,392	APAPAPihnqf	719,527	PQAPSGpsy
452,599	APAPAPagm	573,243	hpFKTIEL	732,069	wtdgGSGGGGgy
452,600	APAPAPamvsa	576,755	RPAGGPqnqf	732,456	yaypATAAAPm
452,601	APAPAPatt	577,220	rsAPGGGSkvpqk	749,095	lPQGLPGlwl
452,602	APAPAPlsv	577,464	sAPGGGSkvpqk	749,416	lvsGAGDGPp
452,830	aPSPAPApt	577,758	slgPPGPPGl	752,975	ypATAAAPm
458,254	rmcvASSSSAl	577,833	sPASTPScl	765,170	ssscGSGGGGispkgsgps
458,283	RPAGGPsasm	577,834	sPASTPSclsa	767,452	TPKVKSkv

Column 1: Epitopes listed according to the IEDB ID number. Epitope details and references at www.iedb.org [69]. Column 2: Sequences common to Bassoon and herpeviruses are in capital letters.

5. Potential relevance of the peptide sharing between herpesviruses and Synapsin-1 and Bassoon for epileptogenesis

Synapsin-I is implicated in the regulation of neurotransmitter release from presynaptic neuron terminals and is the most abundant constituent of the matrix that connects the synaptic vesicles [36,37]. Alterations of Synapsin-I have been associated with epilepsy, learning difficulties, and behaviour disorders [38–42]. In parallel, Bassoon plays fundamental roles in the molecular synaptic dynamics by regulating neurotransmitter release from a subset of glutamatergic synapses, maintaining synapse integrity, and controlling presynaptic P/Q-type Ca (2+) channels, among others [43–48]. Importantly, genetic disruption of Bassoon induces a seizure-prone mouse model characterized by structural and functional alterations in the hippocampus and by early spontaneous seizures mimicking human neurodevelopmental disorders [49].

Hence, it appears reasonable to assume that autoimmune cross-reactions targeting Synapsin-1 and Bassoon may play a role in the epileptogenesis process consequent to herpesviral infections.

6. Spreading to epilepsy-related proteins of the peptide sharing between herpesviruses and Synapsin-1 and Bassoon: the multiple aspects of epilepsy

The peptide sharing between herpesviruses and Synapsin-1 and Bassoon was additionally analyzed for further matches within the human proteome addressing the following question: is the herpesviral peptide sharing illustrated in Table 3 unique to the synaptic Synapsin-1 and Bassoon proteins? Or are the shared peptides also common to other human proteins possibly implicated - when modified or altered or lacking - in epilepsies? The question has its legitimation in previous data [60,61] showing that peptide sharing is widespread feature among human proteins.

Tables 5 and 6 indicate that the herpesviral peptide sharing illustrated in Table 3 is not an exclusive prerogative of the synaptic Synapsin-1 and Bassoon proteins but extends to numerous human proteins involved in epilepsies. This implies that potential cross-reactions triggered by herpesviral infections might have multiple targets in the complex network of proteins that have been related to epilepsy. Of

Table 5
Peptides shared between herpesviruses and Synapsin-1 and also present in human epilepsy-related proteins.

