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Synaptic vesicle protein 2A as a potential biomarker in synaptopathies

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ABSTRACT

Measuring synaptic density *in vivo* using positron emission tomography (PET) imaging-based biomarkers targeting the synaptic vesicle protein 2A (SV2A) has received much attention recently due to its potential research and clinical applications in synaptopathies, including neurodegenerative and psychiatric diseases. Fluid-based biomarkers in proteinopathies have previously been suggested to provide information on pathology and disease status that is complementary to PET-based measures, and the same can be hypothesized with respect to SV2A. This review provides an overview of the current state of SV2A PET imaging as a biomarker of synaptic density, the potential role of fluid-based biomarkers for SV2A, and related future perspectives.

1. Introduction

In the central nervous system, neurons communicate *via* neurotransmitters that are released into the synaptic cleft, where they bind to, and influence, receptors on pre- and post-synaptic neurons (Alberts et al., 1997). Critical to this process are synaptic vesicles (SV), neurotransmitter-containing storage units located in synaptic boutons. The SV protein 2A (SV2A) is an integral 12-transmembrane domain glycoprotein expressed in synaptic vesicles throughout the brain (Bartholome et al., 2017; Mendoza-Torreblanca et al., 2013; Shi et al., 2011). Though the exact physiological role of SV2A remains unclear, SV2A dysfunction or decreased expression has been implicated in neurodegenerative disorders such as Alzheimer's disease (AD) (Robinson et al., 2014) and various neurological conditions, including epilepsy (Crowder et al., 1999; Lynch et al., 2004).

Positron emission tomography (PET) is a molecular imaging technique that can be used to quantify the density of a molecular target, under both physiological and pathological conditions. A PET-derived measure of brain SV2A has the potential to serve as an *in vivo* biomarker of synaptic density; this would prove of value in the investigation of synaptopathies, disorders associated with alterations in the function or density of synapses (Robinson et al., 2014; Stampanoni Bassi et al., 2017; Wang et al., 2017). The rationale for developing a PET tracer targeting SV2A is two-fold: SV2A is a known target for efficient antiepilepsy drugs such as levetiracetam, and a PET tracer binding to SV2A could be used to study the drug receptor occupancy in clinical development of new drug candidates. However, due to its widespread expression in synapses throughout the brain, imaging of SV2A could also potentially be used to assess synaptic integrity in synaptopathies such as Alzheimer's disease (AD). While PET can provide spatial information,

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fluid-based (*i.e.*, cerebrospinal fluid [CSF], plasma or serum) measures could provide complementary information and carry a number of practical advantages. In this review, we discuss the current status of SV2A PET imaging, the potential role of fluid-based SV2A biomarkers, and related future perspectives, including recent calls for the development of multiparty platforms addressing synaptopathy drug discovery.

2. Basic facts about SV2A and its role in synaptic function

SV2A is expressed throughout all brain areas, apart from trigeminal and facial nerve nuclei, and is especially abundant in subcortical areas such as the thalamus and basal ganglia (Bajjalieh et al., 1994). The expression of SV2B and SV2C is more restricted; SV2B is primarily expressed in the cortical regions and in the hippocampus, overlapping in these regions with SV2A, but is absent in most subcortical regions, whereas SV2C on the other hand is only present in the striatum, pallidum, midbrain, brainstem, substantia nigra and olfactory bulb (Bajjalieh et al., 1994; Janz and Südhof, 1999). The total number of SV2 proteins (including SV2B and C isoforms) is highly consistent across vesicles in rat brain homogenates, with 2–5 copies per vesicle (Mutch et al., 2011; Takamori et al., 2006). Two alternative hypotheses regarding the role of SV2A in exocytosis mediated by Ca^{2+} have been suggested, stating that SV2A is either regulating the presynaptic Ca^{2+} levels during repetitive activity or functioning as a target for residual Ca^{2+} (Mendoza-Torreblanca et al., 2013). Malfunctioning SV2A, investigated in knockout mice, results in presynaptic Ca^{2+} accumulation, triggering abnormal neurotransmitter release, destabilizing synaptic circuits and inducing epilepsy (Janz et al., 1999). In neuronal cell cultures, knockdown of SV2A resulted in a 29 % decrease in dendritic spine density (Cohen et al., 2011). When the expression of SV2A was studied during brain development in mice, a marked increase was shown in seven days old mice. This was accompanied by myelinogenesis and synaptic plasticity, indicating that high levels of SV2A are required during postnatal brain development. By contrast, seven day old SV2A knockout mice showed generalized seizures (Crèvecœur et al., 2013a). It has also been suggested that SV2A is responsible for the endocytosis to the SV of the SV protein synaptotagmin-1 (SYT1), and, as such, is involved in maintaining the readily releasable pool of SVs (Yao et al., 2010). Decreased expression of SV2A has thus been shown to result in lowered levels of SYT1 in the SV, a finding confirmed in SV2A/B knock-out mice, where SYT1 and the ratio of SYT1 to synaptophysin (SYN) are markedly decreased, but no effects were seen on levels of VAMP2/synaptobrevin or vesicular glutamate transporter 1 (Yao et al., 2010).

