The Biology of Agitation

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Agitation is a clinical phenomenon with complex pathophysiology. This chapter reviews the biological processes relevant to producing agitation among the variety of illnesses described later in this textbook. A description of the subject literature is provided, followed by greater detail on the genetics, neuroanatomy, neurotransmitters, and other chemical systems implicated in producing agitation.

Overview

Our understanding of the biology of agitation is based on a variety of studies and methodologies, each with different insights and limitations. Different studies include:

1. Observational studies of agitated patients. These studies are most applicable to clinical practice, but often focus on extremes of behavior. Agitation's similarity to other clinical presentations—including aggression, akathisia, panic, and irritability—makes case identification difficult (de Almeida et al., 2005). Because obtaining laboratory samples from agitated patients is often not possible, clinical studies rely on biomarkers retrieved after the resolution of acute agitation.

2. Studies of disease pathology. Understanding the pathology of diseases associated with agitation aids in describing biology relevant to behavioral dyscontrol. This approach has proven especially helpful for describing the neuroanatomy of agitation.

3. Drug studies and trials. Identifying effective pharmacotherapy for agitation has allowed inferences into pertinent neurotransmitter systems based on medications' mechanism of action. However, medications act on complex systems with nonspecific effects, so these studies only inform our knowledge of agitation in a more general way (de Almeida et al., 2005).

4. Animal models. Laboratory studies allow standardized examination of behavior after extensive genetic and environmental manipulation. Animal behaviors that reflect agitation include tail-rattling in mice and aggressiveness in zebrafish (Ziv et al., 2013; Takahashi, Shiroishi, and Koide, 2014; Takahashi et al., 2015). These studies are more removed from clinical practice, but allow greater precision in understanding the mechanisms of behavior change.

One significant limitation in understanding the basic science of agitation is that agitation presents so heterogeneously. Agitation reflects an acute trigger acting on some underlying diathesis in a particular environment. The presentation of agitation ranges from the purposeless hyperactivity of a delirious patient to the instrumental, predatory aggression of an antisocial person (Miczek et al., 2002). Chronic and acute risks of agitation reflect cognition, temperament, psychosis, intoxication, anxiety, choice, and executive function.
Agitation has been described as a “transnosologic” syndrome, a clinical manifestation arising from any number of underlying diagnoses (Lindenmayer, 2000). As a consequence, investigators studying agitation must choose whether to focus on the clinical syndrome (regardless of disease process) versus a diagnosis that may not generalize to other causes of agitation.

Genetics

Some chronic risks of agitation are heritable and genetic. There is an evolutionary advantage to some agitation. Aggression is observed across all animal species and increases proportionally to the aggressiveness of an intruder (Takahashi et al., 2014; Takahashi et al., 2015). Greater motor activity levels enable animals to protect home environments and offspring, and to engage in proactive coping with novel stressors (de Boer, Van der Vegt, and Koolhaas, 2003). More active animals develop routines that are less susceptible to aversive threats—a beneficial habit in some environments (Benus et al., 1991).

Most directly, the genetic risk for agitation can be conferred through highly inheritable illnesses like schizophrenia or borderline personality disorder. Some single gene mutations have been associated with agitation. For example, patients with antisocial personality have been found to have a point mutation in the monoamine oxidase A (MAOA) gene that infers deficient activity of that enzyme and thus abnormal serotonin metabolism (Brunner et al., 1993). Males’ recognized higher risk for aggression may reflect the homozygosity of MAOA conferred by the Y chromosome (Eme, 2010). Genome-wide association studies have identified single polymorphisms correlated with risk-taking and excitement-seeking (Terracciano et al., 2011).

But most agitation is unlikely to be explained by point mutations and single disease models. One reason for this complexity is that phenotypes reflect the interaction of a genome with the environment. Consider that the aforementioned effect of MAOA mutations on antisocial personality may be augmented by childhood exposure to maltreatment (Miczek et al., 2002; Li and Lee, 2010; Buades-Rotger and Gallardo-Pujol, 2014). Changing the parenting conditions of lab animals alters their adrenal activity and susceptibility to agitation (Li and Lee, 2010; Takahashi et al., 2015). The expression of genes may also be changed by environmental conditions: in rats, lysergic acid diethylamide changes the expression of serotonin receptors and related transcription factors (Nichols and Sanders-Bush, 2004).