Peptides[a,b]	Epilepsy-related proteins[c] and associated clinical features[d]
GGPGAP	ACHA4. Neuronal acetylcholine receptor subunit alpha-4. Focal epilepsy characterized by nocturnal seizures with hyperkinetic automatisms and poorly organized stereotyped movements.
SSGGGG	AFG32. AFG3-like protein 2. Spasticity, peripheral neuropathy, ptosis, oculomotor apraxia, dystonia, cerebellar atrophy, and progressive myoclonic epilepsy.
PPPPPPPP	ALG13. Putative bifunctional UDP-*N*-acetylglucosamine transferase and deubiquitinase ALG13. Epileptic encephalopathy, early infantile, 36.
TAAAAA	AP3B2. AP-3 complex subunit beta-2. Epileptic encephalopathy, early infantile, 48.
AAAAAT PPPPPP TAAAAA	ARX. Homeobox protein ARX. Neonatal-onset intractable epilepsy. Epilepsy characterized by frequent tonic seizures, with high-voltage bursts alternating with almost flat suppression phases.
PPPPGA PPPPPP	ATN1. Atrophin-1. Myoclonus epilepsy.
PPPPPPP	CTND2. Catenin delta-2. Myoclonic epilepsy.
AGRGGA GGAGRG	EP2A2. Laforin, isoform 9. Lafora progressive myoclonus epilepsy.
PPPPPPPP	GABR2. Gamma-aminobutyric acid type B receptor subunit 2. Epileptic encephalopathy, early infantile, 59.
GGGSGG	HNRPU. Heterogeneous nuclear ribonucleoprotein U. Epileptic encephalopathy, early infantile, 54
GSSGGGG	KCMA1. Calcium-activated potassium channel subunit alpha-1. Paroxysmal nonkinesigenic dyskinesia, 3, with or without generalized epilepsy.
GGGSGG	PURA. Transcriptional activator protein Pur-alpha. Neonatal hypotonia, encephalopathy with/out epilepsy.
PPPPPG	SHAN3. SH3 and multiple ankyrin repeat domains protein 3. May associate with hyperactivity, auditory overstimulation, epilepsy and bipolar affective disorders, among others.
RPSGPG	SMCA2. Probable global transcription activator SNF2L2. Myoclonic astatic epilepsy.
PPPPGA PPPPPG QPPPPP **PPPPPPP**	SOBP. Sine oculis-binding protein homolog. May associate with temporal lobe epilepsy and psychosis.
GGGSGG[e] **PPPPPPG**	SYGP1. Ras/Rap GTPase-activating protein SynGAP. Several forms of idiopathic generalized epilepsy.

[a] Hexapeptides shared between herpesviruses and Synapsin-1.
[b] Peptides formed by overlapping hexapeptides given bold.
[c] Epilepsy-related proteins given by UniProt accession names and further detailed at UniProtKB (/www.uniprot.org/) [61].
[d] Clinical features further detailed at UniProtKB, PubMed, OMIM.
[e] SYGP1 hosts 4 times the hexapeptide GGGSGG (aa pos: 382–387, 386–391, 1050–1055, and 1054–1059).

Table 6
Peptides shared between herpesviruses and Bassoon and also present in human epilepsy-related proteins.

