Imaging of Synaptic Density in Neurodegenerative Disorders

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PET technology has produced many radiopharmaceuticals that target specific brain proteins and other measures of brain function. Recently, a new approach has emerged to image synaptic density by targeting the synaptic vesicle protein 2A (SV2A), an integral glycoprotein in the membrane of synaptic vesicles and widely distributed throughout the brain. Multiple SV2A ligands have been developed and translated to human use. The most successful of these to date is ^{11}C-UCB-J, because of its high uptake, moderate metabolism, and effective quantification with a 1-tissue-compartment model. Further, since SV2A is the target of the antiepileptic drug levetiracetam, human blocking studies have characterized specific binding and potential reference regions. Regional brain SV2A levels were shown to correlate with those of synaptophysin, another commonly used marker of synaptic density, providing the basis for SV2A PET imaging to have broad utility across neuropathologic diseases. In this review, we highlight the development of SV2A tracers and the evaluation of quantification methods, including compartment modeling and simple tissue ratios. Mouse and rat models of neurodegenerative diseases have been studied with small-animal PET, providing validation by comparison to direct tissue measures. Next, we review human PET imaging results in multiple neurodegenerative disorders. Studies on Parkinson disease and Alzheimer disease have progressed most rapidly at multiple centers, with generally consistent results of patterns of SV2A or synaptic loss. In Alzheimer disease, the synaptic loss patterns differ from those of amyloid, tau, and ^{18}F-FDG, although intertracer and interregional correlations have been found. Smaller studies have been reported in other disorders, including Lewy body dementia, frontotemporal dementia, Huntington disease, progressive supranuclear palsy, and corticobasal degeneration. In conclusion, PET imaging of SV2A has rapidly developed, and qualified radioligands are available. PET studies on humans indicate that SV2A loss might be specific to disease-associated brain regions and consistent with synaptic density loss. The recent availability of new ^{18}F tracers, ^{18}F-SynVesT-1 and ^{18}F-SynVesT-2, will substantially broaden the application of SV2A PET. Future studies are needed in larger patient cohorts to establish the clinical value of SV2A PET and its potential for diagnosis and progression monitoring of neurodegenerative diseases, as well as efficacy assessment of disease-modifying therapies.

Key Words: PET; synaptic vesicle glycoprotein 2A; synaptic density; SV2A; neurodegeneration

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The great strength of PET imaging is its ability to quantify specific physiologic functions and to measure unique elements of the brain, including receptors, transporters, and enzymes. In the area of neurodegeneration, this has yielded a plethora of novel radiopharmaceuticals to target protein aggregates such as β-amyloid (Aβ) and tau, and the search continues for useful tracers for other targets such as α-synuclein. The recent advent of PET synaptic imaging by targeting the synaptic vesicle protein 2A (SV2A) has opened many novel avenues of investigation into neurodegenerative disorders. The general utility of this marker in a wide range of disorders makes it uniquely suited to human studies, including disease diagnosis and differentiation and treatment monitoring. In many cases, the pairing of SV2A PET with a second PET study using a radioligand with a greater disease-specific focus provides unique multimodal information on brain pathophysiology. Here, we review the SV2A target protein, the development and quantification of SV2A PET tracers, synaptic imaging studies on animal models, and clinical studies on Parkinson disease (PD), dementia with Lewy bodies (DLB), Alzheimer disease (AD), frontotemporal dementia (FTD), Huntington disease (HD), progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD). Rodent studies are summarized in Table 1, and human studies are listed in Table 2.

SV2

SV2 is a glycoprotein (*1*) located on secretory vesicles of neurons and endocrine cells (*2,3*). SV2 is critical for synaptic function and is involved in vesicle trafficking and exocytosis (*4*), although investigations continue into its exact functions (*5,6*). SV2 has 3 isoforms (*7,8*) with different distributions in the brain. SV2A is ubiquitously expressed in virtually all synapses, SV2B is more restricted (*7–9*), and SV2C was observed in only a few rat brain areas (*8*). Among glutamatergic and γ-aminobutyric acid–ergic neurons, SV2A is thought to be located in both classes, whereas SV2B might be more restricted to the former and SV2C to the latter (*6*).