Genes may even more indirectly increase the risk of agitation by their complex contributions to temperament and character. Experimental adjustment of aggressiveness affects ostensibly distinct behaviors that are necessary for building resilience and coping, such as the exploration of novel stimuli (de Boer et al., 2003). Genetic expression may be further modified by epigenetic processes like methylation, which has been recognized in modifying behavior (Kumsta et al., 2013). Ultimately, the roles of epigenetics and gene–environment interactions on the risk of agitation are incompletely understood.

Neuroanatomy

Agitation involves conscious and unconscious behaviors as well as motor hyperactivity. These three aspects of agitation are roughly associated with activity in the cortex (conscious behaviors), subcortex and limbic system (unconscious behaviors), and basal ganglia–globus pallidus–substantia nigra circuit (motor hyperactivity) in the
Figure 2.1. Neuroanatomical sites involved in agitation.

central nervous system (CNS). Figure 2.1 is a simplified diagram of anatomical structures relevant to agitation. Actually, these regions are structurally interconnected through numerous pathways and utilize multiple neurotransmitters that are described in greater detail later in this chapter.

The cortex is the seat of executive function, decision making, judgment, and abstraction. Aberrations in the cortex impair a person's capacity to act in a socially appropriate fashion and maintain behavioral control in otherwise benign circumstances. The famous case of Phineas Gage illustrates the behavioral changes wrought by damage to the cortex. Gage was a railroad worker whose frontal cortex was damaged by an iron rod in 1848. Subsequent to the accident, Gage suffered severe personality changes that made him "impatient of restraint or advice" (O'Driscoll and Leach, 1998). Organic processes also cause damage to the cortex, if in a less dramatic fashion. Disease severity in Alzheimer's dementia correlates with damage to the cortex (Kirby and Lawlor, 1995). As the site of more complex thought, the cortex is responsible for cognition distortions and misinterpretations. These cognitive distortions generate agitation among patients with posttraumatic stress or predatory aggression (Siegel and Victoroff, 2009; Taft, Creech, and Kachadorian, 2012). Frontal cortical serotonin transmission is a promising target for drug treatments of impulsivity (Miczek et al., 2002).

Subcortical structures, including the dorsolateral striatum, are considered the seat of mood and emotions. These structures also mediate the physical expression of purposeful movement initiated by the cortex and are associated with subconscious and automated behaviors. Subconscious impulses are those that are beyond the awareness of a person, such as the cravings a drug user experiences after exposure to certain triggers. The mesocorticolimbic system connects a variety of subcortical midbrain structures with the cortex. The hyperactivity of these pathways during agitation and periods of threat speak to the complex conscious and unconscious machinations involved in expressing agitation (Miczek et al., 2002).
Within the subcortical ventral striatum, the nucleus accumbens is associated with behavioral reinforcement, including dangerous behaviors such as substance abuse and aggression (Miczek et al., 2002). It may also be involved in more complicated emotional expressions such as grief (Bosch et al., 2016). That the nucleus accumbens is so closely integrated into pathways connecting the cortex and subcortex suggests that the nucleus may, in some instances, signal to the cortex that conscious action is necessary. In other instances, the nucleus "colors" the expression of behaviors dictated by the cortex. Substance use disorders exemplify the power of the nucleus accumbens: dopamine hyperactivity in the nucleus associates with the reinforcing effects of substance use and may overwhelm a person’s better judgment. Impairment of more complex mentation in the cortex may increase susceptibility to dangerous urges prompted by the nucleus accumbens (Di Chiara et al., 2004).

