Pathogenesis of Human Immunodeficiency Virus Type-1 (HIV-1)-Associated Dementia: Role of Voltage-Gated Potassium Channels

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Abstract: HIV-1-associated dementia (HAD) describes the cognitive impairments and behavioral disturbances which afflict many HIV-infected individuals. Although the incidence of HAD has decreased significantly in the era of HAART, it remains a significant complication of HIV-1 infection as patients with acquired immune deficient syndrome (AIDS) live longer, antiretroviral drugs remain unable to effectively cross the blood-brain barrier (BBB), and HIV-1 resistance grows due to viral strain mutation. Although the precise mechanism leading to HAD is incompletely understood, it is commonly accepted its progression involves a critical mass of infected and activated mononuclear phagocytes (MP; brain perivascular macrophages and microglia) releasing immune and viral products in brain. These cellular and viral products induce neuronal dysfunction and injury via various signaling pathways. Emerging evidence indicates that voltage-gated potassium (K_v) channels, key regulators of cell excitability and animal behavior (learning and memory), are involved in the pathogenesis of HAD/HAND. Here we survey the literature and find HAD related alterations in cellular and viral products can alter MP and neuronal K_v channel activity, leading to MP and neuronal dysfunction and cognitive deficits. Thus, MP and neuronal K_v channels may be a new target in the effort to develop therapies for HAD and perhaps other inflammatory neurodegenerative disorders.

Keywords: voltage-gated K channels, macrophages, neurons, HIV, AIDS, HIV-1-associated dementia

Introduction

Human immunodeficiency virus type-1 (HIV-1)-associated dementia (HAD), a severe form of HIV-1-associated neurocognitive disorders (HAND) (Antinori et al. 2007), describes the cognitive deficits, motor disturbances, and behavioral abnormalities often observed in HIV-infected individuals (Kaul et al. 2001; McArthur et al. 2003; Gonzalez-Scarano and Martin-Garcia, 2005; Kramer-Hammerle et al. 2005; Verani et al. 2005). Although the incidence has significantly decreased since the advent of highly active anti-retroviral therapy (HAART), HAD remains a significant complication of HIV-1 infection as patients with acquired immune deficient syndrome (AIDS) live longer, antiretroviral drugs remain unable to effectively cross the blood-brain barrier (BBB), and HIV-1 resistance grows due to viral strain mutation. Despite more than two decades of investigation, our understanding of the mechanisms for HAD pathogenesis remains incomplete. It is widely accepted that HIV-1-infected MPs (brain perivascular macrophages and microglia) secrete soluble viral and cellular factors causing neuronal dysfunction and damage (Kaul et al. 2001; McArthur et al. 2003; Gonzalez-Scarano and Martin-Garcia, 2005; Kramer-Hammerle et al. 2005; Verani et al. 2005), leading to cognitive impairment. How soluble viral and cellular factors induce cognitive impairment is not fully understood. Emerging evidence indicates that voltage-gated potassium (K_v) channels, key regulators of neuronal excitability and macrophage secretory activity, are involved in the pathophysiological processes of several neurodegenerative disorders (Judge and Bever, 2006; Judge et al. 2006) and in animal behavior (i.e. learning and memory) (Giese et al. 1998; Giese et al. 2001; Solntseva et al. 2003). This review aims at updating our understanding of the role played by K_v channels in HIV-1-associated neuropathology. As K_v channels are expressed on both macrophages and neurons, alteration of the K_v channel activity by soluble viral and cellular factors may result in macrophage and neuronal dysfunction, leading to HAND/HAD. Thus, understanding

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the role played by K_v channels in HAND/HAD pathogenesis could provide molecular and cellular targets for the development of new therapies.

