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Neuropharmacology of attention

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Abstract

Early philosophers and psychologists defined and began to describe attention. Beginning in the 1950's, numerous models of attention were developed. This corresponded with an increased understanding of pharmacological approaches to manipulate neurotransmitter systems. The present review focuses on the knowledge that has been gained about these neurotransmitter systems with respect to attentional processing, with emphasis on the functions mediated within the medial prefrontal cortex. Additionally, the use of pharmacotherapies to treat psychiatric conditions characterized by attentional dysfunction are discussed. Future directions include developing a more comprehensive understanding of the neural mechanisms underlying attentional processing and novel pharmacotherapeutic targets for conditions characterized by aberrant attentional processing.

Keywords

attention; neurotransmitter; prefrontal cortex; vigilance

1. Brief history of constructs of attention and neuropharmacology of attention research.

Attention is a construct that originally was examined by philosophers. Early philosophers tended to identify attention as a process that was crucial for keeping thoughts organized (Tsotsos et al., 2005). These ideas were built upon by considering attention as a requirement for stimuli to move from unconsciousness into awareness. As behaviorism dominated in the first half of the 20th century, fewer researchers examined attention as a psychological construct due to the emphasis on observable behaviors. Beginning around the 1950's several models of attention were proposed. Broadbent (1958) offered a relatively more integrated theory of attentional processing which included processing limits of cognitive systems and emphasized relatively early aspects of information processing. Many other theorists have described attention as a filter of information processing in other forms, including in later processing stages (Cherry, 1953; Deutsch & Deutsch, 1963; Grossberg, 1975; Moray, 1969;

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Treisman, 1969). Posner (1980) went on to identify different components of attentional processing, including alerting, orienting, and search, along with overt or covert control of gaze. Subsequent ideas about attention as a spotlight that could be controlled was described in the mid-1980's by Crick (1984). Collectively, the emphasis on attention has moved from a more general process to understanding the components of this process.

The historical record provides many examples of writings about concoctions designed to treat illnesses, including to enhance cognition (Norton, 2005), thus suggesting that rudimentary forms of pharmacology have long taken place. More modern pharmacology research ensued following the seminal work by Otto Loewi demonstrating a chemical basis for neurotransmission (Loewi, 1961) along with experiments by Dale and colleagues (Dale et al., 1936). Daniel Bovet and others used rationale-based approaches for studying pharmacological processes, by studying the chemical synthesis of particular compound and related compounds and then studying the agonist or antagonist properties of these compounds (Bovet, 1950). The approaches of these researchers laid the groundwork for more contemporary approaches to study how drugs can affect the neural mechanisms underlying some cognitive processes, including attention. Much of the early work to understand brain mechanisms underlying attention employed neuroanatomical or neurophysiological approaches. The upcoming sections describe some of the progress using neuropharmacological techniques to more fully understand the neural basis of attention and how alterations of neurotransmitter systems can impact attentional processing.

2. Neuropharmacological research regarding attention.

2.1. Animal models of attention.

Attentional function is an integral component of cognition and is modulated by neurotransmitter systems throughout several brain structures. Understanding the patterns of normal and abnormal function of these neurotransmitter systems provides insight into attentional processes and the pathology of disorders characterized by attentional dysfunction. Studies examining attention using human participants are able to address more complex aspects of attention and to understand forms of attentional dysfunction using clinical populations. Because of this, attention research involving humans is key to furthering our understanding of the nuances of attentional processes. However, human research on attention has limitations which can be addressed in research using animal models. With animal models, we can examine the relevant brain structures supporting attention and manipulate the neurotransmitters involved in these areas, which furthers our insight into the neural systems of attention and can be applied to disorders of attentional dysfunction, such as Alzheimer's disease and Attention Deficit/Hyperactivity Disorder (ADHD).

