CHAPTER

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Translational Medicine Strategies for Drug Development for Impulsive Aggression

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Impulsive aggressive behavior in humans typically occurs during social interactions in which the "aggressor" perceives a threat to self that results in a swift and angry response to the "other." The swiftness of response is often characterized as "impulsive," while the anger in the response is often characterized as "affective" (Coccaro, 2012). In reality, these two features occur simultaneously, and that is why these kinds of behaviors are referred, interchangeably, as "impulsive" or "affective" aggression. That said, individuals who display impulsive/angry aggressive behavior are not always impulsive or angry between outbursts, even if they score higher on trait measures of impulsivity/anger compared with nonaggressive individuals. Ultimately, the key point is that the aggressive behavior, in these cases, is characterized by its impulsivity and anger in response to a social threat.

Treatment approaches to impulsive aggressive behavior must be developed in the context of what is known empirically about these behaviors. This includes cognitive and systems neuroscience (Coccaro, Sripada, Yanowitch, & Phan, 2011) and neurobiology (Yanowitch & Coccaro, 2011). The following sections discuss the background of impulsive aggression in the context of these areas and, then, potential strategies to test drugs for antiaggressive effects.

I COGNITIVE/SYSTEM NEUROSCIENCE AND NEUROBIOLOGICAL SUBSTRATES OF IMPULSIVE AGGRESSIVE BEHAVIOR IN HUMANS

A Cognitive Neuroscience

The most parsimonious model of impulsive aggression posits that a balance of inhibitory and excitatory neurotransmitter/modulators sets a "threshold" for impulsive aggressive responding to a perceived social threat and that impulsive aggressive behavior occurs when an external (or even internal) stimulus reaches and exceeds this threshold. In this model, individuals with prominent histories of impulsive aggressive (e.g., intermittent explosive disorder, IED; Coccaro, 2012) have a lower threshold for "exploding" than those without this history. This is not the complete model, however, because the potential social threat must first be processed along with cognitive and emotional overlays to that threat. These processes may be referred to as social-emotional information processing (SEIP; Coccaro, Fanning, Fisher, Couture, & Lee, 2017; Coccaro, Fanning, Keedy, & Lee, 2016; Coccaro, Noblett, & McCloskey, 2009), a model based on an earlier conceptual framework referred to as social information processing (SIP; Crick & Dodge, 1996; Dodge, 1991; Dodge, Pettit, Bates, & Valente, 1995; Fontaine, Burks, & Dodge, 2002).

Accordingly, interpersonal conflict may be explained within a multistage sequence of SEIP such that impulsive aggressive behavioral responses are linked to one or more of six (6) stages referred to as (1) encoding (attention to relevant social information), (2) attribution (of the intent of the behavior of the other participant in the social interaction), (3) emotional response whether negative or positive, (4) evaluation of potential responses, (5) decision-making regarding the chosen response, and (6) enactment of chosen response. Research confirms that impulsive aggressive children and adolescents (particularly those with a history of abuse) demonstrate a reduction in the encoding (or identification) of socially relevant information and the presence of a hostile attribution bias (the other person is intending harm to the subject), especially in cases of an ambiguous social interaction (Crick & Dodge, 1996; Dodge et al., 1995). Over the past several

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years, we extended this work to adults, specifically adults with IED (Coccaro, Fanning, Fisher, et al., 2017; Coccaro, Fanning, & Lee, 2017; Coccaro, Noblett, & McCloskey, 2009). In a series of studies, we documented that individuals with IED have reduced encoding of social cues (Coccaro, Fanning, Fisher, et al., 2017), heightened hostile attribution (Coccaro, Fanning, et al., 2016, Coccaro, Fitzgerald, Lee, McCloskey, & Phan, 2016, Coccaro, Lee, & Kavoussi, 2009), negative emotional response (Coccaro, Fanning, et al., 2016; Coccaro, Fitzgerald, et al., 2016; Coccaro, Lee, & Kavoussi, 2009), and a bias to choose directly or relationally aggressive responses to socially ambiguous cues (Coccaro, Fanning, et al., 2016; Coccaro, Fanning, Fisher, et al., 2017; Coccaro, Fanning, & Lee, 2017; Coccaro, Fitzgerald, et al., 2016). Simultaneous analysis of each of these SEIP steps reveals the critical importance of negative emotional response to socially ambiguous cues and the bias to choose aggressive responses to such cues (Coccaro, Fanning, et al., 2016; Coccaro, Fitzgerald, et al., 2016). Notably, aspects of SEIP are reported as abnormal in individuals with focal lesions of orbitofrontal cortex (Wilson, Scalaidhe, & Goldman-Rakic, 1993) and/or amygdala (Adolphs et al., 1999; George et al., 1993) brain areas implicated in the perception (Wilson et al., 1993) and correct identification of facial expression (George et al., 1993; Lane, Fink, Chau, & Dolan, 1997; Rolls, Cahusac, Feigenbaum, & Miyashita, 1993). In addition, PET studies in normal individuals show that recognition of fearful and sad faces (for example) is associated with the activation of the corticolimbic areas (Blair, Morris, Frith, Perrett, & Dolan, 1999). Individuals with lesions in these areas (who are often aggressive) often attribute a negative bias even to neutral facial expressions (Hornak, Rolls, & Wade, 1996). It is possible that deficits in SEIP are associated with aggressive behavior because the misperception of emotional stimuli and deficits in social information processing leads to inappropriate behavioral responses in impulsive aggressive individuals (Rolls et al., 1993). Work in our laboratory and of others also suggest important IED-control differences in SEIP in corticolimbic circuits (see in the succeeding text).

B Systems Neuroscience

Whether we are considering the role of neurobiology (i.e., threshold to explode) or cognitive neuroscience (processes that lead to exceeding this threshold), the generation of impulsive aggressive behavior goes through corticolimbic brain circuits (Coccaro et al., 2011). Among the more important regions in this regard are the orbital prefrontal cortex (OFC), the amygdala, and the temporoparietal junction (TPJ).

The OFC is mapped across the orbital surface of the frontal lobe and receives visual, gustatory, olfactory, auditory, and somatosensory information from primary and secondary association cortices (Rolls, 2004). In addition, the OFC is extensively interconnected with the amygdala (Ongur & Price, 2000), which processes sensory information to create emotionally valenced or conditioned object memories (Cahill, 1995), which bias decision-making processes of the OFC (Bechara, Damasio, Damasio, & Lee, 1999). The OFC plays an important role in three key aspects of impulsive aggression. These include the processing of mental reward and punishment representations: emotion, social information processing, and impulsivity. In the case of emotion, these are mental representations of internal reinforcers such as states of anger. In the case of SEIP, these are mental representations of the reinforcing or punishing attributes of social interactions, which in a social species such as man could have life-or-death consequences. In the case of impulsivity, these are mental representations of time-delayed reinforcers and punishments, such as the cost and benefits of using a resource immediately versus saving it for more beneficial use in the future.

