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The Mechanism of Drug-induced Akathisia

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NEW TREND IN PSYCHOPHARMACOLOGY

Akathisia is a movement disorder characterized by an inner sense of unease, unrest, and dysphoria. It can result in an inability to stand, sit, or lie still, and an intense urge to move around. It is a common side effect of drugs, such as antipsychotics and serotonin selective reuptake inhibitors (SSRIs), but it also occurs spontaneously in patients with Parkinson's disease. Several lines of evidence suggest that akathisia can be attributed to low activity of dopaminergic projections from the midbrain to the ventral striatum. However, the exact pathophysiological mechanism of this extrapyramidal symptom remains unclear. This article describes a possible mechanism for drug-induced akathisia based on the differential functions of the core and shell portions of the nucleus accumbens. These ideas arise from contemporary concepts regarding the mechanisms of compulsion, impulsivity, and depression.

AKATHISIA IS A NEUROPSYCHOLOGICALLY INDUCED MOVEMENT DISORDER

Akathisia is a movement disorder characterized by an urge to move, unpleasant sensations in the legs, and an inner restlessness. The core symptom is the subjective feeling of discomfort that results in objective signs of motor activity and an inability to remain still.[1] A specific variant presents itself primarily as tedious behavior in which the patient shows a compulsion to repeat the same questions and seeks constant reassurance from nearby individuals. It should be emphasized that unlike other extrapyramidal disorders, such as parkinsonism and dyskinesia, akathisia is primarily a psychological symptom and not just a movement disorder; patients experience the urge to move, and motor and behavioral symptoms result from this phenomenon.[2,3]

Akathisia is observed in patients who are undergoing treatment with antipsychotics, antiemetics, and antidepressants. Incidence rates for acute akathisia with conventional neuroleptics vary from 8% to 76%, with 20% to 30% being a conservative estimate.[4] It is less prevalent with second-generation antipsychotics, but remains a clinically relevant extrapyramidal side effect even with these newer drugs.[5] Lipinski and colleagues[6] described it in 9.8%to 25% of patients receiving the antidepressant fluoxetine. Akathisia also occurs spontaneously in Parkinson's disease and is very similar in appearance to restless legs syndrome (RLS) and periodic limb movement disorder (PLMD) in sleep.[2,3,7] However, RLS and PLMD primarily occur at night, and akathisia occurs mostly in the daytime.[8]

DOPAMINERGIC HYPOACTIVITY CAUSES AKATHISIA

Akathisia is believed to be caused by an extensive (>80%) decrease in dopamine $(D)_2$ receptor stimulation.[1] This is in accordance

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with its occurrence in patients suffering from Parkinson disease, and the evidence that RLS and PLMD can be treated with levodopa and dopamine agonists.[7,8] Antipsychotics and certain antiemetics are potent antagonists of the D_2 receptor. However, not all of the published observations are in line with the dopamine deficiency hypothesis.[9] For example, a direct relationship has not been found between parkinsonism—of all extrapyramidal side effects the one most directly related to D_2 antagonism—and akathisia.[1] The atypical antipsychotics clozapine and quetiapine bind loosely to the D_2 receptor and cause little or no parkinson-like symptoms in therapeutic dosages.[10] However, they cause far more akathisia,[9,11] although less than haloperidol.[12]

There are several drugs that have no affinity for the D_2 receptor, but do cause akathisia. The most well known are the SSRIs. It has been suggested that SSRIs induce akathisia (and parkinsonism) by indirectly stimulating serotonin $(5\text{-HT})_{2A}$ receptors, which results in inhibition of DA release.[1,11] This is in line with the hypothesis that atypical antipsychotics give rise to less akathisia than classical drugs by blocking these serotonin 5-HT_{2A} receptors.[1,11,13]

In addition to the 5-HT_{2A} receptors, the blocking of cholinergic muscarinic receptors and β-adrenoceptors are also known to result in therapeutic effects.[1,9,11] The blocking of cholinergic muscarinic receptors is in line with the idea that a deficiency of dopamine and an excess of dopamine in the striatum causes akathisia.[3] In the striatum, D_2 receptors are largely present on cholinergic interneurons, which influence the medium-sized spiny neuron (MSN) of the direct extrapyramidal pathway.[14] When the influence of these cholinergic interneurons is blocked, the D_2 receptor is no longer able to influence the activity of the extrapyramidal circuit.