Tasks designed to measure attention in animals provide an objective assessment of attentional performance across studies and labs. The 5-choice serial reaction time task (5CSRTT) developed by Robbins and colleagues has been widely used in attentional research involving rodents, and is designed similarly to the continuous performance tests used in clinical populations to assess ADHD and attentional deficits in schizophrenia (Robbins, 2002; Rosvold et al., 1956). The task requires rats to sustain visuospatial attention

to several targets over a testing session (Robbins, 2002). Typically, rats must respond to a brief visual stimulus in one of five holes, within an arc of nine holes, in order to receive a food reward. Accuracy and response latency can also be measured in the 5CSRTT to give insight into component processes such as decision-making time or motivation. The task can be modified in terms of number of choices, brightness and duration of stimulus, and presentation of distracters, such as a burst of white noise. Another commonly used measure of attention is a sustained attention task, developed by McGaughy and Sarter (1995). The task requires responses to the presentation of a brief variable visual signal by pressing one lever and the absence of a visual signal by pressing another lever in order to receive reward access. Accuracy on signal trials is measured as relative hits, or the number of correct lever presses following a signal divided by the number of correct and incorrect lever presses. Accuracy on non-signal trials is measured as relative correct rejections, or the number of correct lever presses following no signal presentation divided by correct and incorrect lever presses. The task can be modified to vary signal duration and inter-trial intervals. A house light can be flashed for the purpose of increasing the attentional demands of the task. The 5CSRTT and the sustained attention task are used widely in the literature on attention, and the effects of pharmacological manipulations in brain regions integral to attention are assessed using these tasks, which provides further insight to the mechanisms underlying attentional processes.

The medial prefrontal cortex (mPFC) in rodents is thought to be important for attentional function as well as other higher cognitive processes (Cordova et al., 2014; Robbins, 2002). This region corresponds to the dorsolateral prefrontal cortex in humans and primates, which is an area responsible for processes, such as working memory and preparatory attention (Uylings et al., 2003; Vertes, 2006). Electrophysiological studies using rodents have demonstrated increased activity in the mPFC during the sustained attention task and a modified version of the 5CSRTT, suggesting the importance of this area for attention (Gill et al., 2000; Totah et al., 2009). Increases in neuronal activity in the mPFC are also observed following the presentation of distracters during sustained attention tasks (Gill et al., 2000; Passetti et al., 2000). Furthermore, lesions to the mPFC and to neurotransmitter systems innervating this region result in severe deficits in attention and response inhibition (Broersen & Uylings, 1999; Gill et al., 2000; McGaughy et al., 2002).

2.1.1. Neurotransmitter systems involved in attention.—To further understand the role of the mPFC in attention, neuropharmacological techniques can be employed, allowing direct manipulation of the neurotransmitter systems active in the mPFC, and through these manipulations, changes in attentional performance can be observed. Several neurotransmitter systems project to the mPFC and influence attention.

2.1.1.1. Acetylcholine.: Cholinergic innervation of the mPFC is crucial for attentional performance (Bloem et al., 2014). Studies using microdialysis in rodents have observed increases in acetylcholine (ACh) efflux in the mPFC during the 5CSRTT (Dalley et al., 2001; Passetti et al., 2000). Similar increases in ACh efflux have been found during the sustained attention task, with one study finding a 140% increase in ACh levels during the task, as compared with a 50% ACh efflux during control tasks (Arnold et al., 2002). These

increases in ACh release are not associated with increased attentional performance; however, there is some evidence that ACh increases may instead be related to increased attentional effort (Himmelheber et al., 2000; Kozak et al., 2005). The specific role of ACh in attentional function can be examined with lesions to cholinergic inputs to the mPFC, using the immunotoxin 192 immunoglobulin G (IgG) saporin. Increases in mPFC ACh efflux related to attention are no longer present following cholinergic lesions (Gill et al., 2000). These cholinergic lesions lead to severe deficits in performance on both sustained attention and 5CSRTT-related tasks (Dalley et al., 2004; Gill et al., 2000; McGaughy et al., 2002).