Both medial and lateral OFC are relevant to aggression. The medial OFC is involved in the mental representation of object reward associations (reviewed in Elliott, Dolan, & Frith, 2000), especially when reward associations change or reverse over time (Elliott et al., 2000), a function dependent on interconnections with the amygdala (Ongur & Price, 2000). As with other prefrontal cortex structures, so-called delay neurons of the OFC play a working memory-like task in the sustained representation of anticipated reward during a time delay between stimulus perception and a behavioral response (Hikosaka & Watanabe, 2000). These medial OFC processes would be expected to be relevant to the processing of emotional and social information (Iversen & Mishkin, 1970). Indeed, lesions of the medial OFC are associated with deficits in processing the reward value of stimuli and disinhibited social behaviors (Damasio, 1994). Evidence from human studies indicates that the role of the medial OFC (and related structures) in processing reward associations is relevant to complex mental representations, including the subjective experience of emotions such as sadness, anger, happiness, and fear (Damasio et al., 2000). Because anger is an emotional mental operation, the medial OFC is involved in the processing of anger. In fact, experimentally evoked anger results in metabolic activation of the medial OFC (Kimbrell et al., 1999). The OFC may play a regulating role in the outward expression of anger, as imagined unrestrained physical aggression against another human is associated with decreased medial OFC metabolic activity (Pietrini, Guazzelli, Basso, Jaffe, & Grafman, 2000). These findings are consistent with reports

of the effect of OFC lesions on increased behavioral aggression (Grafman et al., 1996; Zald & Sim, 1996). Thus the medial OFC may play a role in the regulation of emotional states such as anger, subject experience of anger, control of behavioral aggression, evaluation of the social milieu, and cognitive impulsivity.

The lateral OFC is involved in reversal learning and response inhibition. While some reports suggest that the lateral OFC is involved in processing of emotion valence-specific stimuli, such as negative versus positive emotions (Northoff et al., 2000), anger induction (Dougherty et al., 1999), and angry faces (Blair et al., 1999), the valence specificity of these may be due to the invocation of reversal learning and response inhibition functions. For example, angry faces may signal the punishment value of continuing a provocative behavior. This may be true of other facial expressions, however, as evidenced by a functional magnetic resonance imaging (fMRI) study using a visual reversal learning task (Kringelbach & Rolls, 2003). In addition to a role in processing emotionally salient stimuli, the lateral OFC also plays a role in the cortical inhibition of motoric impulsivity, which may serve to suppress impulsive aggressive behavior in response to provocation (Bechara, Damasio, & Damasio, 2000). In summary, both the medial and lateral sections of the OFC play key roles in processing of anger and behavioral impulsivity.

In addition to the OFC, models of human aggression also implicate the amygdala as an important structure in emotion processing and aggression (Davidson, Putnam, & Larson, 2000). This is based on data from stimulation and lesion studies in animals, nonhuman primates, and humans. In animals, stimulation of the amygdala promotes aggressive responding (Adamec, 1991), and its damage changes the nature of social interactions (Amaral et al., 2003; Kluver & Bucy, 1939). Since the amygdala and OFC are anatomically and functionally connected (Amaral & Price, 1984), their effective interactions are critical for decoding emotionally salient information and guiding goal-directed behaviors (Saddoris, Gallagher, & Schoenbaum, 2005), both of which are relevant in the control of aggression. Moreover, the OFC is hypothesized to play a key role in modulating limbic reactivity to threat (Davidson et al., 2000).

Finally, the TPJ is a recent addition to the "default mode network" and is directly involved in social-cognitive processes, including attentional state and thinking about the mental states of others (Krall et al., 2016; Koster-Hale & Saxe, 2013; Molenberghs, Johnson, Henry, & Mattingley, 2016; Price & Drevets, 2012; Saxe & Wexler, 2005). While the precise neuroanatomy and substructures of the TPJ are the subject of intense investigation, the consensus based on available results is that the right TPJ (rTPJ) is extensively involved in attentional processes and interpretation of mental state (Mars et al., 2012; Saxe & Wexler, 2005), with at least the anterior region engaging in both functions based on an activation likelihood estimation (ALE) metaanalysis (Krall et al., 2016). Given the preceding discussion on SEIP, the rTPJ may have a critical role in triggering impulsive aggressive outbursts in impulsive aggressive individuals.

To date, there have been only two experimental medicine studies relevant to the TPJ and emotional processing. The first was a study in healthy volunteers (Lee et al., 2013) that examined fMRI blood oxygen level-dependent imaging (BOLD) signal in response to angry faces after intranasal vasopressin (AVP) with or without treatment with a novel vasopressin 1a (V1a) receptor antagonist. AVP, which is strongly associated with increased aggressive behavior in both animals and humans (see in the succeeding text), resulted in significantly elevated fMRI BOLD signal in the rTPJ and in precuneus, anterior cingulate, and putamen, when given intranasally 60 min prior to the fMRI session. As expected, the elevated fMRI BOLD signals to AVP were blocked in the presence of the V1a receptor antagonist indicting that the rTPJ (as well as other relevant corticolimbic) site is involved in anger-related social-emotional information processing. While we do not know what would be observed in impulsively aggressive individuals under the same study conditions, we have found that acute administration of the specific serotonin-reuptake inhibitor (SSRI), escitalopram, also increased the fMRI BOLD signal in the TPJ in impulsively aggressive subjects (Cremers, Lee, Keedy, Phan, & Coccaro, 2016) compared with that in healthy volunteers. Because these studies are not comparable, it is difficult to say more than that these results indicate that the TPJ may play a prominent contributory role in the manifestation of impulsive aggression.

Not surprisingly, several studies in impulsive aggressive subjects have observed anomalies in brain structure. Studies of impulsive aggressive individuals with borderline and/or antisocial personality disorders report reduced grey-matter volumes in various regions of the frontolimbic system compared with controls (Brambilla et al., 2004), findings that overlap those in individuals with IED. Specifically, individuals with IED have reduced grey-matter volume in frontolimbic areas including the orbital prefrontal cortex, ventromedial prefrontal cortex, anterior cingulate cortex, amygdala, insula, and uncus (Coccaro, Fitzgerald, et al., 2016). In addition, measures of aggression correlate directly with grey-matter volume in these areas. The shape of the amygdala is also abnormal in individuals with IED, with significantly more areas of inward deformation of the amygdala compared with healthy controls (Coccaro, Lee, McCloskey, Csernansky, & Wang, 2015). Diffusion tensor imaging (DTI) also reveals lower fractional anisotropy in two

clusters located in the superior longitudinal fasciculus when compared with psychiatric and healthy controls (Lee et al., 2016), suggesting lower white-matter integrity in long-range connections between the frontal and TPJ regions of the brain and likely problems with connectivity between these brain regions.