Macrophage K_v Channels and Macrophage-Associated Neurodegeneration

Macrophages and HAD neuropathology

Several different macrophage populations exist in the central nervous system (CNS), including transient perivascular macrophages and resident microglia. In healthy individuals, these populations support critical immune and homeostatic functions without pathological consequences (Cotter et al. 2002; Williams and Hickey, 2002). However, under certain circumstances a cycle of macrophage activation can cause neurotoxicity through excessive secretion of inflammatory and immunoactive substances. One such scenario is thought to unfold with HIV-1 infection, wherein transient populations of macrophage carry HIV-1 across the BBB (Gartner, 2000). Indeed, early autopsies of HIV-1 encephalitis (HIVE) patients found extensive monocyte-macrophage brain infiltration, formation of multinucleated giant cells (MNGC), and excess cellularity primarily of macrophage lineage (Michaels et al. 1988b). In situ hybridization (Stoler et al. 1986) and viral antigen co-localization studies (Gabuzda et al. 1986; Michaels et al. 1988a; Kure et al. 1991) also confirmed the primary cellular targets for HIV-1 in the brain are macrophage and microglia (Koenig et al. 1986; Wiley et al. 1986; Meltzer et al. 1990).

Importantly, progression to HAD is well correlated with high numbers of macrophage and microglia in the CNS, even more so than the extent of HIV-1 infection itself (Budka, 1986; Glass et al. 1995). Once in the CNS, infected macrophage provide a sanctuary for the HIV-1 virus (Koenig et al. 1986; Genis et al. 1992; Gendelman, 1997a), while producing immunoactive and inflammatory substances such as viral proteins, pro-inflammatory cytokines, chemokines, excitatory amino acids, nitric oxide, and eicosanoids. In addition to promoting further entry and activation of macrophage, many of these substances have been shown to cause electrophysiological disturbances (Koller et al. 1997; Nath and Geiger, 1998; Balschun et al. 2004; Gonzalez-Scarano and Martin-Garcia, 2005; Verani et al. 2005) and may mediate neuronal dysfunction and/or death (Cotter et al. 1999; Kaul et al. 2001). Therefore, macrophage play a critical role in the pathogenesis HIVE and HAD by mediating viral entry into the CNS, harboring viral reservoirs, promoting further macrophage migration, producing neurotoxic substances, and participating in tissue destructive processes.

Macrophage K_v channels and neurotoxicity

K_v channels primarily function to set resting membrane potentials and repolarize actions potentials in excitable cells. While not typically thought of as electrically excitable cells, human and mouse macrophage have been found to express K_v channels, including $K_v1.3$ and $K_v1.5$ (Gallin, 1991; Mackenzie et al. 2003; Park et al. 2003; Vicente et al. 2003). In particular, elevated $K_v1.3$ expression in periventricular and parenchymal inflammatory infiltrates has been observed in multiple sclerosis patients (Rus et al. 2005), revealing a possible connection to neurological dysfunction. The importance of K_v channel activity in macrophage can be seen in its variable expression level, which depends on the state of activation of the cell (Blunck et al. 2001; Vicente et al. 2003). While patch clamp experiments have shown that freshly isolated monocytes exhibit low numbers of K_v channels, this expression increases significantly during monocyte differentiation to macrophage (Blunck et al. 2001). This increase can be expected to result in greater outward K_v current, and occurs regardless of whether the stimulation leading to differentiation is macrophage colony stimulating factor (MCSF), exogenous lipopolysaccharide (LPS), phorbol myristate acetate (PMA), or HIV-1 Tat protein (Nelson et al. 1992; Schilling et al. 2000; Visentin et al. 2001; Qiu et al. 2002; Gerth et al. 2005).

While the precise functional role of these channels in macrophage has yet to be determined, membrane potential changes are among the earliest observed eventsafter stimulation. Mounting evidence suggests alterations in the K_v channel activity of macrophages may be a key early step in neuroinflammatory disorders, serving to initiate and/or amplify immune responses by controlling macrophage functions such as migration, proliferation, activation, and secretion