Pharmacological studies can examine the specific roles of ACh receptors (AChR) within the mPFC through intracranial infusions of AChR agonists and antagonists. Evidence suggests that both nicotinic ACh receptors (nAChRs) and muscarinic ACh receptors (mAChRs) in the mPFC aid in attentional processes (Chudasama et al., 2004; Hahn et al., 2003; Hahn et al., 2011; Robbins, 2002). Hahn et al. (2003) found that bilateral infusions of nicotine, a nAChR agonist, into the mPFC of rodents resulted in increases in performance on the 5CSRTT, suggesting a specific role of nAChRs in attention. Another study used a more selective approach by administering methyllycaconitine (MLA), an alpha-7 nAChR (α7nAChR) antagonist (Hahn et al., 2011). Blockade of α7nAChRs dose-dependently decreased attentional performance; however, the lowest dose of MLA improved attention, suggesting an inverted U-shape dose-response. The beta-2 nAChR (β2nAChR) subunit expressed in the mPFC is also thought to be critical for attention, as genetic deletion of β2nAChRs induces impairments in attentional performance (Guillem et al., 2011). Acute systemic administration of nicotine increases attentional performance in rats, primates, and humans, and chronic nicotine administration in rats results in improved attention, illustrating the importance of ACh in attention (Bentley et al., 2004; Semenova et al., 2007; Thiel et al., 2005; Witte et al., 1997). However, withdrawal from chronic administration of nicotine in rats results in decreased attentional performance (Semenova et al., 2007). The role of mAChRs in mPFC-mediated attention has been examined as well, showing that intracranial mPFC administration of scopolamine, a mAChR antagonist, increases omissions in the 5CSRTT (Chudasama et al., 2004). Systemic administration of scopolamine in rodents resulted in similar attentional impairments, characterized by decreased accuracy, increased omissions, and increased distractibility (Jones & Higgins, 1995).

2.1.1.2. Dopamine.: Dopaminergic activity in the cortex is associated with key components of cognition, specifically working memory and attentional function in humans, primates, and rodents (Cai & Arnsten, 1997; Granon et al., 2000; Robbins, 2000). Systemic and mPFC administration of dopamine (DA) receptor agonists has been found to alleviate symptoms of attentional dysfunction, such as those seen in ADHD, and DA-based therapies are often used to treat ADHD (Granon et al., 2000; Wender et al., 2001). One study found that infusions of the partial dopamine-1 receptor (D_1R) agonist SKF 38393 into the mPFC led to improvements in response accuracy on an attentional task, while mPFC infusions of the D_1R receptor antagonist SCH 23390 resulted in attentional impairments (Granon et al., 2000). Interestingly, the actions of both pharmacological treatments were baseline specific. SKF 38393 improved performance for rats with low baseline accuracy (<75%) and had no effect on rats with high baseline accuracy (>75%). Similarly, the D_1 receptor antagonist

SCH 23390 only decreased performance for those rats with high baseline accuracy. In the same study, the role of dopamine-2 receptor (D2R) in the mPFC on attention was examined, and following intra-mPFC infusions of the D2R antagonist sulpiride, no changes in attentional performance were observed. Another study found that intra-PFC infusions of a different D_1R agonist, SFK 81297, resulted in improved attentional performance on the 5CSRTT for both medium and high doses of the agonist; however, the lowest doses did not affect attentional performance (Chudasama & Robbins, 2004). These studies suggest a clear role of D_1Rs, but not D_2Rs, in modulating attentional function.

2.1.1.3. Norepinephrine.: The role of cortical norepinephrine (NE) on attention can be difficult to tease apart from that of DA, as both are catecholamines and pharmacological treatments aimed at improving attention often influence both NE and DA activity. Atomoxetine and methylphenidate are common pharmacological treatments for ADHD, and act as both NE reuptake (NET) and DA transporter (DAT) inhibitors, thus extending the availability of extracellular NE and DA (Bradshaw et al., 2016). Atomoxetine blocks NE reuptake at all doses, but only has been found to inhibit DAT at high doses, while methylphenidate blocks both NET and DAT at all doses. Lower doses of methylphenidate administered to the mPFC have been found to substantially increase NE and DA efflux, resulting in increased ability to perform attention-related tasks (Berridge et al., 2006; Bradshaw et al., 2016). Bradshaw and colleagues (2016) found methylphenidate-mediated attentional improvements to occur only in rats who were previously unable to perform at criterion on an attentional set shifting task, while normal rats were unaffected. This finding provides evidence for the efficacy of these psychostimulants in populations with attentional deficits at restoring attentional functioning.