These structural brain anomalies likely underlie results reported in functional magnetic resonance imaging studies in individuals with IED. For example, individuals with IED display greater amygdala response to exposure to angry faces compared with healthy controls whether the stimuli are presented implicitly (Coccaro, McCloskey, Fitzgerald, & Phan, 2007) or explicitly (McCloskey et al., 2016). In addition, life history of aggression measures correlate directly with amygdala response to angry faces, and the connectivity between prefrontal cortex and amygdala appears disrupted in IED compared with healthy controls. Notably, we have found evidence for a functional normalization in amygdala and in prefrontal areas in individuals with IED 12 weeks after antiaggressive pharmacotherapy (Coccaro, Fanning, Phan, & Lee, 2015). Further studies note that acute activation of 5-HT receptors by a single dose of citalopram is associated with an enhanced fMRI signal response to angry faces in the left temporal parietal junction of IED compared with heathy control individuals (Cremers et al., 2016).

C Neurobiology

The complexity of aggression reflects the role of multiple neurotransmitter interactions in regulation of the behavior. In this section, several neurotransmitter systems that have been implicated as potential therapeutic targets are briefly considered. Each is listed separately because an effort to cover the interactions is beyond the scope of this review.

An important consideration in attempting to elucidate the underlying neurobiology and neurochemistry of impulsive aggression is the generally poor translation of preclinical findings into new pharmacologic treatments (major depression is perhaps the best example). In the present case, models of aggressive behaviors utilized in laboratory settings, including resident–intruder aggression, maternal aggression, and defensive aggression, emulate productive behaviors that, in the wild, enhance access to resources and reproductive success. In this context, the regulatory systems for these behaviors almost certainly differ markedly from those governing impulsive or pathological aggression. Until better translational paradigms can be developed, results from any single preclinical model are best viewed cautiously.

1 Serotonin (5-HT)

Studies of impulsive aggression in humans have been ongoing since the late 1970s when lithium was used to treat aggressive behavior in prison inmates (Sheard, Marini, Bridges, & Wagner, 1976). It was already known that lithium had antiaggressive properties in (Sheard, 1970) and could increase 5-HT activity (Perez-Cruet, Tagliamonte, Tagliamonte, & Gessa, 1971) and that 5-HT activity correlated inversely with aggressive behavior (Valzelli & Garattini, 1968), in rodents. In addition to demonstrating an antiaggressive effect in human subjects, lithium reduced impulsive, but not premeditated, aggressive behavior (Sheard et al., 1976). Soon after, cerebrospinal fluid (CSF) studies of the 5-HT metabolite, 5-hydroxyindoleacetic acid (5-HIAA), reported consistent inverse correlations between measures of aggression and CSF 5-HIAA levels (Brown et al., 1982; Brown, Goodwin, Ballenger, Goyer, & Major, 1979). Subsequent studies reported lower levels of CSF 5-HIAA in impulsive violent offenders (Virkkunen, Nuutila, Goodwin, & Linnoila, 1987), indicating that 5-HT may be spefically related to impulsive aggression. Studies using other indices of 5-HT function largely confirmed and extended these findings (Coccaro et al., 1989). That said, a recent metaanalysis of 5-HT studies in aggression suggests that this relationship may be more modest than previously thought. Duke, Bègue, Bell, and Eisenlohr-Moul (2013) analyzed 171 studies on the serotonin-aggression relationship that employed the following: (a) CSF 5-HIAA, (b) acute tryptophan depletion (ATD), (c) pharmacochallenge, and (d) endocrine challenge methods (Duke et al., 2013). The authors found a small ($r = -0.12$), significant inverse relation between measures of 5-HT functioning and aggression overall with pharmacochallenge studies yielded the largest effect size ($r = -0.21$). These results demonstrate that the relationship between 5-HT and aggressive behavior is far more complex than previously appreciated. This should be expected given the complexity of the central 5-HT system, which manifests multiple types of receptors distributed at both pre- and postsynaptic sites, which may also exert unique and perhaps opposing effects on aggression. One must also consider the recognized role of other neurotransmitters (see in the succeeding text) and their interactions in the regulation of complex behaviors such as impulsive aggression. This is especially the case given that central 5-HT function may only account for about 4%–9% of the variance in aggression scores. Thus other neurotransmitters and neuromodulators must also play a role in the neurobiology of impulsive aggression either by inhibiting or facilitating impulsive aggressive responding.

2 Catecholamines (DA and NE)

Compared with 5-HT, much less is known about the role of catecholamines and aggression. Preclinical studies point to hyperactivity of the dopaminergic (DA) system in the mesocorticolimbic pathway during and after a provocative aggressive encounter, possibly reflecting motivational aspects of aggressive behavior

(Miczek, Fish, De Bold, & De Almeida, 2002). In humans, however, CSF homovanillic acid (HVA), the major metabolite of dopamine, has been studied with mixed results. Some studies reported an inverse relationship between CSF HVA concentration (Coccaro & Lee, 2010; Limson et al., 1991; Linnoila et al., 1983; Virkkunen, De Jong, Bartko, Goodwin, & Linnoila, 1989) or DA storage capacity in the striatum/midbrain (Schlüter et al., 2013) and aggression, but this has not been a consistent finding. Because central NE is implicated in orienting to novel stimuli, focusing attention, and enacting behavioral responses (Berridge & Waterhouse, 2003), NE has long been thought to play a role in aggression. Despite this, empirical support for this possibility in humans has been limited and mixed (Oquendo & Mann, 2000).

3 *Glutamate (GLU)*

GLU, the primary excitatory neurotransmitter in the CNS, is thought to play a facilitative role in aggressive behavior based on studies in cats and rodents reporting that defensive aggressive behavior is induced by GLU (and inhibited by GABA and 5-HT) in the hypothalamus (Haller, 2013). Conversely, administration of N-methyl-D-aspartate (NMDA) receptor antagonists or inhibition of GLU synthesis reduces aggression in mice. Consistent with these findings, CSF GLU concentrations correlate positively with measures of both aggression and impulsivity in personality-disordered and healthy control study participants (Coccaro, Lee, & Vezina, 2013). In humans, treatment with memantine, an uncompetitive antagonist at glutamatergic NMDA receptors, reduced agitation and aggression in individuals with Alzheimer's disease (Wilcock, Ballard, Cooper, & Loft, 2011), though no work has been performed in individuals with primary impulsive aggression.