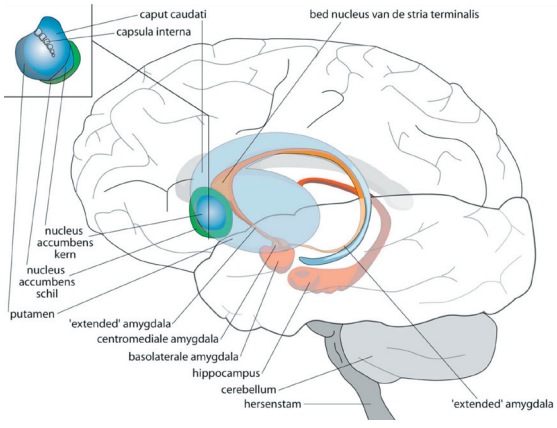
The anti-akathisia effect of β-blockers has been attributed to an interaction between adrenergic neurons originating in the locus coeruleus complex and the dopaminergic neurons in the midbrain.[1] However, this is contradicted by the fact that the interactions between adrenergic neurons from the locus coeruleus and dopaminergic neurons of the ventral tegmental area (VTA) in the midbrain are primarily mediated by α- and not by β-adrenoceptors.[15] β-Adrenoceptors are primarily present in the synapses of adrenergic neurons running from the locus coeruleus complex to the cerebral cortex, the accumbens nucleus, and the dorsal striatum.[16] The nucleus accumbens, in particular, is a good candidate for association with akathisia, because it is involved in processes that motivate rewarding behaviours.

However, before an association between akathisia and dopamine deficiency in the ventral striatum can be assumed, an explanation must be found for the observation that dopamine hyperactivity in the accumbens results in agitation and hypoactivity in the accumbens results in akathisia. This could be accounted for by the different functions of the shell and core portions of the nucleus accumbens.[17] It should be noted that agitation and akathisia differ by the absence and presence, respectively, of an urge to make movements (Figure 1).

ROLE OF THE NUCLEUS ACCUMBENS

The nucleus accumbens is considered to be the area of the striatum that forms the interface between limbic and motor structures.[18] Based on experimental work in animals, it is evident that the shell portion of the nucleus accumbens (NAcbS) is distinguished from the core (NAcbC) and the rest of the striatum by its promotion of general, unconditioned behaviors, such as feeding or defense behavior. By stimulation of the shell subregion, individuals are motivated to display standard behavioural patterns that are cued by "novel" stimuli.[19] The NAcbS

FIGURE 1.
Position of the nucleus accumbens core and shell relative to the dorsal striatum in the human forebrain



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facilitates new behavior that is not necessarily rewarding, but could lead to improvement of the individual's condition.

The NAcbC, on the other hand, seems to be preferentially involved in response-reinforcement learning, whereas the shell is not involved in motor or response learning, per se; rather, the shell integrates basic biological "drives".[18] Thus, the NAcbS can be considered to mediate inter alia curiosity and aggressive dominance. Both parts of the nucleus accumbens are stimulated by dopaminergic neurons from the VTA.

Normally, the prefrontal cortex inhibits the response to immediate reward-bringing stimuli, allowing the individual to opt for behavior that brings a postponed, but larger, reward. This inhibition is thought to be mediated through the NAcbC. When this system is damaged in experimental animals, impulsivity in favor of immediate rewards occurs. Different parts of the prefrontal cortex appear to be involved in different forms of impulsivity (Figure 2).[17] What should be apparent from Figure 2 is that different parts of the cerebral cortex (anterior cingulate cortex, orbitofrontal cortex, and infralimbic cortex) differentially affect the NAcbC and NAbcS, and that these latter structures are also differentially innervated with catecholaminergic fibers from the brainstem. The NAcbC and NAcbS are both densely innervated by dopaminergic fibers, but only the NAcbS receives substantial noradrenergic innervation.