2.1.1.4. Glutamate and γ-aminobutyric acid.: Glutamate and γ-aminobutyric acid (GABA) are excitatory and inhibitory neurotransmitters, respectively, and influence processes throughout the cortex, including attention (Henny & Jones, 2008). Within the mPFC, glutamate is thought to regulate set shifting ability and response inhibition (Murphy et al., 2005; Stefani et al., 2003). The glutamatergic receptor subtypes, *N*-methyl-D-aspartate (NMDA) and alpha-amino-3-hydroxy-5methylisoxazole-4-propionic acid (AMPA), have both been found to influence set shifting (Stefani et al., 2003). Infusions to the mPFC of the NMDA antagonist, MK-801, and the AMPA antagonist, LY293558, result in decreased ability in rats to perform a set shifting task, and NMDA hypofunction specifically inhibits the ability to adjust and inhibit responses, which are important components of attention. Furthermore, intra-mPFC infusions of other NMDA antagonists, M100907 and 3-((*R*)-2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid [(R)-CP], result in attentional impairments in performance on the 5CSRTT (Mirjana et al., 2004; Murphy et al., 2005). These findings suggest that the excitatory role of glutamate enhances attentional function within the mPFC. GABA plays a role in modulating attention through inhibitory effects on cholinergic projections from the basal forebrain (BF) to the mPFC (Moore et al., 1995). Administration of an inverse agonist at the GABA receptor benzodiazepine site within the BF enhanced ACh efflux to the cortex, while BF administration of a benzodiazepine agonist inhibited ACh release to the cortex. In rodents with loss of cortical cholinergic inputs, benzodiazepine inverse agonists improved performance on the sustained attention task for rats with between

50–70% loss of cholinergic inputs (Sarter & Bruno, 1997). This attentional inhibition is further illustrated by systemic administration the of benzodiazepine agonist chlordiazepoxide (CDP), which was found to decrease the ability for rats to discriminate between signal and non-signal trials on the sustained attention task (McGaughy & Sarter, 1995). These studies show that GABA agonists can decrease attentional performance, potentially through inhibition of cortical ACh release.

2.2. Attentional deficits in psychiatric illness.

In humans, attentional function is reliant on a number of interconnected brain networks in the cortex and subcortex. For instance, Mesulam (1981) details numerous interrelated regions which are intimately involved in directed attention and vigilance – encompassing reticular, limbic, parietal, and frontocortical formations – which together create a widespread anatomical network that is responsible for many aspects of attentional processing. Event-related functional magnetic resonance imaging (fMRI) findings from Hopfinger et al. (2000) suggest that the activation of the superior frontal, inferior parietal, and superior temporal cortices directly modulates extrastriatal cortical excitability and, in doing so, facilitates top-down control of voluntary, spatially-selective visual attention. Sarter and colleagues (2001) also emphasize the integral role of prefrontal and parietal inputs, particularly in the right hemisphere, for sustained vigilance. Adequate dopaminergic neurotransmission in the PFC is critical for sustained attentional performance, with Puumala and Sirviö (1998) discerning right frontocortical DA utilization as being strongly correlated with choice accuracy in a task necessitating prolonged vigilance. Corticopetal projections from the BF are integral to normal attentional processing as well, especially in the context of attentionally-taxing circumstances; in fact, while the lesioning of BF cortical innervations substantially disrupts prolonged focus, the integrity of these neurons does not necessarily facilitate or contribute to accuracy in tasks reliant on learning and memory, rather than attentional, processes (Voytko et al., 1994).