Other subcortical structures have been implicated in agitation. In the medial temporal lobe, the amygdala and hippocampus are necessary for emotional recall and memory, respectively. Isolated degeneration of the amygdala has been found to cause agitation, cognitive impairment, and mood changes (Sachdev et al., 2007; Trzepacz et al., 2013). Among patients with Alzheimer’s disease, damage to the amygdala and hippocampus is associated with increased aggression and agitation on standardized assessments (Shibuya-Tayoshi et al., 2005). Medications enhancing hippocampal nerve growth may be effective in the treatment of depression (Fava et al., 2015).

Agitation is defined by psychomotor hyperactivity. Hyperactivity requires action by areas of the brain necessary for producing movement. The basal ganglia, globus pallidus, and substantia nigra are structures with both direct and indirect connections to the cortex and subcortex. Being necessary for movement, these structures are implicated in the motor hyperactivity of agitation (Lindenmayer, 2000). This motor system can also contribute to agitation; Parkinson's and Huntington's diseases afflict the basal ganglia. Obsessive-compulsive disorder has been localized to the basal ganglia and its connections to the frontal lobe (DeLong and Wichmann, 2007). The effect of dopamine-blocking medications in this system cause dyskinesia and akathisia.

The close connections among these regions depend on the integrity of their constituent neurons and interneuron connections. Disease processes disrupt these connections and increase the risk of agitation. For example, the aggregation of tau protein in Alzheimer's disease impairs cortical neurotransmission, which generates behavioral disturbances (Van der Jeugd et al., 2013). In animal models, abnormal pruning of dendritic connections is associated with agitation (Kim et al., 2015). Conversely, cognitive enhancement may reflect healthy neuroplasticity, or the neuron’s ability to change and generate new dendritic connections (Smith, Gibbs, and Farb, 2014). Neuroplasticity is degraded by chronic stress (Radley et al., 2011), whereas treatment trials of stroke patients suggest that serotonin reuptake inhibitors may enhance plasticity and restore motor function (Siepmann et al., 2015).

**Neurotransmitters**

In the body, a range of chemicals is important in the expression of agitation. Some of these agents act as neurotransmitters in communication between neurons (e.g., serotonin). Other agents alter neuronal anatomy and plasticity (e.g., pregnenolone) (Smith et al., 2014) or influence genetic expression (e.g., testosterone) (Ambar and Chiavegatto, 2009).
### Table 2.1: Neurochemical system of agitation and associated diseases, medications, and drugs of abuse

<table>
<thead>
<tr>
<th>Neurochemical system</th>
<th>Diseases causing agitation</th>
<th>Medications treating agitation</th>
<th>Drugs of abuse causing agitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotonin</td>
<td>depression, anxiety, aggression</td>
<td>selective serotonin reuptake inhibitors, tricyclic antidepressants</td>
<td>hallucinogens</td>
</tr>
<tr>
<td>Dopamine</td>
<td>schizophrenia</td>
<td>antipsychotics</td>
<td>cocaine, amphetamines</td>
</tr>
<tr>
<td>GABA</td>
<td>alcohol intoxication</td>
<td>benzodiazepines, anticonvulsants</td>
<td>alcohol</td>
</tr>
<tr>
<td>Glutamate/NMDA</td>
<td>dementia, paraneoplastic encephalitis</td>
<td>memantine</td>
<td>hallucinogens</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>dementia, delirium</td>
<td>acetylcholinesterase inhibitors</td>
<td>nicotine</td>
</tr>
<tr>
<td>Anandamide/Endocannabinoid</td>
<td>unknown</td>
<td>tetrahydrocannabinol, dronabinol</td>
<td>marijuana</td>
</tr>
<tr>
<td>Steroid hormones</td>
<td>Cushing’s disease, adrenal and ovarian tumors</td>
<td>pregnenolone</td>
<td>anabolic steroids</td>
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</tbody>
</table>

GABA-gamma-aminobutyric acid; NMDA-N-meth-D-aspartate

The activity of one agent may also affect the expression and activities of another (Liechti, 2015). Agitation may result from manipulating neurotransmission through medications or drugs of abuse. For example, amphetamines impair presynaptic dopamine reuptake and induce greater release of dopamine from the presynaptic neuron. The result - greater effective dopamine activity in the striatum - is responsible for the psychosis and agitation wrought by these drugs. Numerous pharmacologic agents have been identified that induce hyperactivity, either by direct effect or withdrawal (Sachdev and Kruk, 1996). Table 2.1 summarizes diseases, medications, and drugs of abuse by their neurotransmitter system of action.