4 *γ-Aminubutyric acid (GABA)*

GABA is the primary inhibitory neurotransmitter in the brain with receptors heavily expressed in areas of frontal-limbic regions at both inhibitory-inhibitory and inhibitory-excitatory synapses. Preclinical studies have shown that aggressive animals have reduced brain GABA levels and of glutamic acid decarboxylase (GAD), the enzyme that catalyzes glutamate into GABA. In humans, Lee, Petty, and Coccaro (2009) found an inverse relationship between trait impulsivity (but not aggression) and CSF GABA levels in individuals with personality disorder and healthy control subjects. Despite the null finding for aggression, GABA levels were higher in individuals with a history of suicide attempt, a feature related to aggression. Drugs that enhance GABAergic effects (including the antipsychotic drug clozapine, anticonvulsants topiramate and valproate, and the mood stabilizer lithium) reduce aggression (Comai, Tau, & Gobbi, 2012), suicide and suicide attempts (lithium; Baldessarini, Tondo, & Hennen, 2003), and behavioral dysregulation (carbamazepine; Cowdry & Gardner, 1988). Valproate, an agent that increases GABA, reduced aggression in individuals with IED and Cluster B personality disorder (Hollander et al., 2003). While these studies suggest an inhibitory relationship between GABA and aggression, others suggest a more complex relationship. For example, certain allosteric modulators of $GABA_A$ receptors show a bidirectional relationship with GABA in which case these agents enhance aggression at low doses and reduce aggression at high doses.

D Neuropeptides

1 *Vasopressin (VASO)*

VASO exerts its physiological and behavioral effects by binding to specific G-protein-coupled receptors (GPCRs) in the central nervous system and certain peripheral tissues/sites (Ring, 2005; Serradeil-Le Gal et al., 2002). Three distinct AVP receptor subtypes have been identified –V1a, V1b, and V2. V1a is the predominant VASO receptor found in the limbic system and cortex; V1b receptor is located in limbic system and pituitary gland, although it is less widespread than V1a. The V2 receptor is localized in the kidney where it mediates the antidiuretic effects of vasopressin. It is not generally thought to be expressed in the nervous systems of adult animals or humans.

Offensive and defensive aggressive behaviors are modulated by vasopressin (reviewed in Albers, 2012). Elevated VASO is associated with heightened aggression and exaggerated responses to perceived threats in both animals and humans (Ferris, 2005; Simon, 2002). We recently showed that conditioned fear responses that resulted in a hyperarousal pattern (BOLD signal activation) in the amygdala, hippocampus, and other parts of the Papez circuit in rats were attenuated by treatment with a novel V1a receptor antagonist, AVN576. Intraventricular administration of d(CH2)5Tyr(Me)AVP (Manning compound), a linear V1a antagonist that does not cross the blood-brain barrier and is used for research purposes only, blocks aggression in rodents (Ferris, 2005). Two new V1a antagonist compounds developed by Azevan Pharmaceuticals, SRX246 and SRX251, significantly reduce aggression in rats when given orally or by intraperitoneal (IP) injection (Fabio et al., 2010; Ferris et al., 2006, 2008; Simon et al., 2008). Imaging results in awake animals showed that rats treated with either of these compounds had significantly reduced fMRI BOLD activation in circuits known to mediate responses to threat and drive aggression (Ferris et al., 2008).

In humans, genetic variation of the vasopressin V1a receptor has been linked to differences in metabolic reactivity of the amygdala to emotional stimuli as measured by fMRI BOLD (Meyer-Lindenberg et al., 2009). Experimental manipulation of central vasopressin has

provided proof of a causal role for vasopressin signaling in human behavior. When administered intranasally, vasopressin enhances attention to negative emotional facial expressions (Guastella, Kenyon, Alvares, Carson, & Hickie, 2010; Lee et al., 2013; Thompson, Gupta, Miller, Mills, & Orr, 2004; Thompson, George, Walton, Orr, & Benson, 2006; Zink, Stein, Kempf, Hakimi, & Meyer-Lindenberg, 2010). This effect is entirely consistent with the known relevance of vasopressin to social behavior, expression of vasopressin 1a receptors in the amygdala, and the well-known role of the amygdala in the decoding of visual information pertaining to emotional facial expressions (Lee et al., 2013; Zink et al., 2010). Intranasal vasopressin enhances TPJ and anterior cingulate metabolic activity during processing of social stimuli (Brunnlieb, Münte, Krämer, Tempelmann, & Heldmann, 2013; Rilling et al., 2012) and superior temporal sulcus activity during the expectation of punishment in the Taylor Aggression Paradigm (Brunnlieb et al., 2013). Measurements of central levels of VASO in humans by lumbar puncture were positively correlated with dimensional measures of impulsive aggression (Coccaro, Kavoussi, Cooper, & Hauger, 1998; Coccaro, Kavoussi, Hauger, Cooper, & Ferris, 1998) life history of aggressive behavior. fMRI studies show that VASO activates neural structures involved in fear regulation and social/emotional information processing (Lee et al., 2013; Zink et al., 2010; Zink et al., 2011). This finding is relevant because impulsive aggressive individuals have anomalies in social cognition and are particularly sensitive to social threat (Coccaro, Fanning, et al., 2016).

2 *Oxytocin (OXY)*

Like VASO, OXY plays a role in regulating social behavior, although these two neuropeptides often display opposing effects. While CSF VASO levels correlate positively, CSF OXY correlates inversely with aggression (Lee, Ferris, Van de Kar, & Coccaro, 2009). Oxytocin also reduced laboratory-assessed aggressive behavior among women with high state anxiety, suggesting an aggression-reducing anxiolytic effect of OXY (Campbell & Hausmann, 2013). However, OXY has also been shown to increase negative emotions such as envy and schadenfreude (Shamay-Tsoory et al., 2009) and to increase noncooperation toward members of out-groups (see De Dreu, 2012, for a review), suggesting that its effect on behavior may not always be positive or prosocial. Given the importance of amygdala hyperactivation in impulsively aggressive individuals (Coccaro et al., 2007; McCloskey et al., 2016), it is of note that OXY reduced the enhanced amygdala activation during exposure to angry/fearful faces in females with BPD, suggesting that OXY may reduce sensitivity to social threat in women with this disorder (Bertsch et al., 2013).

3 *Substance P*

The endogenous receptor for substance P is neurokinin-1 (NK1), and this receptor is widely distributed in the CNS, especially in limbic system regions (Yip & Chahl, 2001). Boin close association with 5-HT- and NE-containing neurons (Gobbi et al., 2007). A modulatory role for substance P in aggressive behavior is suggested by the presence of high concentrations of substance P in brain regions relevant to mammalian aggression (e.g., amygdala and periaqueductal grey; Smith et al., 1994). Studies in lower mammals show that substance P promotes aggressive behavior by activating hypothalamic NK1 receptors and induces rage and aggression (Barbeau, Rondeau, & Jolicoeur, 1980; Beyer, Caba, Banas, & Komisaruk, 1991; Bhatt, Gregg, & Siegel, 2003; Elliott & Iversen, 1986; Gregg & Siegel, 2001; Han, Shaikh, & Siegel, 1996; Shaikh, Steinberg, & Siegel, 1993). Conversely, NK1 receptor antagonists reduce defensive aggression in cats (Shaikh et al., 1993). A recent neurochemical study from our group reported a positive correlation between CSF levels of substance P and measures of aggression in personality disorder and control subjects, suggesting that substance P concentrations may facilitate aggression in humans (Coccaro, Lee, Owens, Kinkead, & Nemeroff, 2012). While an antagonist for NK1 receptors is available for human use (aprepitant), no study using this agent has been published to test the hypothesis that blocking NK1 receptors can reduce aggression in human subjects.