Attentional dysregulation is a defining and prominent symptom of several psychiatric conditions, and the frontal cortex is a dominant neural locus of these deficits. One disorder for which dampened attentional capacity is a defining symptom is ADHD. As detailed in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), intrusive inattentiveness, reduced behavioral inhibition, and impulsivity produce potentially profound impairments of occupational and social functioning. Children and some adults with ADHD demonstrate markedly reduced performance in cognitive tasks measuring attentional function, and many of these inaccuracies are attributed to reduced response inhibition and lack of impulse control, such as in stop-signal, go/no-go, and eye movement tasks (Barkley, 1997; Quay, 1997). Many of these inhibitory impairments can be explained by discrepancies in the ventrolateral, medial, and dorsolateral prefrontal cortical areas as well as in the anterior cingulate cortex (Booth et al., 2005). Similarly, shortened reaction times can result in decreased accuracy in tests of attention and on-task behavior for those with ADHD as well (Casey et al., 1997). People with ADHD have significant structural and functional abnormalities in several brain areas that are critical for normal attentional function. For example, a 4.7 percent reduction in total cortical volume, especially in the right frontal hemisphere, and about a 10 percent reduction in the frontal lobe and basal ganglia

have been reported in individuals with ADHD (Castellanos et al., 1996; Swanson et al., 1998). Depletions of both global and local connectivity efficiencies have been reported, most critically in prefrontal, temporal, and occipital regions in both the default mode network and rest-to-task transitions (Uddin et al., 2008; Wang et al., 2009). Hypofrontality, chiefly in the PFC, is key in the development of ADHD-related deficits in attentional performance, both neurologically and behaviorally (Rubia et al., 1999).

Psychostimulants are commonly prescribed to partially normalize the attentional dysfunction of frontostriatal circuitry for those with ADHD. By enhancing excitatory activity in the frontal cortex, these medications not only mitigate deficits in vigilance, but they also help to assuage impulse inhibition impairments that substantially impede upon sustained attention. A meta-analysis by Prasad and colleagues (2013) examining drug treatments that are frequently administered to children with ADHD, such as methylphenidate- and dextroamphetamine-derived compounds, suggests that these classes of drugs significantly improve on-task behavior, concentration, and, as a result, enhance accuracy in academic tasks. Medication interventions for children with ADHD tend to be more effective in alleviating the symptomology than behavioral therapy by itself, and a combination of pharmacotherapy and psychotherapy is not more efficient at decreasing cognitive deficits when compared to drugs alone, although functional and social outcomes may marginally benefit from the combination (Horn et al., 1991; Jensen, 1999). For adults, however, cognitive-behavioral therapy in conjunction with psychiatric medication proves beneficial in synergistically alleviating objective and subjective ADHD symptomatology (Emilsson et al., 2011; Safren, 2005). These findings collectively demonstrate that, by correcting the hypofrontality observed in ADHD, stimulant medications – especially for children – seem to be the most effective first-line treatment for the conduct, cognitive, and attentional challenges associated with this disorder.

Neurodegenerative disorders, including but not limited to Alzheimer’s disease (AD) and Parkinson’s disease (PD), are also associated with profound and progressive loss of cognitive abilities. In the early stages of dementia, subtypes of attention which require greater attentional effort, such as divided and selective attention, are markedly compromised, whereas normal and sustained attention are impaired once the degeneration advances (Perry & Hodges, 1999). One neuroanatomical explanation for the weakening of attentional capacity over time for those with dementia is the gradual loss of function of cortical pyramidal neurons and the degradation of BF cholinergic projections to the PFC, parietal lobe, and thalamus (Lawrence & Sahakian, 1995). Enhancement of frontocortical activity via subcortical cholinergic inputs is integral to all types of attention (Sarter et al., 2001), and the critical loss of these corticopetal fibers is detrimental for these processes. Because of this, it can be speculated that divided and selective attention may be more sensitive to the degradation of BF projections to the frontal cortex early in the disease progression, and sustained vigilance, being less susceptible to cholinergic degradation, would be lost in the later stages of AD and PD. In PD, gradual degeneration of the mesocortical DA system is especially emphasized and is inextricably implicated in the slow attentional and functional dilapidation associated with this disorder (Scatton et al., 1983). The notion of hypoactive or dysfunctional frontocortical responsivity has been further supported by fMRI studies revealing abhorrent parietal and frontal cortical activation in visual attention and visuospatial