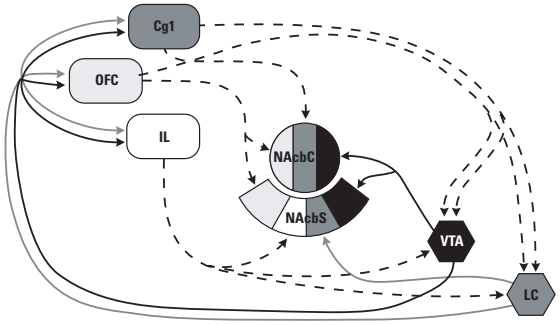
To properly explain the role of dopaminergic neurotransmission in the nucleus accumbens, we must first address its role in drug abuse and dependence.[20] An essential part of addiction is the craving for the addictive substance, which leads to characteristic drug-seeking behavior. This is likely due to a dysfunction in the mechanisms that induce reward-seeking or discomfort-avoiding behaviour. Three anatomical structures are involved in inducing this behavior: the orbitofrontal cortex, the NAcbC (reward-seeking behavior), and the amygdala (fear-activated behavior). All three anatomical structures are richly supplied with dopaminergic terminals originating in the VTA. In people with drug dependence, the orbitofrontal cortex in particular is believed to initiate the drug-seeking behavior. The promotion of this behavior is mediated through the NAcbC and the ventral pallidum; ie, the ventral cortico-striato-thalamo-cortical re-entry circuit of the prefrontal cortex.[20] This is strongly conditioned behavior that leads to habit formation, and is more or less the same as the conditioned behavior that is found in obsessive-compulsive disorder.[21,22]

The infralimbic cortex activates behavioural, neuroendocrine, and sympathetic autonomic systems in response to acute stressful situations.[23] This cortical region corresponds to Brodmann area 25 in rats, monkeys, and humans, and appears to be the only prefrontal area that projects substantially to the NAcbS.[24] It is also known to be metabolically overactive in treatment-resistant major depression, and is the target of deep brain stimulation in this disorder.[25] This corresponds with the feelings of discomfort and dysphoria that accompany akathisia.

THE MECHANISM OF AKATHISIA

Although not intended for that purpose, the model of Dalley and colleagues[17] offers some interesting clues regarding the mechanism of akathisia. Akathisia may result from efforts to compensate for dopaminergic underactivity in the nucleus accumbens. By decreasing

FIGURE 2.
The nucleus accumbens core (NAcbC) and shell (NAcbS) both participate in the ventral cortico-striato-thalamo-cortical circuit and contain dopaminergic terminals that originate in the ventral tegmental area (VTA) of the midbrain[17]



Both portions are affected by glutamatergic terminals from the orbitofrontal cortex (OFC), but only the NAcbS is affected by the infralimbic cortex (IL, subgenual cingulate area, Cg25). Moreover, only the NAcbS is stimulated by β-adrenoceptors in the terminal synapses of adrenergic projections from the locus ceruleus complex. (Scheme adopted from Dalley et al. [17] with permission from the authors and publisher)

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the stimulation of the nucleus accumbens, a dopamine deficiency results in an inhibition of both NAcbC and NAcbS. When an individual is compensating for this deficiency by inter alia increasing the adrenergic input from the brainstem, only the NAcbS is stimulated. This motivates individuals to display, seemingly purposeless, immediate reward-seeking behavior, and results in activation of the corresponding re-entry circuit. Moreover, through feedback mechanisms, the activity of dopaminergic projections from the VTA to the prefrontal cortex may result in increased activity, particularly of the orbitofrontal cortex. This is due to stimulation of the D_1 receptors that are present in these terminals and are not affected by dopamine antagonists. In cortical areas, D_1 receptors are expressed almost exclusively; there are hardly any D_2 receptors.[26]

Several findings support such a mechanism. First, β-blocking agents have therapeutic effects in akathisia. Adrenergic terminals originating in the locus coeruleus complex and ending in the NAcb and prefrontal cortex stimulate β-adrenoceptors at their terminals.[15,16] Moreover, as indicated previously, the NAcbS plays a key role in promoting unconditioned defensive behavior.[18] There are numerous reports of an association between the occurrence of akathisia and different forms of aggression.[27] Therefore, this could be considered to be related, or possibly even a part of the complex behavior of akathisia.

CONCLUSION

Much evidence exists to support the idea that akathisia is related to a decrease in dopaminergic neurotransmission. This likely results in decreased activity of the entire ventral striatum. It can be postulated that this decline results in compensatory enhancement of the activity of adrenergic projections from the locus coeruleus complex. Because these projections selectively stimulate the shell portion of the nucleus accumbens, a mismatch between the activities of the NAcbC and NAcbS results. Relative overstimulation of the NAcbS results in the typical urge to display senseless "curious" or "defensive" behavior, and is accompanied by dysphoric feelings. ***CNS***

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