**Serotonin**

Serotonin is a monoamine neurotransmitter derived from the amino acid tryptophan and produced in the raphe nuclei of the brain stem. More often associated with mood disorders, serotonin is also the foremost neurotransmitter implicated in agitation and aggression. There is a relative deficiency of CNS serotonin among aggressive animal phenotypes, violent criminals, and persons who complete suicide (Brunner et al., 1993; Maes et al., 1995; Beethea et al., 2015). Degeneration of serotonergic pathways also increases the risk of agitation among patients with Alzheimer’s-type dementia (Porsteinsson, Keliz, and Smith, 2014).
In animal models, genetic manipulation of serotonin transmitters predictably modulates aggression (Miczek et al., 2002). Even ecological research correlates the seasonal variation in violent suicides with the availability of serotonin's precursor molecule (Maes et al., 1995). Perturbations in serotonin are implicated in the pathophysiology of depression, schizophrenia, dementia, Parkinson's disease, delirium, and alcohol withdrawal (Van der Mast and Fekkes, 2000). Serotonin is also necessary for more complex executive function, harm aversion, and perhaps the expression of ethical decision making in interpersonal interactions (Siegel and Crockett, 2013).

Serotonin has complex effects in the CNS. No neurotransmitter operates in isolation: serotonergic receptors also modulate dopamine transmission, and several studies suggest that serotonergic activity levels must be examined in the context of other neurotransmitters. For example, the ratio of dopamine to serotonin reuptake inhibition correlates with intoxication and addictiveness of abused drugs (Liechti, 2015). Alcohol consumption and steroid treatment affect CNS serotonergic activity (Takahashi et al., 2014). Although much agitation and aggression reflects a decrease in serotonergic activity, the opposite also occurs: excessive activity causes serotonin syndrome, hyperthermia, hyponatremia, and seizures. Whether provoked by conscious choice, unconscious impulse, or disease pathology, agitation is partly a disorder of serotonergic neurotransmission.

Dopamine

Like serotonin, dopamine is a monoamine neurotransmitter with a wide distribution in the central nervous system. Dopamine is synthesized by neurons of the central nervous system and utilized as an intercellular transmitter to G-coupled protein receptors. Dopaminergic activity in the nucleus accumbens is associated with reward salience. In connections between the cortex and subcortex, dopamine is implicated in the psychopathology of schizophrenia. Given its importance for both higher-order cognition in the cortex as well as more primitive emotional reactivity in the subcortex, dopamine is implicated in most episodes of agitation, regardless of etiology (Miczek et al., 2002). Increased dopaminergic transmission is the primary mechanism of action for many drugs of abuse, particularly cocaine and amphetamines. Medications that antagonize dopamine's G-couple receptors—especially antipsychotics—are used in the treatment of agitation.

Dopamine is present in the basal ganglia and substantia nigra and thus necessary for the production of voluntary movement. The depletion of dopamine in Parkinson’s disease or the reduction of dopamine transmission by medication treatment induces muscle rigidity and dyskinesia. The resulting discomfort can contribute to agitation. Akathisia may result from dopamine antagonism in the substantia nigra (Sachdev and Kruk, 1996).

GABA

Through action on multiple receptor types, gamma-aminobutyric acid (GABA) opens chloride ion channels in the neuronal cell membrane. GABA decreases the excitability of the neuron and renders neurons less prone to “firing.” GABA is found throughout the CNS, although it is particularly prominent in the subcortex. That alcohol, benzodiazepines, and barbiturates act on the GABA system speaks to the role of GABA in agitation (Miczek et al., 2002). Initially and at lower levels, increased GABA activity produces mild behavioral disinhibition and impairs higher cortical function. These lower levels may inhibit some aggression (Miczek et al., 2002), but greater levels of GABA activity cause significant
performance impairment and agitation, as exemplified by a person intoxicated on alcohol. This greater impairment reflects not only active GABA, but also GABA’s effects on increasing dopamine and serotonin transmission (Miczek et al., 2002). Anticonvulsants’ activation on GABA receptors may account for their benefits in decreasing agitation in dementia (Gallagher and Hermann, 2014), although these findings have not reliably extended to other illnesses (Waters, Morrall, and Murdoch-Eaton, 2010; Hirot a et al., 2014).