tasks in either the left, right, or both hemispheres of those with dementia (Hao et al., 2005; Lewis et al., 2003).

Drugs which facilitate cortical cholinergic transmission are prescribed to address the gradual loss of cognitive and attentional function for those with AD and PD (Birks et al., 2009; Rolinksi et al., 2012); in doing so, the natural loss of cholinergic neuron functionality can be transiently overcome. Acetylcholinesterase inhibitors such as donepezil, rivastigmine, and physostigmine denature the enzymes which break down ACh, thereby boosting postsynaptic cholinergic activity and improving clinical outcomes in a dose-dependent manner (McGleenon et al., 2001). While this mechanism of action does not slow the degradation of cells within the basal forebrain cholinergic system, cognitive decline is temporarily halted due to the transient boost in cholinergic neurotransmission. In the context of vigilance, this drug class is more effective in alleviating attentional dysfunction than learning and memory deficits in AD, and these improvements have been observed in the right prefrontal and parietal cortices in the context of attention-dependent responses to visual stimuli (Bentley et al., 2008). Unfortunately, while anticholinesterase therapy can somewhat delay the attentional and general cognitive decline exhibited by individuals with dementing conditions, these compounds lose their effectiveness over time; as the BF and other brain regions continue to deteriorate over the course of the illness, artificially augmenting synaptic ACh eventually becomes unable to compensate for substantial cholinergic neuron loss. In this regard, targeting these neurons, while modestly and temporarily beneficial, has important limitations for treating AD and PD.

Schizophrenia (SZ), another chronic psychiatric condition wherein attentional functioning is diminished, is described in the DSM-5 as having a positive subset of symptoms, including hallucinations, delusions, and sensory disturbances, as well as a negative symptom group comprised of affective, cognitive (including attentional) and social dysfunction. Similarly with ADHD, AD, and PD, SZ is associated with a markedly hypoactive PFC, revealing a strong negative correlation between the severity of cognitive and social deficits and functional outcomes (Green et al., 2000). Regional cerebral blood flow studies from Ingvara and Franzén (1978) and Weinberger et al. (1988) reveal both reduced cerebral blood flow and dopaminergic neurotransmission in frontal regions, especially in the dorsolateral PFC, when compared to healthy controls, and sizeable augmentations in both blood flow and DA concentrations in subcortical structures. Excessive activation of excitatory receptors in the subcortex, primarily through elevated dopaminergic, glutamatergic, and cholinergic neurotransmission, is thought to underlie continual cortical overexcitement which – due to a compensatory biological response to chronic overstimulation – results in frontocortical underactivation (Davis et al., 1991; Moghaddam & Javitt, 2011; Sarter et al., 2005; Tandon & Greden, 1989).

The hypothesis that hyperdopaminergia in the subcortex and hypodopaminergia in the cortex greatly contribute to the psychopathology of SZ is supported by psychopharmacological findings which suggest that exposure to amphetamines, nicotine, and other drugs that directly stimulate mesolimbic and frontocortical DA-and ACh-releasing cells help to alleviate hypofrontality in the DLPFC of individuals with SZ (Dalack et al., 1999; Daniel et al., 1991). However, at high doses, these compounds have been found to induce psychosis-