(Gallin, 1991; Lewis and Cahalan, 1995; DeCoursey et al. 1996; Blunck et al. 2001; Qiu et al. 2002). For example, experiments with LPS-stimulated macrophages have revealed that increased voltage-dependent potassium channel conductance is necessary for macrophage activation and essential for cytokine production (Blunck et al. 2001). Similarly, MCSF and LPS were found to induce voltage-dependent potassium channel expression, while potassium channel blockade inhibited cell growth (proliferation) and nitric-oxide synthase production (activation) (Vicente et al. 2003). Furthermore, potassium channel blockers such as quinine, tetraethylammonium (TEA) chloride, and barium chloride, as well as increased extracellular potassium concentration, have been found to inhibit tumor necrosis factor-α (TNF-α) (Haslberger et al. 1992; Maruyama et al. 1994; Qiu et al. 2002) and interleukin-8 (IL-8) (Qiu et al. 2002) production by activated macrophages. Increased K_v channel conductance has also been linked to increased macrophage motility(Gendelman et al. 2008), which may result in more widespread inflammation. More recently, upregulation of K_v channel expression has been correlated with immune cell activation strongly enough to be considered a functional marker (Rus et al. 2005). Also, K_v channel blockers have now been used to alleviate neuropathology and symptoms in experimental autoimmune encephalomyelitis by reducing immune cell activation, proliferation, and production of interleukins and TNFα (Beeton et al. 2001). Collectively, this research implies increased K_v channel conductance may be a key first step in the activation, migration, proliferation, and secretion of macrophage. The regulation of macrophage activation and resultant cytokine production by K_v channels may mirror macrophage functional processes in vivo, where they are activated by various factors including those released by HIV-1- infected mononuclear phagocytes. As this is the consensus underlying upstream cause of HAD, these potassium channels are attractive targets for treatment.

Neuronal K_v Channels and HIV-1-Associated Neurodegeneration

Neuronal K_v channels and cell excitability

K_v channels are formed by the association of four α-helical subunits, which form homo- or heteromeric tetramers to create a functional channel (Coetzee et al. 1999). There are a number of unique subunits which, when combined with a susceptibility to modulation by diverse factors, account for the large functional variation of these channels. K_v channels are categorized based on their voltage sensitivity (low- or high-voltage-activated) and inactivation tendencies (delayed rectifier (I_k) or A-type (I_A) (Dodson and Forsythe, 2004). Regardless of the type of K_v channel, the negative equilibrium potential of K^+ relative to the action potential threshold lends an essentially inhibitory nature to K^+ currents. Collectively, K_v channels set and stabilize resting membrane potential, repolarize action potentials (APs), and control the discharge frequency by regulating inter-spike intervals, thereby play a crucial role in the generation of neuronal electrical activity and directly influencing neuronal excitability. As mentioned, K_v channels can be modulated by a number of different factors, including membrane potential, redox potential, post-translational modification, organic molecules, peptides (Hille, 2001; Birnbaum et al. 2004), and other bioactive molecules such as pro-inflammatory cytokines. Thus, irregular modulation of K_v channel activity could lead to neuronal dysfunction and disrupt cognition.

Neuronal K_v channels and learning and memory

Recent genetic targeting studies indicate that K_v channel activity is of great importance in memory processes (Giese et al. 1998; Giese et al. 2001; Solntseva et al. 2003). As the number and pattern of APs are thought to encode information (Reike et al. 1997), K_v channel dysfunction may alter information processing and therefore be an important link in memory disturbances. Experiments in several different model systems have now shown decreased K^+ channel current correlates with improved memory and long-term potentiation (LTP), while increased K^+ current corresponds to learning and memory deficiencies (Ghelardini et al. 1998; Alkon, 1999; Solntseva et al. 2003). At present, the effect of altered potassium current is best characterized by studies of K_v4 channels in the distal dendrites, $K_v1.1$ and $K_v2.1$ in the proximal dendrites and soma, and K_v1 in axons and nerve terminals.

In particular, K_v4 channels are now thought to provide a convergence point for LTP signal

transduction pathways (Olds et al. 1989; Alkon et al. 1998; Dineley et al. 2001; Birnbaum et al. 2004). Increasing or decreasing this A-type current inversely affects back-propagating AP (bp-AP) amplitudes (Watanabe et al. 2002), which helps determine the depolarization sensed by NMDA receptors and may underlie learning and memory networking properties (Paulsen and Sejnowski, 2000; Johnston et al. 2003; Birnbaum et al. 2004). Importantly, increased K_v4 current lowers LTP induction probability (Watanabe et al. 2002), while decreased K_v4 current enhances LTP (Frick et al. 2004), increases EPSP-spike (E-S) potentiation (Frick et al. 2004), and improves learning and memory (Lilliehook et al. 2003).

$K_v1.1/K_v\beta1.1$ current has also been demonstrated to have an effect on alternative learning and memory mechanisms in subunit deletion studies (Giese et al. 1998; Giese et al. 2001; Murphy et al. 2004). The deletion of the $K_v\beta1.1$ subunit causes a reduction in I_A amplitude, which in turn reduces frequency-dependent spike-broadening and the slow after-hyperpolarization (sAHP). The end result is increased neuronal excitability, improved Morris watermaze performance, and a decreased threshold for the induction of LTP (Giese et al. 1998; Murphy et al. 2004).