Glutamate

Glutamate is the primary excitatory neurotransmitter in the brain. Its role is often contrasted with that of inhibitory GABA. Although numerous glutamate transporters and receptor targets have been identified, most clinical attention focuses on the N-methyl-D-aspartate (NMDA) receptor (Meldrum, 2000). Glutamate and NMDA receptors contribute to neuronal plasticity, concentration, and memory. Disturbance of the NMDA receptors by paraneoplastic autoantibodies causes anxiety, insomnia, cognitive impairment, and psychosis (Maneta and Garcia, 2014). Glutamatic innervation appears to be lost in the cortex of patients with Alzheimer’s dementia (Hardy et al., 1987), and the NMDA antagonist memantine has been studied in the treatment of this disease (Herrmann et al., 2011). Activity at glutamate receptors is one mechanism of action of the novel drugs of abuse, cathinones and hallucinogens (Liechti, 2015).

Acetylcholine

In the peripheral nervous system, acetylcholine is the primary neurotransmitter at the neuromuscular junction and in the parasympathetic nervous system. Within the CNS, acetylcholine plays key roles in cognition, memory, and reward salience. The loss of cholinergic neurons in the nucleus basalis of Meynert underlies the cognitive degeneration of dementia (Bowman, Stoffers, and Wolters, 2003). Cholinergic deficiency that results from medical conditions or medications also contributes to the development of delirium (Hsieh et al., 2008). Acetylcholine is necessary for maintaining cognition that allows patients to problem solve, tolerate distress, and consciously control agitated behaviors. Cognitive impairment may also render environmental stimuli more threatening. Preserving cholinergic tone through the use of acetylcholinesterase inhibitors is the primary pharmacotherapy for dementia.

Acetylcholine has other CNS actions that are pertinent to agitation. Subcortical stimulation of acetylcholine receptors improves anxiety and mood (Picciotto et al., 2015). Nicotine stimulates the acetylcholine system; in rats and cats, nicotine reduces aggression at low doses, but may increase it at higher doses (Picciotto et al., 2015). Intriguingly, the acetylcholinesterase inhibitor galantamine reduces methamphetamine-induced psychosis in monkeys (Andersen, Werge, and Fink-Jensen, 2007). This finding speaks to the overlap of acetylcholine with dopamine in signaling cognition, mood, reward, and movement.

Anandamide

The endocannabinoid system comprises two cannabinoid receptors and the brain’s endogenous cannabinoid ligand, anandamide. This system is best known as the site of action of tetrahydrocannabinol, the active ingredient of cannabis. Cannabinoid receptors are located in the immune system and throughout the CNS with a concentration in
subcortical structures and the hypothalamus (Ramirez et al., 2005). The natural purpose of anandamide is to moderate appetite, thermal regulation, neuroinflammation, oxidative stress, and excitotoxicity (Waters et al., 2010; Liu et al., 2015). However, evidence for the therapeutic benefits of endocannabinoid agonists in ameliorating neuropsychiatric symptoms is only mixed, for example, in dementia (Van den Elsen et al., 2015). The implications of the cannabinoid system for agitation are best understood through clinical studies associating cannabis use with violence (Willkinson, Stefanovics, and Rosenheck, 2015). This relationship may stem from greater impulsivity and cognitive impairment resulting from cannabis use. Withdrawal from cannabis may promote agitation by increasing irritability, anger, aggression, and restlessness (Haney, 2005).

**Additional Neurochemical Systems**

In addition to neurotransmitters, other chemical signaling systems are implicated in agitation. These systems include hormones and inflammatory markers.