Peptides[a]	Epilepsy-related proteins[b] and associated clinical features[c]
PGPSTA	AGRV1. Adhesion G-protein coupled receptor V1 precursor. Febrile seizures.
EEEELL	ARX. Homeobox protein ARX. Neonatal-onset intractable epilepsy. Epilepsy characterized by frequent tonic seizures, with high-voltage bursts alternating with almost flat suppression phases.
SSSAAA	ATN1. Atrophin-1. Myoclonus epilepsy.
GGGSGA	CAC1A. Voltage-dependent P/Q-type calcium channel subunit alpha-1A. Epileptic encephalopathy characterized by refractory seizures.
AVSSSS	FIG. 4. Polyphosphoinositide phosphatise. Temporo-occipital polymicrogyria, psychiatric manifestations, and epilepsy.
TAAAPA	LAGE3. EKC/KEOPS complex subunit LAGE3. Propensity for seizures.
SPSPSS	LMNB2. Lamin-B2 precursor. Progressive myoclonic epilepsy.
GGGSGA	NMDE4. Glutamate receptor ionotropic, NMDA 2D. Epileptic encephalopathy with severe childhood onset, characterized by refractory seizures, neurodevelopmental impairment.
TPLPPP	PIGN. GPI ethanolamine phosphate transferase 1. Neonatal hypotonia, lack of psychomotor development, seizures.
GSGGGG	PRDM8. PR domain zinc finger protein 8. Progressive myoclonus epilepsy characterized by progressive dysarthria, myoclonus, ataxia, cognitive decline, psychosis, dementia and spasticity, with onset in childhood.
RRRRSR	PRIC1. Prickle-like protein 1 precursor. Progressive myoclonic epilepsy.
GSGGGG	PURA. Transcriptional activator protein Pur-alpha. Neonatal hypotonia, encephalopathy with/out epilepsy.
PPSAPA	PYR1. CAD protein. Epileptic encephalopathy characterized by refractory seizures and neurodevelopmental impairment,
SPSSPS	RHBT2. Rho-related BTB domain-containing protein 2. epileptic encephalopathy. Seizure types are variable and include focal dyscognitive and generalized tonic-clonic seizures, as well as febrile seizures.
APGPGP GAGDGP PGPGPA	SHAN3. SH3 and multiple ankyrin repeat domains protein 3. May associate with hyperactivity, auditory overstimulation, epilepsy and bipolar affective disorders, among others.
TQQQQQ	SMCA2. Probable global transcription activator SNF2L2. Myoclonic astatic epilepsy.
PPGPPG	SOBP. Sine oculis-binding protein homolog. May associate with temporal lobe epilepsy and psychosis.
RRRRSR	SON. Protein SON. Epilepsy, vision problems, musculo-skeletal abnormalities.
GSGGGG PGGGSG	SYGP1. Ras/Rap GTPase-activating protein SynGAP. Several forms of idiopathic generalized epilepsy.
LSPSSP	SYVM. Valine–tRNA ligase, mitochondrial precursor. Variable clinical features: muscle weakness with hypotonia, central neurological disease with progressive external ophthalmoplegia, ptosis and ataxia, delayed psychomotor development, microcephaly and epilepsy.

[a] Hexapeptides shared between herpesviruses and Synapsin-1.
[b] Epilepsy-related proteins given by UniProt accession names and further detailed at UniProtKB (www.uniprot.org/) [61].
[c] Clinical features further detailed at UniProtKB, PubMed, OMIM.

interest, Tables 5 and 6 show that the epilepsy-related proteins potentially subject to post herpetic cross-reactions cover a broad spectrum of epileptic diseases and syndromes.

7. Conclusions

The present review of immune-proteomic data from annotated databases focusses on peptide sharing between herpesviruses and synaptic proteins. It has to be mentioned that the reported analyses deal with linear peptide sequences only, whilst also discontinuous sequences and conformational factors have a relevant role in antigenicity and immunogenicity. Nonetheless, the here described high level of peptide sharing between herpesviruses and human synaptic proteins, in particular Synapsin-1 and Bassoon, appears to be of utmost relevance since it highlights a potential role for herpesviruses infections in epilepsy. The significance of such a finding is amplified by the fact that almost all of the shared peptides are part of immunopositive epitopes, thus outlining a powerful cross-reactivity immune scenario, and, in addition, are also spread in numerous epilepsy-related proteins.

Moreover, the data reviewed here significantly connect to three different issues under debate in epileptology: i) the repeatedly reported association of epilepsy with EBV, HCMV, and HSV 1 and 2 infections [9,27–35]; ii) the etiology of epilepsy as an autoimmune cross-reactive process [62–77] that would lead to brain injury and inflammation, coherently with the clinical observations according to which neuroinflammation contributes or predisposes to seizures [8,78,79]; iii) the concept of epilepsy as a group of seizure disorders that may be caused by alterations of different molecules that are involved in multiple steps of neurotransmission and may have multiple manifestations [80–82].

In synthesis, this study offers a molecular platform for future experimental research aimed at defining the autoimmune pathogenesis of epilepsies [62–69], the role of infections [6–10], and the cross-reactivity mechanisms [8,24–35].

Declaration of Competing Interest

None.

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