4 *Neuropeptide Y*

Animal models of aggression suggest that NPY can increase aggressive behavior (Karl et al., 2004; Kask & Harro, 2000; Rutkoski, Lerant, Nolte, Westberry, & Levenson, 2002). Our group reported a positive correlation between CSF NPY and measures of aggression (Coccaro, Lee, Liu, & Mathé, 2012), suggesting that NPY concentrations may facilitate aggression in humans as well. Unfortunately, to date, no antagonists for NPY receptors are available for human use so an experimental study in human subjects is not currently possible.

5 *Inflammatory Cytokines*

Inflammatory cytokines such as interleukin-1β (IL-1β; Hassanain, Bhatt, Zalcman, & Siegel, 2005; Hassanain, Zalcman, Bhatt, & Siegel, 2003) and interleukin-2 (IL-2; Bhatt & Siegel, 2006) modulate aggressive behavior in animals (i.e., defensive-rage aggression model in cat). In addition, IL-2 levels are higher in mice bred for high aggression versus low aggression (Petitto, Lysle, Gariepy, & Lewis, 1994) and knockout of TNF-α receptors eliminates aggressive behavior in mice (Patel et al., 1999). In human studies, circulating levels of C-reactive protein (CRP; Suarez, 2004, Marsland, Prather, Petersen, Cohen, & Manuck, 2008), a marker of inflammation, and IL-6

(Marsland et al., 2008; Suarez, 2003) also correlate positively with self-assessed hostility and tendency toward aggression in healthy adult subjects. Our group reported similar findings in personality-disordered individuals (Coccaro, 2006) and in individuals with recurrent, problematic, impulsive aggressive behavior with intermittent explosive disorder [IED; (Coccaro, Fanning, et al., 2016; Coccaro, Fitzgerald, et al., 2016; Coccaro, Lee, & Coussons-Read, 2014)]. In these studies, we found that plasma CRP (Coccaro, 2006; Coccaro et al., 2014), plasma IL-6 (Coccaro et al., 2014), and plasma sIL-1RII protein (Coccaro et al., 2016) are lowest in individuals with IED compared with psychiatric and healthy controls and that each inflammatory marker correlates directly with measures of aggression. Neurochemical studies from our group report a similar correlation with measures of aggression with CSF CRP (Coccaro, Lee, & Coussons-Read, 2015a) and with soluble CSF sIL-1RII receptor protein (Coccaro, Lee, & Coussons-Read, 2015b). While inflammatory states may reduce synaptic 5-HT by shunting tryptophan catabolism away from 5-HT to kynurenine, study of tryptophan metabolites in IED subjects reveals no change in kynurenine levels, suggesting a direct effect of these inflammatory mediators on aggressive behavior (Coccaro, Lee, et al., 2016). While studies of antiinflammatory agents have been ongoing in depression (Köhler et al., 2014), such studies have not yet been published in impulsive aggressive individuals.

II TESTING THE ANTIAGGRESSIVE EFFICACY OF PSYCHOPHARMACOLOGIC AGENTS

The classic psychopharmacologic approach to testing potential psychotropic therapeutics involves double-blind, placebo-controlled, clinical trials to determine safety and efficacy. Impulsive aggressive behavior, however, is highly variable in the short term (weeks), and such trials will likely show reductions in aggressive behavior simply due to natural ebb and flow of these behaviors during the treatment period. This is because impulsive aggressive behaviors are a function of the stable tendency to respond aggressively to social threat and the variable presence of social threats in the environment, making the use of double-blind placebo-controlled trials for impulsive aggression critical. This feature of impulsive aggression introduces an element of complexity in measuring efficacy because it increases the potential for a strong placebo response.

A Who to Study?

Typically, clinical trials are performed in individuals with a particular disease (e.g., internal medicine) or disorder (e.g., psychiatry). However, developing pharmaceuticals for impulsive aggression is complicated by the fact that impulsive aggression occurs along a dimension. That said, research in the past two decades has determined that one can define a disorder of impulsive aggression by using DSM-5 criteria for IED (Coccaro, 2012). The validity of IED is supported by a number of data sets from family (Coccaro, Lee, & Kavoussi, 2010), neurobiological (Coccaro, Lee, & Kavoussi, 2009), neuroimaging (Coccaro et al., 2007; Cremers et al., 2016; McCloskey et al., 2016), and treatment (Coccaro, Lee, & Kavoussi, 2009) studies. Perhaps most important are data suggesting that IED represents a taxon (Ahmed, Green, McCloskey, & Berman, 2010) and not simply the presence of elevated levels of impulsive aggression, even though aggression, itself, is a dimensional construct. This is likely because IED represents impulsive aggression with a specific set of features that includes clinically significant distress and/or impairment and not simply a high aggression score. While the prevalence of IED by DSM-5 criteria is not known at this time, the prevalence of IED by DSM-IV criteria was conservatively estimated at 5.4% lifetime and 2.7% for the past year (Kessler et al., 2006). Reanalysis of these data using integrated research criteria (on which the DSM-5 criteria were based) estimates the lifetime prevalence at 3.6% and the past year prevalence at 2.2% (Coccaro, Fanning, & Lee, 2017). Since the survey data (Kessler et al., 2006) generating these estimates did not include assessment of high-frequency, low-intensity verbal/nondestructive outbursts, which can be present in the absence of low-frequency, high-intensity destructive/assaultive outbursts that were the hallmark of DSM-IV IED (Coccaro et al., 2014), both sets of numbers represent an underestimate of the prevalence of IED. Thus, DSM-5 IED represents a sizable group of potential patients for which antiaggressive pharmaceuticals could be developed. In addition to those meeting DSM-5 criteria for IED, one could also consider developing antiaggressive pharmaceuticals for individuals with impulsive aggression due to secondary causes (e.g., schizophrenia, bipolar disorder, and traumatic brain injury). In these cases the DSM-5 IED criteria can still be used to identify such individuals as long as all subjects in the trial meet all but the exclusionary criteria and belong to an identifiable group of subjects.