In 2004, Lynch et al. demonstrated that SV2A is the target of the antiepileptic drug levetiracetam (*10,11*). This led the pharmaceutical company UCB to identify a novel generation of antiepileptic drugs with increased SV2A affinity and antiseizure potency, ultimately resulting in the development of brivaracetam (*12,13*).

DEVELOPMENT OF SV2A PET RADIOLIGANDS

The first attempt to develop a SV2A PET radioligand was ^{11}C-levetiracetam (*14*), but this tracer did not progress, probably because of its low binding affinity to SV2A (K_i = 1.74 μM) (*15*). Subsequently, high-affinity SV2A-specific ligands were synthesized

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TABLE 1
Literature with ^{11}C-UCB-J PET in Animal Models of Neurodegenerative Disorders

Species	Model	Procedures or genotypes	Subjects	Outcome measure	Decrease	Reference
Mouse	AD	APP/PS1	9	SUVR	26% (hippocampus)	(*48*)
Rat	PD lesion	6-OHDA (20 μg) local injection in striatum	3	SUV	6% (striatum)	(*51*)
Rat	HD lesion	QA (20 μg) local injection in striatum	4	V_T	39% (striatum)	(*51*)
Rat	HD lesion	QA (40 μg) local injection in striatum	4	V_T	55% (striatum)	(*51*)
Mouse	PD	Heterozygous Thy1-αSyn mouse model line 61	10	AUCR	12% (hippocampus)	(*49*)
Mouse	AD	ArcSwe transgenic mouse model	11	AUCR	—	(*49*)
Mouse	HD	Heterozygous Q175DN knock-in mouse model	19	V_T (IDIF)	20% (striatum)	(*50*)
Rat	PD	6-OHDA local injection in medial forebrain bundle and rostral SN	4	V_T (IDIF	9% (striatum)	(*52*)

APP/PS1 = Swedish (APP KM670/671NL) and PSEN1-L166P mutations; 6-OHDA = 6-hydroxydopamine; QA = quinolinic acid; AUCR = area under curve ratio; ArcSwe = arctic (APP E693G) and Swedish (APP KM670/671NL) mutations; IDIF = image-derived input function. Listing is in chronologic order.

and evaluated (*16,17*). Three of the SV2A ligands were radiolabeled as ^{11}C-UCB-A (4-(3,5-Difluorophenyl)-1-((1-methyl-1H-imidazol-5-yl)methyl)pyrrolidin-2-one) (*18*), ^{18}F-UCB-H (1-((3-Fluoropyridin-4-yl)methyl)-4-(3,4,5-trifluorophenyl)pyrrolidin-2-one) (*19–22*), and ^{11}C-UCB-J ((*R*)-1-((3-(^{11}C-methyl-^{11}C)pyridin-4-yl)methyl)-4-(3,4,5-trifluorophenyl)pyrrolidin-2-one) (*23*), and all were evaluated in nonhuman primates. Of these, ^{11}C-UCB-J possessed the most suitable pharmacokinetics, that is, rapid and high brain uptake, reversible binding kinetics, and relatively low nonspecific binding in white matter (*23*). ^{11}C-UCB-A showed slower brain penetration in nonhuman primate brains, making quantitative analysis more challenging. Furthermore, ^{18}F-UCB-H showed relatively low specific binding in the nonhuman primate brain, probably because of lower binding affinity (negative log of half-maximal inhibitory concentration, pIC$_{50}$, 7.8 for UCB-H, vs. 8.2 for UCB-J) (*16,23*).

Subsequent SV2A human imaging data were highly consistent with preclinical data; that is, ^{11}C-UCB-J has ideal imaging characteristics (*24*), with ^{11}C-UCB-A possessing slow binding kinetics (*25*) and ^{18}F-UCB-H having low specific binding in the brain (*26*).