like symptoms in healthy subjects and exacerbate the positive symptoms in those with the disorder, ultimately making them unviable long-term treatment options for SZ. In the opposite vein, both typical and atypical antipsychotic agents, such as olanzapine, risperidone, and quetiapine, assuage the activity of DA neurons and corticopetal dopaminergic afferents in an attempt to promote balanced dopaminergic neurotransmission throughout the brain (Lieberman et al., 2005; Nordström et al., 1993). Clozapine, another atypical antipsychotic that is frequently given to those with treatment-resistant SZ, is a cholinergic receptor antagonist that alleviates psychosis and related symptoms by lessening forebrain ACh release (Kane et al., 1988). While effective in decreasing positive symptomology, such as hallucinations and delusions, antidopaminergic and anticholinergic medications are not able to effectively alleviate cognitive and social withdrawal. Because of this, the cognitive deficits in SZ, including pervasive attentional dysfunction, have proven more difficult to treat (Goldberg et al., 1993; Tamminga, 1998).

2.3. Practical and ethical considerations of pharmacotherapeutics.

While the use of pharmacotherapeutics is effective in alleviating many of the attentional deficits observed in psychiatric and neurodegenerative conditions as well as enhancing vigilance in normal subjects, there are limitations to what can be addressed through drug treatment. For example, it is neither feasible nor practical to dispense drugs directly into the brains of humans – such as administration to the cholinergic or excitatory prefrontal cortical networks in the context of attention. Because of this, a majority of therapeutic compounds are introduced systemically, most often via subcutaneous, intravenous, or oral routes of administration. Despite the clear benefit and ease of administration, there are pharmacokinetic downfalls to enteral and parenteral absorption. Referred to as the hepatic first pass effect, the amount of a drug taken orally is significantly reduced in the gastrointestinal tract before it reaches the circulatory system, and its bioavailability is then further diminished through liver-mediated enzymatic metabolism before it can enter the central nervous system (CNS) and induce its psychotropic influence (Rowland, 1972). Because orally-consumed medications must pass through numerous bodily systems before reaching the brain, the interim between administration and improved attentional capacity is prolonged when compared to local dispensation. Injections, which are slightly more efficient – particularly for drugs or doses of drugs that, when swallowed, are rendered largely ineffective by digestive enzymes – are still filtered by the liver and, as such, share similar weaknesses as oral administration (Hussain, 1998).

The intranasal route of administration is useful in bypassing some of the limitations of intestinal and circulatory absorption. While still technically systemic in nature, it circumvents the considerable drawbacks to the previously-mentioned methods of delivery. Insufflation not only allows for quicker penetration of the blood brain barrier and faster transportation into the brain, but a larger concentration of the inhaled substance reaches the CNS as well, as it is not first partially metabolized by the liver (Constantino et al., 2007). Because many pharmacotherapies, including sizeable molecules and peptides, are easily and readily absorbed by the large surface area of the nasal epithelium and transported to the brain via capillaries, nerves, glands and immune cells in both humans and non-human mammals, and because it is relatively painless and non-invasive, intranasal administration

remains a favored delivery method for both clinicians and patients (Hussain, 1998; Pires et al., 2009).

In addition to the pharmacokinetic challenges, the pharmacodynamics of systemically-delivered drugs are often troublesome for human research and treatment as well. Psychotropic drugs which infiltrate the CNS are dispersed indiscriminately throughout the brain, helping to ensure that pertinent and desired regions are reached; however, areas outside of those being purposefully targeted are also exposed to their influence. As such, when a psychoactive agent is transported chiefly by means of the circulatory system, be it through oral consumption, injection, or intranasal routes of administration, it can be impossible to precisely target certain receptor systems and attain region-specific effects at the exclusion of other neighboring networks, and this oftentimes produces unforeseen and unintended consequences.