**Hormones**

Hormones are signaling chemicals that regulate activities of other, distant cells. Some hormones are produced within the CNS (e.g., oxytocin), while others are produced outside the CNS (e.g., testosterone). Regardless of where they are produced, hormones affect the expression of mood, thoughts, and behaviors. By virtue of their complex interactions with neurotransmission, hormonal signaling systems may produce acute agitation or increase a persons’ risk for developing agitation.

Steroid hormones are derived from cholesterol and produced by endocrine cells of the adrenal cortex, testes, ovaries, and placenta. Steroid hormones like testosterone, glucocorticoids, and pregnenolone affect agitation and aggression. Testosterone is commonly considered to drive aggression, although the evidence for this supposition is ambiguous. Administering testosterone to laboratory animals induces aggression and alters serotonin metabolism (Ambar and Chiavegatto, 2009), but observational studies of humans have not consistently associated higher levels of testosterone with aggression (de Boer et al., 2003). Glucocorticoids are produced in the adrenal cortex, but almost all cells contain glucocorticoid receptors. Steroid pharmacotherapy (e.g., prednisone) activates this system and may cause anxiety, mood disorders, and psychosis. Elevated glucocorticoid hormone levels also confer elevated aggressiveness in zebrafish – a perturbation correctable by administering the serotonin reuptake inhibitor fluoxetine (Ziv et al., 2013). The steroid hormone pregnenolone modulates synaptic plasticity and has been investigated as a pharmacotherapy in schizophrenia (Smith et al., 2014). Pregnenolone reverses schizophrenia-like behavior in mice with a knockout gene for the dopamine transporter (Wong et al., 2012). These experimental findings illustrate the diverse effects of hormones and their importance to neurotransmission.

Peptide hormones are built on a protein structure rather than cholesterol. Examples of peptide hormones are oxytocin and vasopressin. Oxytocin is produced in multiple endocrine organs as well as the hypothalamus. Oxytocin plays a role in helping mammals form attachments and complex social interactions (Kumsta and Heinrichs, 2013). Its expression is decreased among persons with greater stress, anxiety, or significant psychiatric morbidity (Myers et al., 2014). Mutations in the oxytocin receptor gene have been postulated to interact with environmental stressors to increase an individual’s risk for mood disorders (Myers et al., 2014). Another peptide hormone, vasopressin, is critical for osmotic regulation as well as
social communication and interpersonal functioning (de Wied, Diamant, and Fodor, 1993). No clinical studies have studied the direct effect of peptide hormones on agitation.

Inflammatory Markers

Hyperinflammatory states exist in multiple psychiatric conditions, including schizophrenia and depression (Kiecolt-Glaser, Derry, and Fagundes, 2015; Volk et al., 2015). Similarly, agitation and aggression correlate with elevated levels of circulating cytokines and interleukins. These relationships may be more than correlative; in experimental models, the injection of interleukins into mammals’ CNS can provoke and potentiate aggressive behavior (Zalcman and Siegel, 2006). In observational studies, infection with the parasite *Toxoplasma gondii* has been associated with suicidal behaviors (Zhang et al., 2012). Available evidence suggests that inflammation among patients with agitation is likely, but the significance of this connection remains unclear. Inflammatory states may drive psychiatric illness. Or it may be that inflammation results from glucocorticoid dysregulation, sleep changes, or alterations in the body’s natural biome.

Agitation: More than a Sum of Parts

A range of anatomic pathways, genotypes, neurotransmitter systems, and inflammatory states is associated with agitation. How all these systems fit together remains somewhat mysterious. In practice, a patient who is agitated demands acute management, and underlying risk factors often remain elusive to the clinician. It is challenging to study, in vivo, neurotransmitters as they act in complex feedback loops across numerous anatomic pathways. Moreover, some factors that play a role in agitation, like interpersonal trust and social decision making, are difficult to describe biologically.

Agitation is not easily disassembled into a series of biological processes. Nonetheless, although every episode of agitation is unique, commonalities exist to form a basis for assessment and treatment.

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