On the basis of the initial success of ^{11}C-UCB-J, ^{18}F-labeled SV2A radioligands with similar chemical backbones became of interest, as the half-life of ^{11}C (20.4 min) limits its broad applicability. Initial work focused on ^{18}F-UCB-J, which provided nonhuman primate data similar to that of ^{11}C-UCB-J (*27*); however, the radiosynthetic process was unsuitable for routine production. The subsequent focus was on mono- and difluorinated UCB-J analogs, that is, ^{18}F-SynVesT-1 ((*R*)-4-(3-Fluoro-5-(fluoro-^{18}F)phenyl)-1-((3-methylpyridin-4-yl)methyl)pyrrolidin-2-one (^{18}F-SDM-8, ^{18}F-MNI-1126) (*28,29*) and ^{18}F-SynVesT-2 ((*R*)-4-(3-([^{18}F]Fluoro)phenyl)-1-((3-methylpyridin-4-yl)methyl)pyrrolidin-2-one (^{18}F-SDM-2) (*30*). In humans, ^{18}F-SynVesT-1 displayed outstanding characteristics, that is, very high brain uptake, fast and reversible kinetics, excellent test–retest reproducibility, and binding specificity to SV2A (*31,32*). Compared with ^{11}C-UCB-J, ^{18}F-SynVesT-1 displayed higher binding potential (BP_{ND}). Recent human scans with ^{18}F-SynVesT-2 showed a slightly lower BP_{ND} but with faster kinetics. The availability of these ^{18}F-labeled SV2A PET radioligands provides the opportunity for multicenter clinical studies of various neurodegenerative disorders.

SV2A AS A BIOMARKER OF SYNAPTIC DENSITY

Synaptic vesicle proteins, such as SV2A, have previously been established as histologic markers of synaptic density (*33–35*) because of their localization to synaptic boutons. SV2A is a promising biomarker of synaptic density as it is ubiquitously and homogeneously present in synaptic vesicles (*7*), with a low variation in copy number per vesicle (*36*). To examine whether SV2A PET provides an index of synaptic density, a baboon underwent an ^{11}C-UCB-J scan, followed by postmortem brain tissue studies. The PET-measured ^{11}C-UCB-J distribution volume (V_T) correlated well with the regional SV2A distribution measured by a homogenate binding assay and Western blotting. Importantly, there was also a good correlation between SV2A and the gold standard synaptic density marker synaptophysin in Western blot and confocal microscopy experiments; that is, SV2A can be used as an alternative to synaptophysin for quantification of synapse density (*24*). Analogous biochemical studies with resected human tissue after epilepsy surgery also show promising results. Additional studies with postmortem human tissue are required to further validate SV2A as a biomarker of synaptic density.

QUANTIFICATION OF SV2A PET RADIOLIGANDS

Modeling studies of SV2A PET in humans revealed that the best models to quantify V_T values are the 1-tissue-compartment model (1TC) for ^{11}C-UCB-J (*37–39*), ^{18}F-SynVesT-1 (*32*), and ^{18}F-SynVesT-2 and Logan graphical analysis for ^{18}F-UCB-H (*26*). Excellent test–retest reproducibility and low-noise V_T images can be obtained with the 1TC model for ^{11}C-UCB-J (*37*) and ^{18}F-SynVesT-1 (*31,32*). Activation studies in humans showed that V_T was unaffected by visual stimulation, whereas K_1, the tracer influx constant, increased in the visual cortex (*40*).