B Development of Clinical Trials Testing Antiaggressive Efficacy

Reviewing the evolution of the clinical psychopharmacology of impulsive aggressive behavior, the first notable study was a double-blind, placebo-controlled trial of lithium in prison inmates (Sheard et al., 1976). The rationale was based on preclinical data suggesting that

lithium had antiaggressive effects in rodents (Sheard, 1970). Work in clinical pharmacology then languished until the availability of the 5-HT selective reuptake inhibitor (SSRI), fluoxetine. At that time, the idea that a 5-HT agent could have antiaggressive efficacy was predicated on substantial and consistent psychobiological data suggesting central 5-HT system hypofunction was associated with impulsive aggressive behavior (Brown et al., 1979; Coccaro et al., 1989; Linnoila et al., 1983). Soon after, an open label study with fluoxetine was published in patients with DSM-IIIR borderline personality disorder (Norden, 1989). This was followed by a small placebo-controlled, double-blind study of the effect of fluoxetine on anger in the same types of patients. Each paper suggested antiaggressive effects of fluoxetine, which led to the first double-blind, placebo-controlled study of fluoxetine in individuals with prominent histories of impulsive aggressive behavior (now defined as IED). This study was preceded by work to determine the optimal structure of antiaggressive trial (Coccaro, Harvey, Kupsaw-Lawrence, Herbert, & Bernstein, 1991). Most importantly, this work involved the development of outcome measures and led to the modification of the overt aggression scale (OAS; Yudofsky, Silver, Jackson, Endicott, & Williams, 1986), which was developed for inpatient settings, for outpatient trials (OAS-M; Coccaro et al., 1991). In addition, issues related to how to enter appropriate subjects into such studies and study duration needed to be addressed. For this first study (Coccaro & Kavoussi, 1997), the investigators selected personality-disordered subjects who scored above a relevant threshold on a measure of aggression (later, this approach was replaced by a current diagnosis of IED and a sufficiently high score on the OAS-M). To limit the number of potential "placebo responders," threshold scores on the OAS-M were required during a single-blind, 2-week, placebo lead-in phase prior to randomization. To allow a long enough period to see reliable antiaggressive effects, the investigators set the randomization phase at 12 weeks. Overall, antiaggressive effects in the fluoxetine group appeared within the first few weeks and continued through to the end of the trial in completers and in all subjects in a last observation carried forward analysis (LOCF; Coccaro & Kavoussi, 1997; Coccaro, Lee, & Kavoussi, 2009). While encouraging, attrition in both groups was about 50% by the end of trial, suggesting that impulsive aggressive subjects constitute a difficult group for an extended clinical trial. Two later trials confirmed the antiaggressive efficacy of fluoxetine (George et al., 2011; Silva et al., 2010). In addition, other studies have added further insight into the antiaggressive efficacy of fluoxetine. First, a small study reported a positive correlation between prolactin responses to pharmacochallenge with d-fenfluramine (PRL[d-FEN]) before study and the antiaggressive response manifest by OAS-M scores at the end of the trial (Coccaro, Kavoussi, & Hauger, 1997). This finding suggested that the more dysfunctional the 5-HT system (as reflected by PRL[d-FEN]), the lower the antiaggressive response was to fluoxetine. Given that the magnitude of the PRL[d-FEN] response is related to stores of newly synthesized 5-HT and to the sensitivity of postsynaptic 5-HT receptors (Coccaro, Kavoussi, Cooper, & Hauger, 1998), it is reasonable to posit that the more dysfunctional the 5-HT synapse, the less effective an SSRI will be as an antiaggressive agent. A second study (Silva et al., 2010) reported that subjects carrying the ss allele for the 5-HT transporter protein (5-HTT; a genotype associated with the production of a limited number of 5-HTT) responded less well to fluoxetine. This is not surprising because fluoxetine binds to 5-HTT and, thus, the fewer 5-HTT proteins, the lower degree of entry of 5-HTT blockade and the lower the SSRI enhancement of synaptic 5-HT. In addition, there is an inverse relationship between platelet 5-HTT number and aggression scores, indicating that a lower number of 5-HTT proteins are associated with both aggression (Coccaro, Lee, & Kavoussi, 2009) and a weaker clinical response to an SSRI intervention (Silva et al., 2010). A third study reported that antiaggressive responses to fluoxetine (a placebo arm was not included) were associated with increased activation of prefrontal cortical regions with the PET ligand fludeoxyglucose (FDG; New et al., 2004). Consistent with this finding are preliminary data suggesting that, compared with placebo, putative antiaggressive agents (fluoxetine and divalproex) reduce the fMRI BOLD response to angry faces in the amygdala and tend to rebalance the relative activation to angry faces between the amygdala (lower) and prefrontal cortex (Coccaro, Fanning, Phan, & Lee, 2015).

These data provide a number of insights into issues of relevance for the design of antiaggressive clinical trials. First, it is advisable to test agents that act on neuronal systems shown to have an influence in aggressive responding, as was exemplified by the first clinical trials of fluoxetine. Specifically, since SSRIs attach to the 5-HTT, the possibility that more aggressive individuals will have fewer 5-HTT proteins than less aggressive individuals means that SSRIs may not be very efficacious in those with moderate to severe aggression histories. Add to this the likelihood that postsynaptic 5-HT receptors are increasingly less responsive to increases in synaptic 5-HT the more aggressive the individual, the more likely that other, non-SSRI, interventions need to be investigated. This could mean selective 5-HT receptor agonists, such as lorcaserin, a 5-HT2$_c$ receptor agonist developed for weight management (Greenway, Shanahan, Fain, Ma, & Rubino, 2016). This could also mean other agents targeting other neurotransmitter/modulator systems, such as vasopressin, oxytocin, glutamate, GABA, and inflammatory cytokines.

III EXPERIMENTAL MEDICINE APPROACHES TO THE DEVELOPMENT OF ANTIAGGRESSIVE AGENTS

The risk and cost of developing or even repurposing potential antiaggressive agents, like other psychiatric drugs, are very high. The success rate for psychiatric drugs once an IND is obtained is 6.2%, which is lower than the overall 9.6% approval rate across all therapeutic classes (Thomas et al., 2016). The cost of new drug development is controversial, with recent estimates for the pharmaceutical industry reaching $2.6 billion (DiMasi, Grabowski, & Hansen, 2016). This figure has been challenged because it includes the "cost of failures" and the "cost of capital." The latter was calculated at 10.5% per year and accounts for $1.163 billion, or 44%, of the $2.6 billion figure (Avorn, 2015). Estimates for the cost of a single successful compound that allow for the cost of failure are slightly less than $200 million, although this figure does not include in-kind contributions from academic and philanthropic groups (DNDi, 2013). Regardless, the cost is very high, years of effort are required, and the risk/reward ratio is poor. This raises the question of whether experimental medication approaches can improve the development process. First, whether an agent is likely to exhibit antiaggressive properties quickly or only after a period of adaptation, like many psychotropics in the thymoleptic space, should be determined. If the agent is expected to rapidly exhibit benefit, a simple experimental study in which one dose of the agent is given and its effect on an aggression measure can be assessed at its peak exposure level, Cmax. These studies would be strengthened with a pharmacodynamic approach that incorporates assessments over a specified time period based on pharmacokinetic data. This is particularly important for CNS agents because PK based on circulating levels of a drug in blood and brain PK may differ. Studies in animals are critical in this context given the significant cost of a human brain PK study (if such work can be undertaken).