Meanwhile, clusters of $K_v2.1$ channels regulate both intrinsic and neuronal excitability during high frequency stimulation (Murakoshi and Trimmer, 1999; Du et al. 2000; Pal et al. 2003). Dephosphorylation of $K_v2.1$ channels shifts their activation curves to more hyperpolarized potentials and increases their open channel probability (Murakoshi et al. 1997). The increased delayed rectifier current (I_K) leads to a diminished LTP, which is reversible by re-phosphorylation, demonstrating a strong link to this potassium channel activity (Misonou et al. 2004).

Finally, several K_v1 subtypes have been implicated in gating axonal signal propagation (Debanne et al. 1997; Debanne et al. 1999), while suppressing hyperexcitability and reducing aberrant firing (David et al. 1995; Bajetto et al. 1999; Zhou et al. 1999) in both axons and presynaptic compartments (Dodson et al. 2003). In addition, in presynaptic compartments several subtypes contribute to raising the AP threshold (Dodson et al. 2003) and limiting the AP duration and related neurotransmitter release (Sekirnjak et al. 1997; Southan and Robertson, 2000; Elezgarai et al. 2003), while allowing for cumulative inactivation upon repeated depolarization to broaden the AP and enhance transmitter release (Jackson et al. 1991; Thorn et al. 1991). The relationship between these channels and learning and memory can be easily extrapolated from these results, but has yet to be explicitly demonstrated.

Neuronal K_v channels and apoptosis

Perhaps just as relevant as the electrophysiological consequences of increased neuronal K_v channel current is the ability of K_v channel activity to mediate apoptosis. The correlation between increased potassium channel current and apoptosis is robust and occurs across multiple cells types throughout the body, including smooth muscle cells, eosinophils, enterocytes, lymphocytes, thymocytes, T cells, and neurons (for reviews see (Yu, 2003; Burg et al. 2006). In repeated experiments, apoptotic volume decrease (AVD) and depression of apoptotic effectors were found to be mediated by K^+ efflux and intracellular K^+ depletion, leading to cell shrinkage, caspase activation, cytochrome c release, endonuclease activation, DNA fragmentation, and eventual apoptosis. In neurons these changes were accompanied by increased delayed rectifier K^+ current and could be prevented by potassium channel blockers or medium with high K^+ concentration (Yu et al. 1997; Wang et al. 2000; McLaughlin et al. 2001; Xiao et al. 2002). Therefore, while tissue homeostasis requires well regulated apoptosis, chronic increases in neuronal K_v current could initiate apoptotic sequences leading to premature cell death (i.e. neurodegeneration).

Neuronal K_v channels and HAD pathogenesis

Neuropsychiatric decline in AIDS patients is correlated with increasing numbers of macrophage in the brain (Glass et al. 1995), and the associated neuronal damage is closely associated with markers of macrophage activation (Adle-Biassette et al. 1999). This suggests the source of neuronal dysfunction may be the release of soluble factors from infected and/or activated macrophage. Cytokines, chemokines, excitatory amino acids, arachidonic acid metabolites, nitric oxide (NO), and viral proteins (HIV-1 gp120, Tat and Nef) are now thought to be the primary causes of HAD related neuronal injury (Lipton, 1991;

Genis et al. 1992; Tyor et al. 1992; Gelbard et al. 1994; Toggas et al. 1994; Bukrinsky et al. 1995; Nottet and Gendelman, 1995; Xiong et al. 2000; Yeh et al. 2000; Kaul et al. 2001; Carlson et al. 2004). Emerging evidence indicates this damage could be mediated through excessive neuronal K_v channel activation.

Macrophage-conditioned media (MCM)

Whole cell patch clamp recordings performed in our lab have demonstrated immune-activated MCM increases both transient A-type current and delayed rectifier K^+ current (Hu D et al. 2007; Keblesh et al. 2007). Using TEA, a K_v channel antagonist, it was possible to block the MCM-associated increase of I_K. Furthermore, the biological relevance of this was assessed by neuronal viability in the presence or absence of TEA, allowing us to conclude the MCM-mediated K_v channel current is correlated with diminished cell survival.