For quantification of specific binding, a reference tissue is required, and the centrum semiovale (CS) has been proposed on the basis of in vitro biochemical data (*24*), showing negligible specific binding. However, there was a small displacement of ^{11}C-UCB-J in the CS with levetiracetam and brivaracetam (*24,41*), consistent with autoradiography data (*42*), and the CS V_T overestimates the gray matter

TABLE 2
Literature with SV2A PET in Human Studies of Neurodegenerative Disorders

Population	Subjects	Tracer	Outcome measure	Major finding	Reference
PD and CN	12 PD	^{11}C-UCB-J	BP_{ND}	≤45% lower binding in PD; largest in SN (45%), with multiple cortical areas included	(*56*)
PD (early drug-naïve) and CN	12 PD	^{11}C-UCB-J	V_T	Lower binding in PD ranged from 15% (caudate) to 8% in multiple areas; SN was 7%	(*57*)
PD and CN	30 PD	^{11}C-UCB-J	BP_{ND}	Lower binding in PD from 15%; largest in SN	(*58*)
PD and CN	21 PD	^{11}C-UCB-J	SUVR-1	Lower binding in PD in SN	(*60*)
DLB/PDD and CN	13 DLB/PDD	^{11}C-UCB-J	SUVR-1	Lower binding in DLB/PDD in multiple areas	(*60*)
AD and CN	10 AD/MCI	^{11}C-UCB-J	BP_{ND}	41% lower binding in hippocampus of AD	(*69*)
AD and CN	24 AD/MCI	^{18}F-UCB-H	V_T	Lower binding in hippocampus (31%), cortex (11%–18%), and thalamus (16%) of AD	(*71*)
AD and CN	34 AD/MCI	^{11}C-UCB-J	DVR_{Cb}	Extensive cortical and subcortical reductions of DVR_{Cb} in AD	(*72*)
AD and CN	12 AD	^{18}F-UCB-H	V_T	33% decrease in right hippocampus in AD (trend level)	(*82*)
AD and CN	38 AD/MCI	^{11}C-UCB-J ^{11}C-PiB	DVR_{Cb}	Inverse association between global amyloid deposition and hippocampal SV2A binding in participants with aMCI but not mild dementia	(*74*)
AD and CN	10 MCI	^{11}C-UCB-J ^{18}F-MK-6240	SUVR	Higher ^{18}F-MK-6240 binding inversely related to lower ^{11}C-UCB-J binding in medial temporal lobe	(*75*)
AD and CN	7 AD	^{11}C-UCB-J ^{18}F-flortaucipir	BP_{ND}	Higher regional ^{18}F-flortaucipir uptake with lower ^{11}C-UCB-J uptake	(*76*)
AD and CN	10 AD/MCI	^{11}C-UCB-J ^{18}F-flortaucipir	DVR_{Cb}	Entorhinal cortical tau inversely associated with hippocampal synaptic density	(*77*)
AD and CN	14 AD/MCI	^{11}C-UCB-J ^{18}F-FDG	DVR_{Cb}	Similar reduction of ^{11}C-UCB-J and ^{18}F-FDG in medial temporal lobe of AD, but smaller reduction of ^{11}C-UCB-J in neocortex than ^{18}F-FDG	(*78*)
bvFTD and CN	1 bvFTD	^{11}C-UCB-J	BP_{ND}	Lower binding in frontotemporal and subcortical regions	(*81*)
Presymptomatic C9orf72 mutation carriers and CN	3 carriers	^{11}C-UCB-J	BP_{ND}	Decrease in thalamus in carriers	(*81*)
bvFTD and CN	12 bvFTD	^{18}F-UCB-H	V_T	41% decrease in right parahippocampal area in bvFTD (trend level)	(*82*)
HD (premanifest and early stage) and CN	18 HD	^{11}C-UCB-J	BP_{ND}	Lower binding in putamen (−19%), caudate (−16%) in premanifest; putamen (−33%), caudate (−31%), whole gray matter (−12%) in early stage	(*85*)
PSP and CN	14 PSP	^{11}C-UCB-J	BP_{ND}	≤50% lower binding in cortical and subcortical areas	(*89*)
CBD and CN	15 CBD	^{11}C-UCB-J	BP_{ND}	≤50% lower binding in cortical and subcortical areas	(*89*)

PDD = PD dementia; MCI = mild cognitive impairment; DVR_{Cb} = V_T ratio (cerebellum reference); PiB = Pittsburgh compound B; aMCI = amnestic MCI; bvFTD = behavioral-variant FTD. Listing is in chronologic order per disorder.

nondisplaceable V_T (V_{ND}) (*38,43*). Nevertheless, CS V_T significantly correlates with gray matter V_{ND}, suggesting that it remains a useful proxy reference region (*43*). However, for disorders with white matter pathology, V_T (*44*) or V_T normalized by plasma protein binding (f_p) (*45*) is a useful outcome measure.