If the agent is expected to work over time, then the study should include a pretreatment phase of at least 2 weeks after which the aggression measure is used. While agents that should work over weeks (e.g., SSRIs, lithium, divalproex, and related thymoleptics) might require subchronic treatment, SSRIs typically suppress aggression acutely in analog laboratory paradigms (see in the succeeding text). Agents that might work immediately include those that stimulate or block the actions of amine (e.g., GABA) or peptide (e.g., VASO) neurotransmitter/neuromodulators. It is also important to note that such studies must include a placebo control. When assessing the acute antiaggressive effect of an agent, a within-subject design provides for the most power. This is more difficult, of course, when assessing the subacute effects. In this case, investigators are likely to be constrained to a parallel group design, which requires more subjects and resources compared with a study testing for an acute antiaggressive effect.

Second, what measure of aggression should be used in experimental medicine studies? Here, it is important to note that it is nearly impossible to observe impulsive aggressive behavior in a controlled setting. Even the most impulsively aggressive individuals can keep their behavior "under control" in a laboratory environment unless exposed to a sufficiently provocative social threat. This latter situation is fraught with difficulty due to not only issues of research ethics (i.e., deliberately provoking aggressive responses leads to intense scrutiny by Institutional Review Boards) but also the limitation that provocation scenarios are difficult to standardize across subjects. If frank provocation is not allowed, it is very unlikely that a change in aggressive behavior will be observed in the course of short-term exposure to a putative antiaggressive agent. Thus, other kinds of assessments are needed when designing an experimental medicine design to assess antiaggressive efficacy.

Measures of aggression fall into three basic categories: (a) paper and pencil assessments, (b) clinical rating assessments, and (c) analog laboratory assessments. Before detailing the ways in which aggression can be assessed, we should reiterate that it is very difficult to observe impulsive aggressive behavior in a controlled setting. Paper and pencil assessments are simple to administer but are typically trait measures of behavior not likely to manifest sufficient change for use in experimental medicine studies. Altering the time scale of a trait measure (e.g., from "in general" to the "past week"), however, does not typically improve the measure's performance for clinical trials because the statements subjects rate themselves on are inherently trait in nature. This is not necessarily true for measures of emotional states such as "anger" because these are designed to demonstrate change over short time intervals. That said, "state anger" is not the same as "aggression," even if these measures are strongly correlated.

Clinical rating assessments for aggression are few in number and have their own limitations. The assessment used in most clinical trials is the OAS-M (Coccaro et al., 1991). The assessment scale was modified to provide a frequency/severity weighted assessment of overt aggressive behavior across verbal aggression, aggression against objects, others, and self. The OAS-M Aggression score has good internal consistency ($\alpha = 0.78$; unpublished data) and excellent interrater reliability (kappa $>$ 0.95; (Coccaro et al., 1991; Endicott, Tracy, Burt, Olson, & Coccaro, 2002) and has been used in several clinical trials of impulsive aggression (Coccaro & Kavoussi, 1997; Coccaro, Lee, & Kavoussi, 2009; George et al., 2011; Hollander et al., 2003; McCloskey, Noblett,

Deffenbacher, Gollan, & Coccaro, 2008; Silva et al., 2010). Despite this, OAS-M Aggression scores can vary substantially when assessed weekly. This is because impulsive aggressive behaviors vary with the number of social threat stimuli individuals are exposed to over short time periods. This reduces the power of the OAS-M Aggression score as an outcome measure for experimental medicine studies investigating acute antiaggressive effects. On the other hand, OAS-M Aggression scores represent a good outcome measure in studies designed to assess the antiaggressive effects of a drug over weeks to months.

There are currently only two analog laboratory measures of aggression, both of which were developed 20 or more years ago. The first is the Taylor Aggression Paradigm (TAP; Taylor, 1967), and the second is the point-subtraction-aggression paradigm (PSAP; Cherek, 1981). In both paradigms, provocation is standardized and not specific to the subject, which can be the case in anger provocation scenarios (Spoont, Kuskowski, & Pardo, 2010).

In the TAP, the provocation is a mild electric shock given to the subject when he/she loses a reaction time trial. The shock levels are individually tailored and never set above 90% of the shock level the subject deems "uncomfortable." Because electric shock is a physical stimulus, it is considered analogous to a physical threat to the subject. Because this occurs in the context of a social setting, it represents a physical social threat. The "cover story" given to the subject is that the strength of the shock was selected by the person they are paired with. While the subject never meets this person, the activity occurring around the subject supports the cover story they are paired with a real person. During the TAP, the strength of the shocks are increased over time, and subjects can increase, decrease, or not change the strength of shock they select to be delivered to the other person when that other person loses a reaction time trial. Generally speaking, higher shock levels from the other person lead to higher shock levels selected by the subject. We have found that impulsively aggressive subjects with IED set significantly higher shocks compared with healthy volunteers or nonaggressive psychiatric controls, clearly supporting the idea that mean shock levels set against the other person during the TAP reflect aggressive responding (Giancola & Parrott, 2008). Most important for the purpose of experimental medicine studies, the TAP has been used extensively to test the effect of various agents on aggression. All such TAP studies have been done as parallel group designs due to a desire to administer the TAP to subjects only once even though this increases the number of subjects needed compared to a within-subject design. In response to this concern, we have repeated the TAP on four occasions over 3 months and have found that aggressive responding during the TAP is quite stable. Accordingly, our data suggest that the TAP can be used effectively in a within-subject design. To date, the TAP has been utilized to examine antiaggressive effects of various agents including the SSRI, paroxetine (Berman, McCloskey, Fanning, Schumacher, & Coccaro, 2009).

In the PSAP, the provocation is the loss of earned points worth a minimal amount of money (e.g., 10 or 25 cents). Again, subjects are paired with another person. Both people are set in front of monitor and a "button box" and are tasked with pressing button "A" as many times as they can during a 25-minute session. One hundred presses of the "A" button earn the subject a point (exchangeable for money at the end of the study). At the same time the "other person" can press Button "B" ten (10) times and take a point from the other subject who pressed100 times. This provocation is experienced as a frustration/obstacle social threat rather than as a physical social threat. In turn, the subject can do three things: (a) ignore the point loss and continue to press the "A" button, (b) press the "B" button ten times and cause the other person to lose a point (aggressive option), or (c) press the "C" button ten times and be protected from further point loss for a variable period of time ("escape option"). Selecting either button "B" or "C" protects the subjects from further point loss of a time. The number of "B" presses is the index of aggressive responding (Cherek, Moeller, Schnapp, & Dougherty, 1997), though we have had clearer results when using the ratio of "B" button responses to "All" button responses. Unlike the TAP, the PSAP has been used in within-subject designs when exploring the effect of pharmaceuticals on aggression. To date, the PSAP has been utilized to examine antiaggressive effects of various agents such as d-fenfluramine (Cherek & Lane, 2001) and paroxetine (Cherek, Lane, Pietras, & Steinberg, 2002), among others. While we have found that the TAP and PSAP correlate with other measures of aggression, these correlations are modest. In addition, TAP and PSAP are weakly correlated, which may be due to the likelihood that they reflect different aspects of aggression; that is, aggression in response to a physical social threat versus a frustrating/obstacle social threat.