3. Clinical implications of a SV2A biomarker

3.1. Epilepsy

Expression of the SV2A protein has been found to be reduced with 40 % in brain tissue resected from the seizure onset zone in patients with temporal lobe epilepsy unresponsive to pharmacological treatment (Crèvecœur et al., 2013b; Feng et al., 2009). Levetiracetam, an antiepileptic drug that binds SV2A which was approved for use in the USA in 1999 by the Food and Drug Administration (Gillard et al., 2006; Lynch et al., 2004; Shi et al., 2011), has shown itself useful in the management of seizures. However, the drug-target interaction, as well as the mechanism of action, is still unclear. Further, SV2A protein expression has been shown to predict the efficacy of levetiracetam therapy among glioma patients (de Groot et al., 2011), a population in which seizures are experienced by between 50 and 80 % of the patients. Biomarkers for SV2A may therefore be useful, both in predicting the outcome of pharmacological treatments and in localizing the seizure onset zone for surgical planning.

3.2. Alzheimer's disease

AD is the most common cause of dementia (Adlard et al., 2014), characterized neuropathologically by the abnormal accumulation of amyloid-β plaques and formation of neurofibrillary tangles composed of hyperphosphorylated tau, as well as synaptic- and neurodegeneration. The amyloid-β oligomers that downstream form the amyloid-β plaques have been identified as the species exerting the toxic effects causing synaptic loss (Klein, 2013). Amyloid-β oligomers accumulate at excitatory synapses mainly at postsynaptic terminals, but presynaptic sites of the synapse are also affected (Pickett et al., 2016). Similarly, it is not the neurofibrillary tangles composed of tau that are believed to cause neurodegeneration, but soluble tau oligomers that have synaptotoxic effects, with suggested mechanisms including overactivation of glutamatergic neurotransmission, calcium dysregulation and reductions of the memory-associated protein KIBRA (Forner et al., 2017). Overexpression of amyloid-β and tau accelerates synaptic and cognitive impairment (Lasagna-Reeves et al., 2011; Zempel and Mandelkow, 2012).

While not specific for AD, neurodegeneration is important for the staging of the disease and for the prediction of clinical progression (Jack et al., 2018). PET imaging of glucose metabolism using fluorine-18 labelled fluorodeoxyglucose ([^{18}F]FDG) has long been used to differentiate AD from other neurological conditions, based on its characteristic pattern of decreased metabolic activity. [^{18}F]FDG, however, is metabolized in both neurons and glial cells (astrocytes, microglia and oligodendroglia) and not a direct marker of synaptic loss and it is sensitive to blood glucose levels, medication and physical and sensory activity at the time of the PET scan. In addition, recent evidence indicates that [^{18}F]FDG PET signal, which has been used as an index of neuronal activity, is also sensitive to astroglial metabolism (Zimmer et al., 2017). Other imaging approaches used in the diagnosis of AD include ^{99m}Tc-HMPAO SPECT or [^{15}O]H_2O PET, for evaluation of deficits in cerebral blood flow, showing similar patterns of loss as [^{18}F]FDG. ^{99m}Tc-HMPAO SPECT, however, suffers from limited spatial resolution, and the short half-life of [^{15}O]H_2O PET limits its use to centers with access to cyclotron production (Herholz et al., 2002; Ishibashi et al., 2015). *Post mortem* examination of hippocampal expression of SV2A has shown significant loss in the outer molecular layer in patients with AD, as compared to controls (Robinson et al., 2014). Higher loss of SV2 has further been associated with impaired global cognition evaluated using the Mini-Mental State Examination (MMSE) (Robinson et al., 2014). Achieving a better understanding of how alterations in synaptic density in AD relate to amyloid-β and tau pathology carries great potential for a more accurate prediction of disease progression and the discovery of new treatment strategies.

3.3. Parkinson's disease

Parkinson's disease (PD) is the second most common progressive neurodegenerative disease. According to the Global Burden of Disease Study, an estimated 6.2 million people presently live with the disease, a number that, similar to AD, is predicted to increase (GBD 2015 Neurological Disorders Collaborator Group, 2017). The pathogenesis of PD is believed to involve the accumulation of toxic oligomeric forms of the presynaptic neuronal protein α-synuclein. These are thought to affect synaptic function, ultimately resulting in impaired synaptic plasticity, altered dopaminergic neurotransmission, and the loss of dopaminergic neurons in the striatum (Bellucci et al., 2015). These processes precede the appearance of the motor, cognitive and olfactory symptoms in PD by several decades, with the number of dopaminergic neurons depleted by 50–70 % by the time the clinical features appear (Seifert and Wiener, 2013). Focusing on the regeneration of synapses instead of the restoration of extracellular dopamine may represent a conceptual shift in the development of new treatments for PD (Tsui and Isacson, 2011). As such, biomarkers for synaptic density may be of

value both in the early diagnosis of PD and in the tracking of its progression, but also as a means to accelerate the development of novel disease-modifying interventions.

3.4. Other neuropsychiatric disorders

The SV2A-targeting antiepilepsy drug levetiracetam has also been proposed to be useful as a neuroprotective drug in the treatment of other neurological disorders, such as management of seizures following stroke and traumatic brain injury (Shetty, 2013), reducing chorea in Huntington's disease – demonstrating a decrease in the chorea subscore on the Unified Huntington Disease Rating Scale (Zesiewicz et al., 2006), reducing anxiety and mania in various psychiatric disorders (Farooq et al., 2009) a potential use in management of tics in Tourette's syndrome in a subpopulation of the patients (Martínez-Granero et al., 2010) and significantly reduced abnormal movements in tardive dyskinesia (Woods et al., 2008). Though clinically diverse, these conditions all involve synaptic alterations; the monitoring of synaptic density may thus both provide insight into the pathogenesis of these disorders as well as prove useful in the prediction of treatment efficacy and therapeutic response monitoring.