To avoid arterial sampling, there are 2 analysis approaches: using a reference tissue model or using the SUV ratio (SUVR). Since 1TC is the optimal model for ^{11}C-UCB-J, SRTM and SRTM2 were suitable. However, estimating k_2', the efflux rate from the CS, is challenging for ^{11}C-UCB-J. For scanning time, SRTM2 was shown to work well, with an acquisition of about 90 min (*46*). For shorter scans, SRTM2 had poorer performance, and the variance of k_2' estimates increased. When the 1TC k_2 value of CS is similar between cognitively normal (CN) subjects and patients, SRTM2 with a population average k_2' is a promising method to generate BP_{ND} images, although this approach requires validation in each population.

After bolus injection, the tissue-to-plasma ratio (i.e., the apparent V_T) continued to increase through a 2-h scan and overestimated the 1TC V_T (*47*). However, the overestimation in gray matter and CS tended to cancel out while computing the SUVR (ratio of target tissue to CS). Although the SUVRs also increased monotonically, a good match between SUVR-1 and 1TC BP_{ND} was observed at 60–90 min after injection regardless of subject conditions (*38,45,46*). Similar results have been found for ^{18}F-SynVesT-1 (*32*), which should allow the use of SUVR.

PRECLINICAL SV2A PET

Several preclinical SV2A studies were conducted on animal models of neurodegenerative diseases. A transgenic AD mouse model (APP/PS1) was scanned with ^{11}C-UCB-J and showed significantly lower SUVR in the hippocampus than did the wild type. In addition, after 1 mo of treatment with saracatinib, a Fyn kinase inhibitor, a significant SUVR increase in the hippocampus was found (*48*). Other SV2A PET studies have shown significant SV2A tracer binding decreases in mouse models, such as heterozygous Thy1-αSyn for PD (*49*) and heterozygous Q175DN knock-in for HD (*50*). In the PD model, a 12% decline was seen in the hippocampus using an area under the curve ratio between hippocampus and blood as the outcome measure (*49*). The HD mouse model showed a 20% lower V_T in the striatum as estimated using an image-derived input function (*50*).

In rats, striatal lesion models with 6-hydroxydopamine for PD and quinolinic acid for HD showed significant striatal decreases in ^{11}C-UCB-J binding (*51*). With 6-hydroxydopamine injected in the medial forebrain bundle and substantia nigra (SN), ipsilateral striatal reductions were found, demonstrating network effects within the brain circuits (*52*). These preclinical results support the use of SV2A PET to assess disease-specific synaptic deficits and the possibility of monitoring treatment effects. These rodent studies are summarized in Table 1.

PD AND DLB

Studies of PD have demonstrated the involvement of several neurotransmitter systems beyond dopamine and the importance of using new tools and biomarkers to investigate this condition (*53,54*). Growing evidence has drawn attention to the significance of exploring synaptic changes in this condition (*55*).

Matuskey et al. conducted the first in vivo investigation of SV2A/synaptic density in 12 subjects with mild bilateral PD and 12 matched CN subjects using ^{11}C-UCB-J. A lower BP_{ND} was found in PD, with between-group differences in subcortical regions including the SN (−45%), red nucleus (−31%), and locus coeruleus (−17%). Interestingly, lower synaptic density was also observed in cortical areas, including the posterior cingulate cortex (−15%), parahippocampal gyrus (−12%), orbitofrontal cortex (−11%), and ventromedial prefrontal cortex (−11%) (*56*).