To date, TAP and PSAP protocols have largely been used to assess the role of drugs of potential abuse on aggression (e.g., alcohol, opiates, and cocaine). That said, some studies have been conducted using agents of interest in the treatment of aggression including agents related to 5-HT—paroxetine (Berman et al., 2009), fenfluramine (Cherek & Lane, 2001), and ipsapirone (Moeller et al., 1998)—and to GABA: baclofen (Cherek, Lane, Pietras, Sharon, & Steinberg, 2002), gabapentin (Cherek, Tcheremissine, Lane, & Pietras, 2004), and tiagabine (Lieving, Cherek, Lane, Tcheremissine, & Nouvion, 2008), with each showing evidence of acute antiaggressive effects. Except for the SSRIs, however, none of these

agents have advanced to Phase II clinical trials. While similar studies involving intranasal administration of vasopressin (Brunnlieb et al., 2013) or oxytocin (Alcorn 3rd., Rathnayaka, Swann, Moeller, & Lane, 2015) have yet to demonstrate evidence of antiaggressive effects, these studies were performed in nonaggressive healthy individuals in whom it would be difficult to observe pro- or antiaggressive effects.

Recently, we began pilot work using the TAP and PSAP in the context of experimental medicine studies of potential antiaggressive agents based on our own neurotransmitter-based studies (e.g., aprepitant for substance P and lorcaserin for 5-HT2_c). In order to create a protocol that is feasible in a single day, we administer the drug in question in the morning, wait until the drug is presumed to reach Cmax, and then ask the subject to complete a TAP session and a PSAP session each of which takes about 45 minutes start to finish. While much work with the PSAP has involved multiple sessions a day over several days, a single session is sufficient for an experimental medicine study (Golomb, Cortez-Perez, Jaworski, Mednick, & Dimsdale, 2007).

Another approach to drug development is to design a program that aligns preclinical and experimental medicine studies. The strength of this paradigm is in its potential to allow extensive neurobiological studies in preclinical models that can then inform the experimental medicine translational study design. The opportunity to use this approach to derisk potential antiaggressive agents and thus impact development time and costs has been enhanced with the now routine availability of imaging technologies that can be used in awake nonhuman species and in humans.

Two studies that are part of the development program for SRX246, a new V1a receptor antagonist that is being tested for the treatment of anger, aggression, and irritability in multiple indications (see clinicaltrials.gov: NCT02055638 for the treatment of intermittent explosive disorder, NCT02507284 for the treatment of Huntington's disease, and NCT02733614 for the treatment of PTSD), exemplify the potential utility of aligning preclinical and experimental medicine studies. SRX246 and a highly similar compound, SRX251, significantly reduced aggression in rats when given orally or by IP injection (reviewed in Simon et al., 2008; Fabio et al., 2010). In a subsequent fMRI study in awake animals, rats receiving these compounds had significantly reduced BOLD activation in circuits known to mediate responses to threat and drive aggression (Ferris et al., 2008). After an IND for SRX246 was received and Phase I clinical trial data established safety, an experimental medicine fMRI study was designed based on the preclinical findings (Lee et al., 2013). The results showed that while intranasal arginine vasopressin (AVP) administration led to an exaggerated BOLD response to angry faces in regions recognized for their involvement in responses to fear and negatively valanced emotional stimuli, treatment with oral SRX246 (120 mg BID in capsules) significantly attenuated BOLD activation seen in response to VASO. Among the major sites where SRX246 treatment blunted the change in BOLD signal seen in response to AVP were the amygdala, anterior cingulate cortex, and temporoparietal junction, all regions that are part of a neural circuit implicated in excessive aggression, fear, and the processing of emotional stimuli (Coccaro, Kavoussi, Cooper, & Hauger, 1998; Coccaro, Kavoussi, Hauger, et al., 1998; Hayes, Vanelzakker, & Shin, 2012; Price & Drevets, 2012). Studies in the rhesus monkey brain and postmortem human brain have shown that these regions, as well as other parts of the limbic system and cortex, are enriched in V1a receptor (Lu, Simon, Palkovits, & Brownstein, 2013; Young, Toloczko, & Insel, 1999). The experimental medicine fMRI study provided a well-powered, lower-cost, more rapid test of potential therapeutic utility compared with a small POC Phase II trial. The results also provided validation in terms of circuitry where the compound exerted its effects, which provided important mechanism of action data. These observations not only reduce the development risk for the compound but also provided a strong basis for further development of V1a receptor antagonists as a novel treatment for irritability/aggression.

In addition to the importance of assessing the behavioral effects of potential antiaggressive agents, the Lee et al. (2013) study demonstrates that experimental medicine studies also can be enhanced by assessing the effects of the agents in question on functional brain outcome measures. We suggest that after TAP/PSAP sessions are completed, subjects receive MRI scanning to assess changes in corticolimbic activation to relevant stimuli (e.g., anger faces and videos of ambiguous social interactions that result in an aggressive encounter, such as the V-SEIP) associated with administration of the agent in question. For example, we have found that chronic exposure to antiaggressive agents suppresses amygdala responses to angry faces (Coccaro, Fanning, Phan, & Lee, 2015) and that acute exposure to an SSRI (s-citalopram) is associated to a reduction in fMRI BOLD activation in the TPJ (Cremers et al., 2016). While the latter study was not coupled with a simultaneous laboratory assessment of aggression, experimental medicine studies should include some form of functional neuroimaging to more robustly link potential behavioral effects to the agent being tested. Thus, antiaggressive effects appearing in experimental medicine studies for a particular agent, particularly if they are coupled with the expected changes in corticolimbic function (e.g., blunting of amygdala and enhancement of prefrontal responses to emotional stimuli), should provide the rationale to conduct a Phase II clinical trial of that agent.

IV CONCLUSION

As the scientific understanding of impulsive aggression has evolved, the opportunity has arisen to apply a translational medicine approach to the development of treatments of impulsive aggression. A neural circuit model, combined with the psychological model of social and emotional information processing, allows for the targeting of neural circuits involved in the impulsive aggressive responding with biological interventions. Past experience with this population has led to the recognition that a sophisticated approach is required in designing clinical trials in this population. Critical issues regarding measurement of impulsive aggressive behavior in human research volunteers must be addressed in the design of such clinical trials. Some of the difficulties inherent in measuring the change of aggressive behavior over time may be addressed with innovative approaches, such as the measurement of laboratory analogues and functional markers of neural circuit activation.

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