4. Current state of imaging biomarkers

The development and application of SV2A PET tracers has the potential to significantly improve the understanding of the function and role of the protein such as providing critical information on the SV2A target engagement of antiepileptic drugs in clinical development, and enable the characterization of the distribution and expression of SV2A in epileptic patients. Further applications include clinical diagnosis of *e.g.* AD, monitoring of drugs targeting synaptic function and increased understanding of the role of synaptic degeneration in brain disorders. A PET ligand targeting SV2A would provide an estimate of the protein density, which would be assumed to reflect the overall synaptic density in a brain region. It is however not clear, yet, to which degree this measurement is affected by SV2A dysfunction, changes in expression within the vesicles or the number of vesicles within the synapse and the overlap and differences of such processes in different neurological disorders. There are also findings indicating that while SV2A is expressed throughout almost the entire brain, the levels vary between regions (Bajjalieh et al., 1994).

Given the proven clinical efficacy and affinity to SV2A of levetiracetam (Lynch et al., 2004), it is noteworthy that [^{11}C]levetiracetam and a structurally diverting analogue labelled with technetium-99m have been synthesized for potential use in PET and single photon emission tomography (SPECT), respectively (Cai et al., 2014; Rashed et al., 2018). *In vivo* evaluation has not yet been reported for these candidate tracers, but the affinity to SV2A (K_i = 1.6 μM for structurally unmodified levetiracetam) is likely too low for optimal *in vivo* imaging (Gillard et al., 2006). Generally speaking, the usefulness of a compound as a PET ligand depends on its selectivity to the biological target (ranging from 30-fold to > 100-fold), its affinity to the target (K_d) (usually in the low nM range) but also the relationship between affinity and density of the target ($B_{max}/K_d \geq 10$) (Andrés and Schmidt, 2017; Honer et al., 2014; Mathis et al., 2017). Low K_d reflects a high association rate and relatively slow dissociation rates of the ligand-target binding, which is needed for use with radionuclides with short half-lives. The high affinity, however, is also important in order to distinguish the specific from non-specific binding, one of the greatest impediments of PET imaging of the central nervous system. Moderate lipophilicity (logD = 1–3), relatively low molecular weight (> 700 Da) and the ability of parent compound – but not radiolabelled metabolites – to cross the blood-brain barrier are other important properties of a successful PET ligand (Mathis et al., 2017).

Concurrently, UCB Pharma (Braine-l'Alleud, Belgium) initiated a research program with the purpose of better understanding the role and function of SV2A, and to identify high affinity ligands with suitable properties for development as SV2A PET ligands (Mercier et al., 2014). Mercier and colleagues presented a selection of their > 500 compounds tested for SV2A potency (Mercier et al., 2014): three compounds, UCB-A, UCB-H and UCB-J, were outlined as lead compounds based on their pharmacological and labelling properties and not the least if amenable for labelling.

4.1. Preclinical validation

The three lead compounds identified by UCB Pharma were further developed in cooperation with three sites: the [^{11}C]UCB-A compound was studied in Uppsala, Sweden, [^{18}F]UCB-H in Liège, Belgium, and UCB-J, labelled both with carbon-11 and fluorine-18, at Yale University, New Haven, USA.

In Uppsala, [^{11}C]UCB-A was produced in 3–5 GBq quantities ready for injection *via* a two-step synthesis route including ^{11}C-methylation and deprotection (Estrada et al., 2016). Frozen section autoradiography, biodistribution and dosimetry, and a study of *in vivo* tracer binding with competing compounds for displacement studies were all performed in Sprague-Dawley rats to study the characteristics of [^{11}C]UCB-A (Estrada et al., 2016). The *in vitro* studies showed that binding of [^{11}C]UCB-A was blocked in a dose dependent manner by administration of the reference SV2A ligands levetiracetam and seletracetam, with IC_{50} values of 0.78 and 0.14 μM, respectively. Further dynamic PET scanning was performed in six pigs, including blocking studies and metabolite analysis. The PET binding studies also confirmed the ability to block or displace [^{11}C]UCB-A uptake with reference compounds in both species, and the baseline studies demonstrated a rather slow accumulation and washout, where t_{max} had not been reached at 90 min when the PET scan ended. The metabolite analysis in pigs demonstrated a slow metabolism with 77 ± 3 % of tracer still intact at 75 min post injection. Tracer kinetics were best described by a one-tissue compartment (1-TC) model at baseline and a two-tissue compartment model (2-TC) after blocking (Estrada et al., 2016). The biodistribution and dosimetry studies indicated that [^{11}C]UCB-A distributed rapidly from blood to organs, with the highest uptake in adrenals and brain, and showed that the effective doses were 2.9 μSv/MBq in male rats and 4.9 μSv/MBq in female rats, allowing for up to 5 administrations of 400 MBq in humans (Estrada et al., 2016).