Along with the general shortcomings of systemic administration, there are other limitations to consider when treating attentional dysregulation – or other conditions necessitating drug intervention – using pharmacotherapeutics. As an individual receives chronic, long-term drug treatment, it is not uncommon that the therapeutic compound gradually loses effectiveness, occasionally necessitating an increase in dosage to attain a comparable psychological effect. This phenomenon is a consequence of the consistent agonism of the target receptors, which, over time, can result in their desensitization and downregulation. This is especially true of dopaminergic and cholinergic receptors, both of which are targets for both therapeutic and recreational attention-enhancing drugs. For example, use of nicotine and amphetamines (such as Adderall), both of which are well-known enhancers of vigilance and alertness in both normal individuals and those with hypofrontality-related cognitive deficits (including ADHD, AD, and SZ), results in substantial loss of cholinergic and dopaminergic receptor responsivity and may ultimately lead to their epigenetic downregulation (Pidoplichko et al., 1997; Renthal et al., 2009). Prolonged drug exposure and the resulting neurobiological alterations can also lead to undesirable and noxious withdrawal symptoms upon cessation, as physiological and psychological well-being are oftentimes substantially reduced following sudden termination of stimulatory medications. Finally, unforeseen long-term neurological alterations – which cannot be determined until post-mortem analyses – may occur following extended pharmacotherapeutic treatment.

3. Future directions.

The impact of receptor activation by drug treatments or neurotransmitter systems, particularly for metabotropic receptors, needs to be further studied. For example, how do changes in second messenger systems contribute to subsequent attentional processing? Our work has shown that protein kinase C inhibition can impair attentional performance (Robinson et al., 2012) and other laboratories have shown that inhibition of cyclic-AMP-dependent protein kinase disrupts attention (Paine et al., 2009). An important future research area is to understand how drug- and neurotransmitter-induced changes in second messenger systems can impact subsequent attentional processing. Changes in these protein kinases have been well-studied with respect to learning and memory (Sun et al., 2015). For attention, they may impact learning to guide changes in top-down allocation and focus of attention.

Additional research aimed at understanding the impact of attention-related neurotransmitter release on downstream intracellular mechanisms will be important to develop a more comprehensive understanding about the neurobiology underlying attentional processing.

As was previously described in this manuscript, the bulk of the research related to attention has focused on traditional neurotransmitter systems. Recent work demonstrates a role for neuropeptides in attention. For example, modulation of galanin can impact attention and memory (Barreda-Gómez et al., 2015; Wrenn et al., 2006). Additionally, the hypocretin/orexin system can also impact attentional performance (Fadel & Burk, 2010). A challenge for future research will be to establish how these neuropeptide systems integrate with well-established neural pathways involved in attention (Asua et al., 2018). For example, these neuropeptides may have trans-synaptic effects on attention by affecting the activity of subcortical areas that then influence cortical neurotransmission. In addition, neuropeptides may directly influence cortical neurotransmission via direct projections as well as interact with other neurotransmitters in cortical regions. Future research into these issues will be critical for developing novel pharmacotherapeutic targets to address conditions involving attentional impairments.

The development of positive and negative allosteric modulators for several neurotransmitter systems has been an important development. For example, muscarinic cholinergic receptors have considerable conservation of orthosteric sites between muscarinic-1, muscarinic-3, and muscarinic-5 receptors, making it challenging to develop drugs that target selective receptor subtypes (Bock et al., in press). However, there is more distinctiveness in the allosteric sites, potentially allowing for more selective receptor targeting. Additionally, those allosteric modulators that only act when a neurotransmitter is bound to its receptor site allow for enhancement of normal neurotransmission, rather than receptor stimulation that is independent of receptor activation. The continued development of allosteric receptor ligands is an important future research area for improving conditions characterized by aberrant attentional processing.

In addition to improving pharmacological tools for studying and treating conditions characterized by dysfunctional attentional processing, future research should emphasize the particular forms of attentional dysfunction within these conditions. For example, future research needs to facilitate a better comprehension of the neural circuitry engaged by different subcategories of attention. Such information will be useful in allowing for more targeted treatments for conditions characterized by attentional deficits. Moreover, this research may lead indicate the use of pharmacological treatments, such as stimulants and acetylcholinesterase inhibitors, for multiple pathologies associated with similar underlying deficiencies in attentional processing.

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