In a related study, Wilson et al. compared SV2A PET in 12 drug-naïve early PD patients and 16 CN subjects. Similarly, the PD group had a significantly lower ^{11}C-UCB-J V_T in the striatum, thalamus, brain stem, dorsal raphe, and cortical regions. Differences in this cohort were less pronounced in the SN (−7%). This study also investigated the correlation between clinical symptoms and V_T values, revealing a negative correlation between synaptic density in the brain stem and clinical rating scores. Furthermore, 8 PD patients underwent a longitudinal ^{11}C-UCB-J PET scan at a 1-y interval with no significant changes detected (*57*).

In a third study, Delva et al. used ^{11}C-UCB-J, comparing 30 patients with PD and 20 CN subjects (*58*) and reported significantly lower BP_{ND} in the SN (−15%). They also reported lower BP_{ND} in dorsal striatum (−7%), caudate (−6%), and putamen (−6%) in the PD group. No correlation between BP_{ND} values and clinical symptoms was found.

DLB is closely related to PD with 4 major characteristics: parkinsonism, visual hallucinations, cognitive fluctuations, and rapid-eye-movement sleep behavior disorder (*59*). Andersen et al. used ^{11}C-UCB-J to compare synaptic density in 21 nondemented PD subjects, 13 patients with PD dementia or DLB, and 15 age-matched CN subjects using SUVR-1 as the outcome, with cerebellar white matter as a reference region (*60*). The nondemented PD group showed lower values only in the SN compared with CN subjects. The brain changes in the DLB/PD dementia group were more extensive, with significantly lower SUVR-1 values in the SN, occipital cortices, parietal cortices, primary sensorimotor cortex, middle frontal gyrus, and orbitofrontal cortex.

These preliminary investigations with ^{11}C-UCB-J have shown its ability to assess PD changes and the potential to add to the understanding of its pathophysiology and potentially improving diagnosis of conditions such as PD and DLB. Further studies with larger samples are currently ongoing to reach that goal.

AD

From a diagnostic perspective, AD is increasingly viewed along a continuum from preclinical AD to mild cognitive impairment and to AD dementia. The clinical dementia stage of AD is coupled to a distinct pathology with formation of plaques composed of Aβ, neurofibrillary tangles, and synaptic density loss (*61*). Synapses are crucial for cognitive function, and synaptic density loss is a robust and consistent pathology in AD (*62*). Cognitive impairment in AD is closely associated with synaptic density loss (*63*). Synaptic density damage is observed in the earliest stages of clinical AD with loss of synapses and several presynaptic proteins (*64*). Thus, the ability to assess synaptic density in vivo can be extremely valuable in studies of AD and in monitoring efficacy of potential therapies.

PET imaging is heavily used in AD studies to measure glucose metabolism (i.e., ^{18}F-FDG), β-amyloid plaques, and neurofibrillary tangles under the amyloid-tau-neurodegeneration (AT(N)) framework (*65*). ^{18}F-FDG PET is widely used to differentiate AD

from FTD and to track disease progression by measuring neuronal activity (*66*). However, ^{18}F-FDG is not a direct biomarker of synaptic density and is affected by stimulation, medication, and blood glucose level (*67,68*). SV2A PET can provide a direct indicator of synaptic density in AD.

In the first SV2A PET AD study with ^{11}C-UCB-J, 10 AD (all Aβ+) and 11 CN subjects were compared (*69*). Reduced hippocampal binding was hypothesized on the basis of early degeneration of entorhinal cortical cell projections to the hippocampus via the perforant pathway (*70*) and postmortem studies (*64*). BP_{ND} using CS as the reference region (*43*) was lower by 41% in the hippocampus of AD patients than in CN subjects and was larger than the volume loss (22%) measured by MRI (*69*). Statistically significant correlations were found between hippocampus BP_{ND} and cognitive tests, including an episodic memory score and the clinical dementia rating sum of boxes (*69*). Bastin et al. used ^{18}F-UCB-H in 24 patients with mild cognitive impairment or AD (all Aβ+) and 19 CN subjects (*71*), and V_T was lower in the hippocampus (31%), cortical regions (11%–18%), and thalamus (16%). Hippocampal binding was directly related to patients' cognitive decline and unawareness of memory problems.