[^{18}F]UCB-H has been synthesized within 150 min and obtained in 30 % radiochemical yield by a four-step synthesis route involving nucleophilic ^{18}F-fluorination of the pyridine precursor, reductive amination and ring closure (Warnock et al., 2014). In the preclinical work on [^{18}F]UCB-H, the affinity to human and rat SV2A was studied in both recombinant and native tissues using binding competition, demonstrating an IC_{50} of 40 nM for recombinant human SV2A and similar in native tissue (Warnock et al., 2014). *In vivo* properties were studied in Sprague-Dawley rats, including a test-retest study. [^{18}F]UCB-H exhibited a rapid uptake phase, reaching peak uptake (t_{max}) around 5 min post injection, followed by a fast wash-out phase and faster metabolism than for [^{11}C]UCB-A in pigs, with < 20% intact tracer remaining after 60 min as measured with HPLC (Warnock et al., 2014). Brain content of the parent compound and metabolites were also studied in rats, showing that > 90% of the brain radioactivity was related to the parent compound at 20 min post injection (Becker et al., 2017). Brain uptake of [^{18}F]UCB-H can reliably be quantified using Logan graphic analysis as well as by using population-based input functions, and a test-retest reproducibility of around 10 % was found for the whole-brain V_T (Becker et al., 2017; Warnock et al., 2014). It has further been shown that the chirality of [^{18}F]UCB-H has a significant impact on SV2A affinity, and that the *(R)*-enantiomer has a 10-fold higher affinity than the *(S)*-enantiomer, but that it has no impact on the uptake pattern (Becker et al., 2017). Preliminary data of [^{18}F]UCB-H in rhesus and cynomolgus nonhuman primates confirmed a higher signal of the *(R)*-enantiomer compared to the racemate (Carroll et al., 2018). Preclinical dosimetry

studies of [^{18}F]UCB-H were performed in male mice, indicating an effective dose of 18.8 μSv/MBq, rendering it suitable for a single administration of 325 MBq (Bretin et al., 2013).

[^{11}C]UCB-J was synthesized in 11 % radiochemical yield by palladium-mediated cross-coupling of a pyridine-trifluoroborate precursor with [^{11}C]methyl iodide (Nabulsi et al., 2016). The t_{max} of [^{11}C]UCB-J in rats occurred 5 min post injection, with rapid equilibration with plasma and only very low levels of two of the three metabolites found in brain tissue (Nabulsi et al., 2016). *In vitro* binding studies of [^{11}C]UCB-J showed an SV2A affinity of 7 nM, 10-fold higher than the affinity to SV2C, and 100-fold higher than SV2B affinity (Nabulsi et al., 2016). Nonhuman primate studies have been performed for [^{11}C]UCB-J in both rhesus monkeys and in a baboon (Finnema et al., 2016; Nabulsi et al., 2016). The rhesus monkey studies demonstrated the ability to block [^{11}C]UCB-J binding using levetiracetam. T_{max} was reached 5–8 min post injection in the cortical regions, with around 25 % of the parent compound intact after 90 min. White matter uptake, represented by the centrum semiovale, was significantly lower than the cortical uptake. Tracer kinetics both in rhesus monkeys and the baboon were best described using a 1-TC model, similarly to [^{11}C]UCB-A (Finnema et al., 2016; Nabulsi et al., 2016). Correlations between regional *in vivo* SV2A signal, defined as [^{11}C]UCB-J V_T, and *in vitro* measurement investigated in the baboon euthanatized after the scan, showed high correlations across grey and white matter regions ($R^2 = 0.72$) though a more moderate association was found when only including grey matter regions ($R^2 = 0.31$) (Finnema et al., 2016). In the same tissues, *in vitro* tissue analysis using optical density by Western blot showed a high correlation between SV2A and synaptophysin (SYN), the "gold standard" marker of synaptic density. Both SV2A and SYN signals were absent or weak in the centrum semiovale (Finnema et al., 2016). Dosimetry studies were also performed in rhesus monkeys, demonstrating an effective dose of 4.5 μSv/MBq for [^{11}C]UCB-J, comparable to that of [^{11}C]UCB-A (Nabulsi et al., 2016).

The successful synthesis of single enantiomer [^{18}F]UCB-J has briefly been described and involved preparation from an organoiodonium salt or ylide precursor under conditions for nucleophilic substitution with [^{18}F]fluoride (Li et al., 2017). As expected, [^{18}F]UCB-J displayed similar imaging properties as [^{11}C]UCB-J. Preclinical work to develop a fluorine-18 labelled SV2A ligand has also been performed by Invicro. The synthesis of [^{18}F]MNI-944 (racemate of [^{18}F]UCB-J) was not reproducible and the investigations continued with difluoro-substituted derivates of UCB-J that were less challenging to label. [^{18}F]MNI-1038 (racemate), [^{18}F]MNI-1126 (*(R)*-enantiomer) and [^{18}F]MNI-1128 (*(S)*-enantiomer) were compared to [^{18}F]MNI-944, [^{18}F]UCB-H ([^{18}F]MNI-942) and [^{18}F]MNI-1080 (racemate of [^{18}F]UCB-H), in rhesus and cynomolgus monkeys (Constantinescu et al., 2018). [^{18}F]MNI-1126 was identified as the best candidate based on its favorable kinetic properties: tracer kinetics was best described by 1-TC, t_{max} was reached at around 7 min post injection in pons and cerebellar lobes and 50 min in anterior cingulate and cortical structures, V_T in grey matter was around 25–30 mL/cm^3 and sensitive to blocking with levetiracetam, whereas the V_T in centrum semiovale was approximately 80 % lower and less impacted by pre-blocking (Constantinescu et al., 2018). After 60 min, 27 % of the injected tracer was still intact.

Independently from the work performed by Invicro, Yale has also pursued studies of fluorine-18-labelled derivatives of UCB-J, [^{18}F]SDM-2 (Cai et al., 2017) and [^{18}F]SDM-8 (Li et al., 2018), the latter identical to [^{18}F]MNI-1126. In preclinical evaluation in non-human primates, these compounds exhibited high brain uptake, fast kinetics, and high specific binding in brain.