Cellular factors: Cytokines

Two substances which are elevated in HAD and can increase neuronal potassium channel current are the pro-inflammatory cytokines TNF-α and interleukin-1β (IL-1β). Elevated synthesis (Epstein and Gendelman, 1993b; Gelbard et al. 1994) and release (Nicolini et al. 2001) of TNF-α has been demonstrated in several HAD experimental models. Also, analysis of patient brain tissue after autopsy has revealed increased TNF-α mRNA expression correlating with symptom severity (Glass et al. 1993). TNF-α is known to increase the permeability of the BBB to HIV-infected cells (Fiala et al. 1997), induce expression of cell adhesion molecules, and upregulate monocyte chemoattractant protein-1 (MCP-1) (Nottet, 2005). In addition, whole-cell patch-clamp recordings have now shown application of recombinant human TNF-α to cultured embryonic rat cerebral cortex neurons results in an increase of A-type K^+ current (Houzen et al. 1997). Additional electrophysiological recordings revealed TNF-α applications inhibit LTP in the CA1 in a dose-dependent manner (Tancredi et al. 1992), while even low doses completely abolished LTP in the dentate gyrus (Cunningham et al. 1996).

A similar upregulation of IL-1β has also been observed in HAD patients and models (Genis et al. 1992; Epstein and Gendelman, 1993a; Nicolini et al. 2001; Zhao et al. 2001; Barak et al. 2002). IL-1β is also believed to induce cell adhesion molecule expression and upregulate MCP-1 (Brabers and Nottet, 2006). In addition, electrophysiological recordings demonstrate the application of IL-1β can increase both transient and delayed rectifier K^+ currents in a dose-dependent manner (Szucs et al. 1992). This increased outward conductance causes synaptic inhibition and likely disrupts neuronal plasticity (Zeise et al. 1992), an idea supported by studies demonstrating pretreatment or superfusion of IL-1β diminishes LTP (Bellinger et al. 1993; Cunningham et al. 1996). In one notable experiment, i.c.v. injection of gp120 in rats stimulated IL-1β production and behavioral abnormalities, which could be attenuated with IL-1β antagonist pretreatment (Barak et al. 2002).

Cellular factors: AA, glutamate, BDNF

In addition to the aforementioned cytokines, several other cellular products are known to effect potassium channels, including arachidonic acid (AA), glutamate, and brain derived neurotrophic factor (BDNF). In a model for HAD, AA in HIV infected monocyte/glia co-cultures is converted to its metabolites at an abnormally high rate (Genis et al. 1992). Under normal conditions, AA suppresses I_A current in CA1 pyramidal cells, thereby increasing the postsynaptic response to stimulation and lowering the threshold for LTP (Ramakers and Storm, 2002). In contrast, the metabolic products of AA have been found to dampen excitability by increasing the open channel probability (Piomelli et al. 1987) and the current (Zona et al. 1993) of sustained potassium channels. In HAD, the increased conversion of AA to its metabolites may reduce AA suppression of I_A while increasing metabolite enhancement of I_K, compromising the reliability of synaptic transmission (Colbert and Pan, 1999).

Recent evidence also suggests HAD related enhancement of glutaminase activity could result in an overabundance of glutamate (Erdmann et al. 2006). In experiments involving glutamate application, neuronal $K_v2.1$ channels were dephosphorylated (Misonou et al. 2004) and the activation curves shifted, resulting in greater open channel probability and current (Murakoshi et al. 1997). Further, $K_v2.1$ dephosphorylation leads to a dendritic beading which has been linked to

potassium channel related LTP diminishment (Gelbard et al. 1994; Misonou et al. 2004; Bellizzi et al. 2005). Perhaps just as importantly, increasing $K_v2.1$ current has been shown to cause apoptotic loss of cell volume (Pal et al. 2003).

HAD models have further shown decreases in the concentration of BDNF (Nosheny et al. 2004). In addition to an essential role in neurogenesis, neuronal development, and neuronal survival, recent studies demonstrate BDNF down-regulates the expression of $K_v1.2$, $K_v1.4$, and $K_v4.2$ (Park et al. 2003) and may be essential for long-term potentiation and other forms of activity-dependent synaptic plasticity (Korte et al. 1996; Hartmann et al. 2001; Zakharenko et al. 2003). Interestingly, BDNF was found to reduce gp120 related neurotoxicity (Nosheny et al. 2005), possibly via down-regulation of A-type potassium channel genes and their associated currents.