In a subsequent ^{11}C-UCB-J study in a larger cohort of early AD patients ($n = 34$) and CN subjects ($n = 19$), more extensive cortical and subcortical reductions in SV2A binding were seen, which were more widespread than reductions in gray matter volume (*72*). Here, the outcome measure was V_T ratio with cerebellum as an alternative reference region, which provided a more robust signal than the small CS region. These findings better reflect the pathologic findings of reduced cortical synaptic density in AD postmortem studies (*73*).

The pattern of relationships between SV2A PET for synaptic density with amyloid (*74*), tau (*75–77*), and ^{18}F-FDG (*78*) have been investigated in AD. We measured ^{11}C-UCB-J V_T ratio and ^{11}C-PiB for Aβ deposition and observed a significant inverse association between global Aβ deposition and hippocampal SV2A binding in participants with mild cognitive impairment but not mild dementia (*74*). A paradoxic positive association between hippocampal Aβ and SV2A binding was found (*74*), suggesting that fibrillar Aβ is still accumulating in the early stages of disease before plateauing at later stages (*74*).

A study of 10 patients with mild cognitive impairment and 10 CN subjects found an inverse association between tau deposition (^{18}F-MK-6240) and ^{11}C-UCB-J within the medial temporal lobe (*75*). Decreased performance on cognitive tests was associated with both increased tau and decreased SV2A binding in the hippocampus, although in a multivariate analysis only tau binding was significantly related to cognitive performance (*75*). Similarly, higher regional ^{18}F-flortaucipir uptake was reported with lower ^{11}C-UCB-J uptake across the subjects in a cohort study of 7 AD patients (*76*). Both higher ^{18}F-flortaucipir and lower ^{11}C-UCB-J uptake were associated with altered synaptic function by magnetoencephalography spectral measures (*76*). A third correlation study between ^{11}C-UCB-J and ^{18}F-flortaucipir in 10 AD patients and 10 CN participants showed that entorhinal cortical tau was inversely associated with hippocampal synaptic density, reflecting synaptic failure due to tau pathology in entorhinal cortical neurons projecting to the hippocampus (*77*).

A study comparing ^{11}C-UCB-J and ^{18}F-FDG in 14 AD patients and 11 CN participants found that these measures showed a similar magnitude of reduction in the medial temporal lobe of AD patients (*78*). However, the reduction of ^{11}C-UCB-J in the neocortex was smaller than that of ^{18}F-FDG. The highest intertracer correlations were found in the medial temporal cortex. Interestingly, there was a similar pattern of ^{11}C-UCB-J delivery and perfusion (e.g., K_1) and ^{18}F-FDG uptake (e.g., Patlak K_i). Thus, measures of synaptic loss and perfusion or metabolism that can be obtained with a single dynamic ^{11}C-UCB-J scan provide complementary information on the pathophysiology of AD (*78*).

FTD

FTD is commonly misdiagnosed as AD or other neuropsychiatric disorders because of its 2 major patterns: gradual or progressive changes in behavior or language impairments. The affected population is usually younger than AD patients (35–75 y), and 20%–40% of patients have a family history of FTD (*79*). Previous studies have provided evidence of synaptic dysfunction and loss in FTD (*80*). Malpetti et al. assessed in vivo synaptic density in 3 presymptomatic C9orf72 mutation carriers, 1 symptomatic patient with the behavioral variant (bvFTD), and 19 healthy controls (*81*). In the presymptomatic group, they reported a prominent decline in thalamic ^{11}C-UCB-J binding, with a minor reduction in the cortex. The patient with bvFTD demonstrated extensive synaptic loss in the frontotemporal regions. Salmon et al. assessed use of ^{18}F-UCB-H PET in 12 patients with probable bvFTD compared with 12 CN subjects and 12 AD patients and reported decreased binding in the right anterior parahippocampal gyrus in bvFTD (*82*). Anosognosia correlated with synaptic density in the caudate nucleus and the anteromedial prefrontal cortex. Ongoing studies in bvFTD are being conducted to further characterize this disorder.