Fig. 1 shows the chemical structures of selected SV2A PET ligands.

4.2. Clinical validation

Preliminary data on the clinical validation of [^{11}C]UCB-A in six epilepsy patients and two healthy controls has confirmed the slow kinetics of the tracer in a PET-MR study performed with arterial blood sampling (Lubberink et al., 2017). While a reversible 2-TC model best described the data, the model failed to provide robust estimates of V_T and BP_{ND}. The peak activity in brain was reached 70–80 min post injection, and centrum semiovale was demonstrated to be a useful reference region for quantification of uptake together with Logan graphic analysis. The metabolite analysis indicated a rather slow metabolism of UCB-A, although faster than previously shown in pigs, with 50 % of the parent compound intact after 90 min (Lubberink et al., 2017). The average grey matter V_T was 24 mL/cm^3 compared to 3.2 mL/cm^3 in centrum semiovale, indicating a high dynamic range. Initial results show a considerable reduction in cortical V_T after blocking with levetiracetam (unpublished data).

The effective dose of [^{18}F]UCB-H in humans was 15.4 μSv/MBq, similar to the preclinical estimate of 18.8 μSv/MBq, and in the normal range for fluorine-18-labelled PET tracers, with the urinary bladder wall, the gallbladder wall and the liver receiving the highest dose (Bretin et al., 2015, 2013). T_{max} within the brain was reached at 5–10 min post injection, followed by a fast wash-out phase in a cohort of two younger and two older healthy controls (Bahri et al., 2017). After 90 min, an average of 17 % of the intact tracer remained. The 2-TC model described the experimental data best, but similar to [^{11}C]UCB-A, Logan was found to provide more robust estimates of V_T values, ranging from 4.3 mL/cm^3 in the centrum semiovale to around 8 mL/cm^3 in putamen (Bahri et al., 2017). BP_{ND} estimates were derived from distribution volume ratio using the centrum semiovale; the BP_{ND} was overall found to be higher in older controls, however, likely due to a slightly higher V_T in the white matter of younger subjects.

The most extensive clinical validation of the SV2A tracers has been performed using [^{11}C]UCB-J (Finnema et al., 2017, 2016). Investigated in 10 young healthy controls and three patients with epilepsy, [^{11}C]UCB-J exhibited favorable kinetic properties, with a t_{max} around 10–25 min post injection, followed by a rapid wash-out phase. Kinetics were well described by a 1- or 2-TC model, and reliable measurements of the BP_{ND} could be produced using the simplified reference tissue model (Finnema et al., 2017, 2016). V_T ranged from 5.2 mL/cm^3 in the centrum semiovale to 22.5 mL/cm^3 in the putamen, indicating a wider dynamic range than for [^{18}F]UCB-H. Levetiracetam was shown to displace [^{11}C]UCB-J binding substantially in cortical regions, but with less effect on the uptake in centrum semiovale, confirming both the specificity of cortical [^{11}C]UCB-J uptake, and the mainly non-specific nature of the uptake in white matter. The test-retest reproducibility of [^{11}C]UCB-J was investigated in five healthy controls, showing a mean variability of 3–9 % across regions (Finnema et al., 2017). The remaining fraction of intact tracer was around 30 % 90 min post injection.

Fig. 2 shows representative parametric V_T images of [^{11}C]UCB-A, [^{18}F]UCB-H and [^{11}C]UCB-J in healthy controls.

4.3. Clinical research

Given the novelty of SV2A PET imaging, available data from clinical research are still limited. However, preliminary data from several studies have recently been reported at scientific conferences.

In order to investigate the potential of SV2A PET imaging as a biomarker for neurodegeneration in AD, dynamic [^{11}C]UCB-J scans were performed in 10 amyloid-β positive patients with amnestic mild cognitive impairment (MCI) or mild AD and 11 age-matched amyloid-β negative healthy controls, with successful arterial plasma sampling performed on nine patients and eight healthy controls (Chen et al., 2018). Parametric images showing V_T and the influx rate constant K_1, proportional to blood flow, were created using the 1-TC model. In addition, the simplified reference tissue model was used to estimate regional BP_{ND} using the centrum semiovale as reference region, alleviating the need for arterial plasma sampling. Significantly lower [^{11}C]UCB-J uptake (V_T) and binding (BP_{ND}) was found in the hippocampus of patients. No difference was however seen in the V_T of the centrum