Viral products

The viral protein Nef has also been detected in brain tissue (Ranki et al. 1995) and sera (Deacon et al. 1995) of AIDS patients. Furthermore, this soluble protein shares functional sequences with scorpion peptides known to interact with potassium channels (Garry et al. 1991; Werner et al. 1991) and has been demonstrated to reversibly increase total K^+ current (Werner et al. 1991). These increased potassium currents may account for the neurotoxic effects Nef application causes in cultured human neurons (Trillo-Pazos et al. 2000).

Treatment with K_v Channel Antagonists

K_v channel blockade ameliorates macrophage-associated tissue damage

Reactive macrophage/microglial response leading to inflammatory tissue damage is now considered characteristic of a wide range of neurodegenerative disorders, including Alzheimer's disease, multiple sclerosis, and HIV associated dementia (Gendelman et al. 1998; Cotter et al. 1999; Rus et al. 2005). Consequently, many therapeutic approaches now attempt to modulate neuroinflammation in conjunction with symptomatic treatments (Judge and Bever, 2006; Judge et al. 2006). In light of the role of K_v channels in macrophage activation, secretion, migration, and proliferation, interest in developing effacious immunomodulatory K_v channel antagonists as an means of limiting neurodegeneration is growing (Judge and Bever, 2006; Judge et al. 2006). The use of both nonspecific K_v channel blockers (4-AP and 3,4-DAP) and highly selective blockers (margatoxin, kaliotoxin, and correolide) have been used to inhibit immune responses in rodent experimental allergic encepholomyelitis (EAE) models for multiple sclerosis (MS) (Beeton et al. 2001) and have now been clinically tested for treatment of patients with MS (Bever, 1994; Bever et al. 1994). In another in vivo study, injection of the K_v channel blocker quinidine in rats was found to ameliorate symptoms of clinical experimental allergic neuritis, an accepted animal model for human Guillain–Barre syndrome that is the peripheral nervous system counterpart of EAE in the CNS(Mix et al. 1989). Importantly, as expected the neuroprotective effects of these K_v channel inhibitors were accompanied by reduced inflammation in target tissue.

K_v channel blockade ameliorates HAD related neuronal dysfunction

Our lab has previously demonstrated i.c.v. injection of severe combined immunodeficient (SCID) mice with virus infected macrophage leads to impaired spatial learning and diminished long-term potentiation (Zink et al. 2002; Anderson et al. 2003), while also establishing that macrophage conditioned media increases neuronal I_A and I_K in culture(Hu D et al. 2007). We next studied the effects of systemic administration of the K_v channel antagonist 4-AP on LTP and animal behavior in our murine model of human HIV disease. We found the injection of HIV-1-infected human MDMs produced encephalitis, impaired spatial learning, and diminished long-term potentiation, which were ameliorated with administration of 4-AP (Keblesh et al. 2007).

At present it is difficult to estimate the relative contribution of neuronal and macrophage K_v channels. While 4-AP may protect neuronal physiology by blocking neuronal K_v channels, it may also mediate neuroprotective effects via inhibition of proinflammatory cytokine production from MDMs (Blunck et al. 2001; Qiu et al. 2002) and/or reduction of the migration, proliferation, and activation of additional macrophage. It is therefore

our view that both macrophage and neuronal K_v channels be considered worthy targets for the development of new therapeutic strategies for chronic inflammatory and neurodegenerative disorders.

Summary

At present the complete mechanism of HIV-associated dementia has yet to be elucidated and as such, there is no effective prescribable treatment to date. At the same time, the role of voltage-gated potassium channels in the processes of macrophage activation, secretion, migration, and proliferation is just now beginning to be appreciated, while the effects of macrophage secreted cellular and viral factors on neuronal voltage-gated potassium channel current, and the significance of this for the neuron, are only gradually becoming clear. While this line of investigation into K_v channels and HAD pathogenesis is young it is also promising, and we hope to have provided a clear starting point and encouragement for future research in this area.

Acknowledgements

This work was supported by NIH grant R01 NS041862.

Disclosure

The authors report no conflicts of interest.

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