HD

HD is an autosomal dominant disease caused by an expanded CAG triplet in the Huntington chromosome. Clinical characterizations of HD are progressive movement disorders (including chorea), cognitive deficits (culminating in dementia), and psychiatric symptoms (e.g., depression) (*83*). The pathogenesis of HD is not clear, but studies have found synaptic and neuronal dysfunction and death in the cortex and striatum in HD patients (*84*). Lower SV2A levels (~25%) were observed in the cortical area in HD gene carriers than in controls by ^{3}H-UCB-J autoradiography and SV2A immunofluorescence in human brain tissue (*50*). Recently, an in vivo human PET study found a significant loss of SV2A in multiple regions including the putamen (−28%), caudate (−25%), and whole gray matter (−9%) in the HD group ($n = 11$) compared with the CN group ($n = 15$), with similar findings in the premanifest HD mutation carrier group ($n = 7$) (*85*). Striatal ^{11}C-UCB-J binding correlated positively with clinical measures in motor and cognitive domains (*85*).

PSP AND CBD

PSP and CBD are both neurodegenerative primary tauopathies and have similarities in clinical symptoms (e.g., motor, behavioral, and cognitive abnormalities) (*86*) but are considered different disorders because different tau strains and brain regions are affected (*87*). Previous work has suggested that oligomeric tau leads to synaptic loss (*88*), which may play an essential role in PSP and CBD. Recently, Holland et al. found widespread (≤50%) cortical and subcortical reductions in ^{11}C-UCB-J binding in both PSP ($n = 14$) and CBD ($n = 15$) compared with controls (*89*), consistent with postmortem data (*88*). They also reported a negative

correlation between global ^{11}C-UCB-J binding and the PSP and CBD rating scales and a positive correlation with the revised Addenbrooke Cognitive Examination (*89*).

FUTURE CONSIDERATIONS

In summary, PET imaging of SV2A provides a direct measure of synaptic vesicles and is a proxy for synaptic density. High-quality PET radioligands labeled with ^{11}C and ^{18}F have been developed and validated for application in human studies. The potentially general utility of synaptic imaging has prompted wide initial application of these tools. Here we have focused on SV2A PET in studies of neurodegenerative disorders, both preclinically (Table 1) and clinically (Table 2). In general, these PET studies indicate SV2A loss to be specific to disease-associated brain regions and consistent with synaptic density loss. Although the loss of synaptic density may not be specific to neurodegeneration, the regional pattern of synaptic loss could potentially provide insights for differentiating various types of dementia.

In addition, clinical studies have been performed in epilepsy (*90*), schizophrenia (*91,92*), depression (*44*), posttraumatic stress disorder (*44*), stroke (*93*), cocaine-use disorder (*45*), and cannabis-use disorder (*94*), as well as in normal aging (*95*). The utility of SV2A as a general marker of synaptic density is promising and warrants formal validation by comparison of in vivo SV2A PET signal to postmortem evaluation of SV2A and synapse levels in the human brain. Further studies also warrant use of ^{18}F-labeled radioligands in larger patient cohorts to establish the potential clinical applications of SV2A PET imaging, including the early detection of synaptic density loss, differential diagnosis among different types of dementia, and the monitoring of disease progression. SV2A PET could also be used as an outcome measure for trials of disease-modifying therapies, particularly those that target the preservation and restoration of synapses. Overall, SV2A PET is an exciting new tool in the nuclear medicine arsenal and holds great promise as a novel in vivo biomarker for dementia and neurodegeneration.

DISCLOSURE

The radioligand ^{18}F-SynVesT-1 is contained in the international patent application PCT/US2018/018388, "Radiolabeled Pharmaceuticals and Methods of Making and Using Same," filed on February 15, 2018, and Richard Carson is listed as an inventor. Sjoerd Finnema is a full-time employee of Abbvie. No other potential conflict of interest relevant to this article was reported.

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