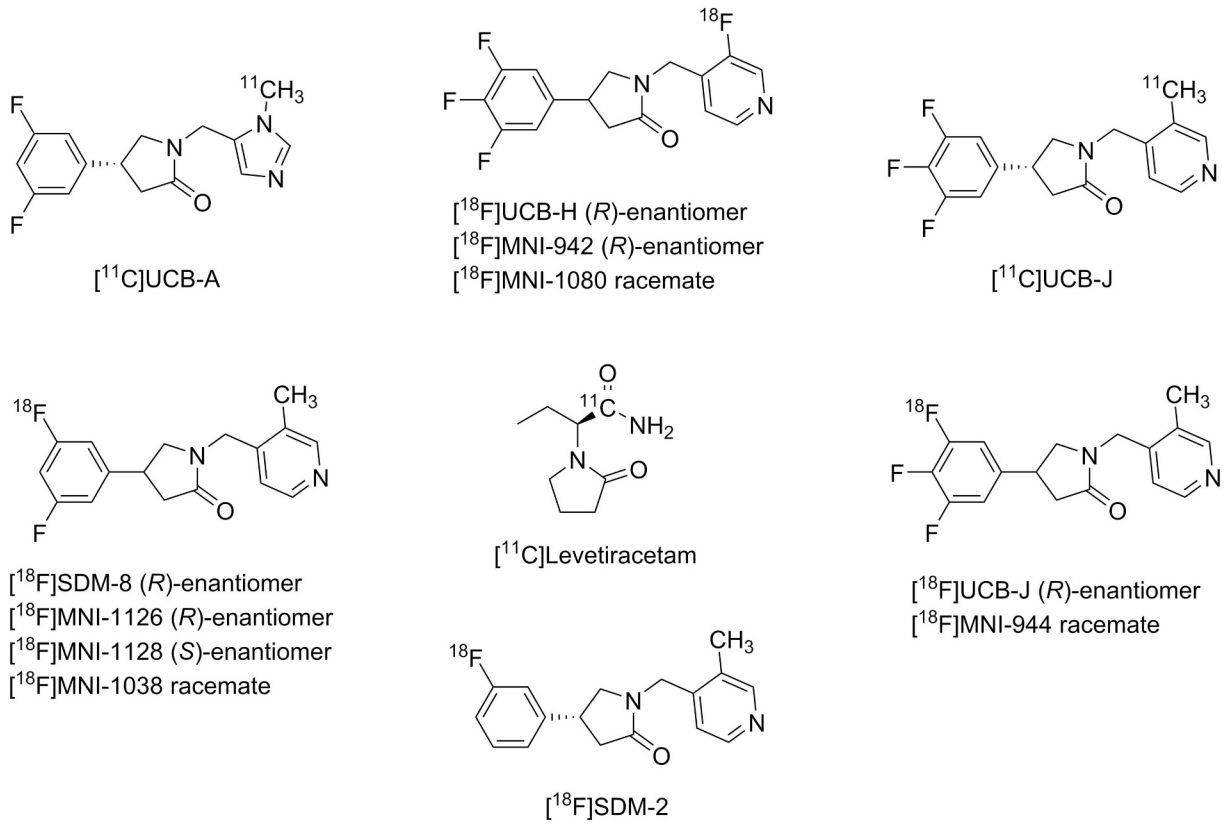

Fig. 1. Selection of labelled compounds developed for SV2A receptor imaging with PET.

semiovale, supporting the use of this region as a reference region for [^{11}C]UCB-J PET imaging (Chen et al., 2018). Preliminary data have shown an age dependent reduction in V_T in both subcortical structures and centrum semiovale, however, these findings may be due to differences in free fraction or partial volume effects (Carson et al., 2018).

Compared to the typical pattern of hypometabolism seen in AD using [^{18}F]FDG, the spatial extent of decreases in [^{11}C]UCB-J uptake were significantly more confined. The reduction in hippocampal binding is in line with the early loss of entorhinal cortical cell projections to the hippocampus, and reductions of hippocampal SV2A seen in *post mortem* studies in AD brain tissue (Braak et al., 2011; Robinson et al., 2014). Similar findings have also been reported for [^{18}F]UCB-H in AD, where a significant decrease in synaptic density was reported in medial temporal structures, centered on the entorhinal cortex and extending to the amygdala and basal forebrain (Salmon et al., 2017). The pattern of [^{11}C]UCB-J K_1 images, assumed to represent cerebral blood flow, were more similar to typical [^{18}F]FDG patterns seen in AD. Indeed, images showing parameters related to blood flow have previously been suggested as an alternative to [^{18}F]FDG metabolic imaging (Chen et al., 2015; Hsiao et al., 2012; Rodriguez-Vieitez et al., 2016). This suggests that SV2A PET imaging could provide information on two distinct processes, *i.e.*, synaptic density and cerebral blood flow, depending on arterial blood sampling or the use of a valid reference region (Chen et al., 2018).

[^{11}C]UCB-J binding has also been shown to be decreased in the seizure onset zone of temporal lobe epilepsy patients, with asymmetry indices ranging from around 40–65 % in the hippocampus (Finnema et al., 2016). Further, preliminary data from studies using [^{11}C]UCB-J have shown decreased SV2A binding in patients with major depressive disorder (Holmes et al., 2018) and reductions of SV2A binding in the

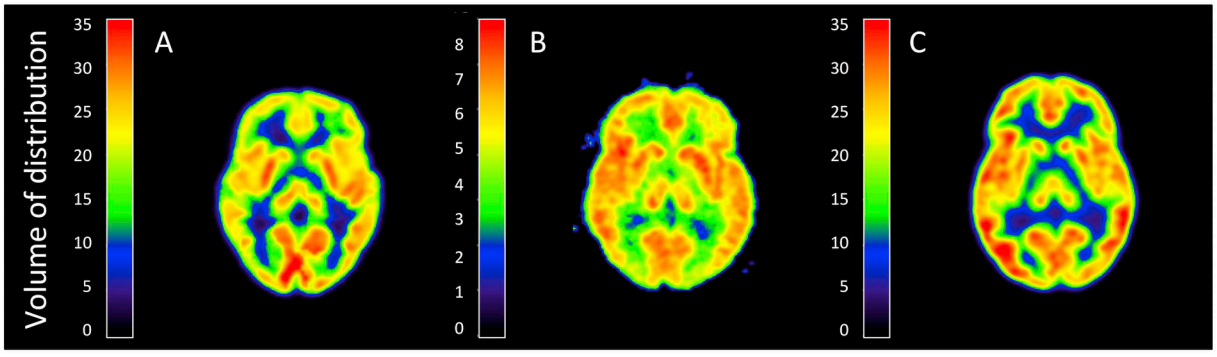

Fig. 2. Typical volume of distribution (V_T) images of (A) [^{11}C]UCB-A, (B) [^{18}F]UCB-H, and (C) [^{11}C]UCB-J in healthy controls. The [^{11}C]UCB-J image, acquired on a high-resolution research scanner, was post-smoothed with a 4 mm Gaussian filter to obtain similar spatial resolution as the other two images. Note the difference limits on the color scales. [^{18}F]UCB-H, and [^{11}C]UCB-J images are courtesy of Drs. Christine Bastin and Eric Salmon, University of Liége, and Drs. Mika Naganawa and Richard Carson, Yale University PET Center.

substantia nigra and other parts of the brain in a small cohort of PD patients (Matuskey et al., 2018).

The usefulness of [^{11}C]UCB-J in drug development was recently demonstrated in a drug receptor occupancy study of the investigational new epilepsy drug padsevonil in healthy controls (Koole et al., 2018). This study also validated the centrum semiovale as reference region and standardized uptake ratios (SUVR) as a semi-quantitative approach, concluding that a SUVR estimated over 60–90 min post injection provides an accurate estimate of the tracer binding (Koole et al., 2018).

It remains unclear what increased or decreased SV2A-ligand binding represents in the living brain and if the signal reflects similar processes in neurodegenerative and psychiatric diseases and if the method is sensitive enough to detect early changes, or if it will only be valuable in later stages of the disease progression. Future research should examine if reduced SV2A-binding represents synapse loss, reduced protein expression in inactive neurons or neurons about to degenerate or if it is actively degraded by proteases.

5. Current state of fluid biomarkers for neuronal loss

Bodily fluids such as cerebrospinal fluid (CSF) and plasma are considered to be important sources for biomarkers reflecting neurodegeneration. Although PET carries the advantage of providing topographical information, there is little doubt that an accessible fluid biomarker would be preferable in a diagnostic setting, for participant screening or repeated sampling in clinical trials. CSF is the superior source for fluid biomarker development given its direct contact with the extracellular space of the brain where biochemical changes of relevance to neuronal health should be reflected. Advances in the last decade have proven that “core” CSF biomarkers can accurately reflect key elements of disease and contribute substantially to a diagnostic conclusion, even at the preclinical phase (*e.g.*, Aβ_{1-42}, P-tau and T-tau for AD) (Blennow and Zetterberg, 2018).

Despite the CSF biomarkers now being apart of the research diagnostic criteria for AD (Dubois et al., 2014), the degree of synaptic degeneration might be a better predictor of cognitive decline than amyloid or tau pathology (Blennow et al., 1996). Moreover, given the dynamic plasticity of the synapse, a fluid biomarker of its function would be a more useful tool in monitoring of disease modifying therapies, functioning as a “state” biomarker for the intensity of synaptic degeneration or damage, in contrast to “stage” biomarkers that measure the stage of the accumulated synaptic loss, see also (Blennow and Hampel, 2003).

Early non-targeted proteomics highlighted candidate proteins involved in mechanisms at the pre- and post-synaptic terminals. However, at that time, there was no robust biomarker for synaptic dysfunction. CSF concentrations of the pre-synaptic proteins synaptosomal-associated protein 12 (SNAP-25) and SYT1 have been shown to be significantly increased in established and pre-clinical AD (Brinkmalm et al., 2014; Öhrfelt et al., 2016; Zhang et al., 2018). This is thought to reflect the substantial synaptic degeneration and loss in AD (Masliah et al., 2001). Indeed, the levels of both SNAP-25 and SYT1 are reduced in cortical areas of *post mortem* tissue of pathologically confirmed AD cases (Brinkmalm et al., 2014).

The dendritic protein neurogranin (Ng) is the most evaluated synapse-related protein measured in neurodegeneration. After developing novel monoclonal antibodies to measure neurogranin by enzyme-Linked immunosorbent assays (ELISA), increased levels of Ng have been reported in several studies (Hellwig et al., 2015; Kvartsberg et al., 2015; Portelius et al., 2015) but surprisingly, this observation seems to be specific for AD and not for other neurodegenerative diseases (Wellington et al., 2016), a finding replicated in a large cohort of patients with different neurodegenerative diseases (Portelius et al., 2018). The increases of CSF alpha-synuclein in AD and Creutzfeldt-Jakob disease (Hall et al., 2012; Oeckl et al., 2016), and correlation with CSF tau suggests the potential role of CSF α-synuclein as a biomarker for synapse dysfunction (Magdalinou et al., 2015). In contrast, CSF α-synuclein seems to be decreased in synucleinopathies such as Parkinson's disease and dementia with Lewy bodies (Parnetti et al., 2011; Tokuda et al., 2006).

Being the main focus of this review, SV2A peptides, predominantly from the lumen domain, have been detected in CSF using in-depth explorative proteomics (Schutzer et al., 2010). Despite this, there is currently no validated immunoassay for the detection of SV2A in bodily fluids. A blood biomarker reflecting central nervous system SV2A is unlikely given the substantial expression from pancreas (The Human Protein Atlas, 2018). As previously stated, *post mortem* tissue studies have also demonstrated decreased expression of SV2A in AD compared to controls (Robinson et al., 2014). One might hypothesize that concentrations of CSF SV2A may act in the same manner as the majority of synaptic proteins and increase in diseases with extensive neuronal loss. However, synaptic proteins with similar postulated functions as SV2A have been shown to decrease in AD compared to healthy controls (Duits et al., 2018; Simonsen et al., 2008). Contactin-2, a soluble cell-adhesion protein located on synaptic membranes, are also decreased in AD *post mortem* brain and CSF (Chatterjee et al., 2018). Indeed, our preliminary investigations into SV2A seem to also suggest that this is in fact the case. Unexpectedly, these protein groups (involved in vesicular transport and synaptic stability) are markedly elevated at the MCI stage of the disease potentially reflecting early events in the pathophysiological cascade (Duits et al., 2018). These results are promising and suggest that this class of molecules should be explored further as potential biomarkers for synaptic degeneration in AD and other neurodegenerative diseases. Similar to SV2A imaging, we currently do not know exactly what a change in the concentration of a synapse-derived molecule in a biofluid means (altered release or secretion of the molecule into the fluid because of synapse loss, increased or decreased synaptic activity, or altered clearance).

6. Discussion and future prospects

The recently announced Innovative Medicines Initiative call focusing on synaptopathy drug discovery emphasizes the current view in the field of the importance of developing reliable biomarkers for synaptic deficits. Highlighting the need to “demonstrate the value of these new tools and methods for supporting drug discovery and development efforts across a spectrum of therapeutic CNS indications, including neurodegenerative, neurodevelopmental and psychiatric disorders,” the anticipated impact of this initiative is to identify and validate pharmacologically tractable targets following an improved understanding of how synaptic dysfunction contributes to these varied disorders (European Commission, 2018). Early discussions surrounding the utility of SV2A PET revolved around its potential use as a reliable marker of neurodegeneration in AD, less sensitive to confounding factors as compared with [^{18}F]FDG, a widely used measure assumed to largely reflect synaptic loss. Preliminary findings using [^{11}C]UCB-J in a small cohort of AD patients, however, showed a pattern of decreased activity much less pronounced as compared to [^{18}F]FDG (Chen et al., 2018). At this point, it is still too early to draw any conclusions as to whether the two in fact images very different pathologic processes. It is clear, however, that there are many potential insights into the pathogenesis of AD to be made with a suitable PET biomarker for SV2A at hand.

In order to achieve a wider use of PET based biomarkers for SV2A, two main points need to be addressed: development of a fluorine-18-labelled ligand with optimal kinetic properties, and the validation of a simplified method of quantification. The short half-life of carbon-11 is not a limitation at this stage, as the usefulness of the ligand is still under investigation at centers with the necessary infrastructure and expertise. Should SV2A ligands, however, live up to the initial hopes of being a more reliable biomarker for neurodegeneration than [^{18}F]FDG, carbon-11 limits use to imaging facilities with on-site production. For SV2A ligands to replace [^{18}F]FDG in clinical applications further down the

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road, fluorine-18 labelled ligands would be the most feasible option. For the currently most promising and most used ligand, [^{11}C]UCB-J, there are some concerns regarding the validation of an ideal brain reference region completely unaffected by displacement, and the underlying reason for the demonstrated reduced binding in the centrum semiovale with age must be clarified as it may complicate use in longitudinal studies (Carson et al., 2018). To date though, the centrum semiovale is still the most favorable alternative and it is likely suitable for use as a reference region in cross-sectional studies. In this early stage, PET imaging using [^{11}C]UCB-J should ideally be performed both using dynamic scanning and arterial blood sampling, which results in an experimental setup demanding for both patients and imaging sites. While specific CSF composition and detection of SV2A are still under investigation, other synaptic measures have shown value as state markers in disease progression, and may, analogous to the case of PET and CSF based biomarkers for amyloid-β and tau, provide complementary understanding of the etiology and potential treatments strategies of synaptopathies.

6.1. SV2A imaging: a sunrise of good fortune or a false dawn?

While the optimal PET tracer for targeting SV2A may still be under development, some questions remain in terms of the usefulness of SV2A as a proxy for synaptic density and for tracking synaptic loss. The density of SV2 isoforms has been shown to be consistent across the brain of rats, however, the expression of SV2A seems to vary across regions. Further, in addition to the aforementioned age-dependent decrease in SV2A density (as measured by [^{11}C]UCB-J), it is not known whether a decrease in SV2A binding strictly reflects neuronal loss, as it could also represent decreased density of SV2A in vesicles, dysfunctional SV2A or a decreased number of vesicles. Conversely, it is also not known whether a damaged neuron could in fact remain to contain the same density of SV2A proteins. Before these aspects have been elucidated, the relevance of SV2A as a biomarker of synaptopathies remains to be demonstrated.

Declaration of interest

HZ has served on scientific advisory boards for Roche Diagnostics, Eli Lilly, Samumed, CogRx and Wave, has received a travel grant from Teva and is a co-founder of Brain Biomarker Solutions in Gothenburg AB, a GU Ventures-based platform company at the University of Gothenburg. KB has served as a consultant or at advisory boards for Alzheon, BioArctic, Biogen, Eli Lilly, Fujirebio Europe, IBL International, Merck, Novartis, Pfizer, and Roche Diagnostics, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB, a GU Venture-based platform company at the University of Gothenburg. The other authors declared no potential conflict of interest with respect to the research, authorship and/or publication of this article.

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