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Hypothetical dopamine dynamics in mania and psychosis — its pharmacokinetic implications

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ABSTRACT

The symptoms of psychosis and mania are both related to dopaminergic hyperactivity. In psychosis, it is proposed that post-synaptic receptor sensitization causes dysfunctional salience processing, leading to the development of delusional symptoms. In various animal models of psychosis, the mechanism of post-synaptic sensitization is related to the increased proportion of high-affinity D2 receptors. On the other hand, psychostimulant-induced increase in synaptic dopamine can serve as a model for manic distractibility. In this study, brief models were constructed to identify the differences in dopaminergic hyperactivity between psychosis and mania, and the effects of antipsychotics were sought in terms of the dynamics of dopamine receptor occupancy. According to the study, it was found that antipsychotics with small K_{off} value had advantages in restoring the receptor occupancy to normal level in the psychosis model, while in the mania model, those with large K_{off} value showed a better profile.

1. Introduction

Delusion is one the most important symptoms of psychosis. The delusion of reference is a belief that events in the person's surroundings have important personal meaning. Delusion can be understood as an unfounded attribution of salience to incidental events. The increased salience hypothesis of psychosis (Howes and Kapur, 2009; Miller, 1976; Panksepp, 1998) proposes that psychosis is an increased attribution of personal significance to otherwise neutral stimuli. Because dopaminergic activity is related to the processing of salience information associated with environmental stimuli (Robinson and Berridge, 1993; Schultz et al., 1997), the increased salience hypothesis fits well with the traditional dopaminergic hyperactivity hypothesis of psychosis or schizophrenia.

However, the hyperdopaminergic state also serves as a model for mania, and dopamine blocking agents are effective in alleviating manic symptoms as well as psychotic symptoms (Cipriani et al., 2011). Psychostimulant drugs increase extracellular dopamine by inhibiting the dopamine transporter (DAT) and produce behavioral effects compatible with mania (Johanson and Uhlenhuth, 1980; Silverstone et al., 1983). Although the manic state has a variety of distinct behavioral characteristics, distractibility and pressure of speech (verbosity) are symptoms that can distinguish mania from schizophrenia (Andreasen, 1979; Andreasen and Grove, 1986). Similarly, flight of ideas, increased goal-directed activities, and distractibility are symptoms that provide good discrimination between mania and normality (Agrawal et al., 2010). While these symptoms have only single-factor structure in some samples (Agrawal et al., 2010), distractibility was singled out as a factor independent of other mania-related thought disorders in other samples (Cuesta and Peralta, 2011). The two symptom groups of mania may originate from different mechanisms. If we consider that dopaminergic neurons can be in either a tonic resting state or in a stimulated-burst state (Grace and Bunney, 1984), and if we also assume that the dopaminergic burst discharge is related to the salience of environmental stimuli (Robinson and Berridge, 1993; Schultz et al., 1997), the enhanced psychomotor and goal-directed activity symptoms would be related to hyperactivity during the burst. In contrast, the resting hyperactivity would be related to increased distractibility where the individual reacts indiscriminately to trivial stimuli.

Animal models of both psychosis and mania can be constructed using DAT inhibitors. However, the protocols differ. A model for the manic state can be created by a single administration of high-dose psychostimulant to a drug-naïve animal (Lyon, 1991). This treatment results in increased extracellular dopamine concentrations and animals

Abbreviations: CO, competitive inhibitor; [D], molar concentration of antipsychotics in the extracellular fluid; DAT, dopamine transporter; D2R, dopamine D2 receptor; D2H, high-affinity D2R; D2L, low-affinity D2R; EC50, half-maximal effective concentration; Kd, dissociation constant of dopamine for D2R; Ki, dissociation constant of antipsychotics for D2R; Kon, on-rate constant of antipsychotics; Koff, off-rate constant of antipsychotics; NC, non-competitive inhibitor.

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show increased explorative behavior in this state. In contrast, models for psychosis commonly require repeated long-term administration of psychostimulants (Martin-Iverson, 1991). Repeated treatments with psychostimulants elicit behavioral sensitization (Pierce and Kalivas, 1997; Post and Rose, 1976). Sensitized animals show alterations in the dopaminergic system, such as increases in high-affinity dopamine 2 receptors (D2H) (Seeman, 2011). Similar behavioral effects are observed in human subjects using psychostimulants. For example, acute administration of a psychostimulant can elicit transient mood-enhancement and increased pleasurable goal-directed behavior. With repeated use, some users develop a psychotic state, with persecutory or referential delusions (Ujike and Sato, 2004). Although some controversy remains, psychostimulant-induced sensitization has been proposed as a model of spontaneous psychoses, such as schizophrenia (Seeman, 2011; Lieberman et al., 1997).

To understand the hypothetical difference in dopaminergic system hyperactivity between mania and psychosis, brief simulations of both conditions were performed and the dynamics of dopaminergic signaling were analyzed in terms of the symptoms of mania and psychosis. The effects of antipsychotic drugs on these altered dynamics were also investigated and the clinical relevance was examined.

2. Methods

2.1. Resting and burst phases

Dopaminergic neuronal firing can occur in two distinct states. One is tonic firing, with relatively regular low frequency (ca. 5 Hz), which is related to the resting or basal extracellular fluid (ECF) level of dopamine. The other is phasic release with irregular bursts of firing (ca. 20 Hz) alternating with relative silence (Dreyer et al., 2010; Rice and Cragg, 2008; Venton et al., 2003). Burst firing is induced by reward-predicting stimuli (Schultz et al., 1997). This model was extended and it was assumed that the dopamine burst was related to the salience of current environmental stimuli and causes goal-pursuing activity. It was also assumed that the resting dopamine level is related to the readiness-to-react state when there is no salient stimulus. When the latter is increased pathologically, distractibility would be expected to ensue. To set up the models and specific parameters for simulation, we referred to theoretical and experimental research on dopamine dynamics under normal and pathological conditions, and estimated the ECF dopamine levels and postsynaptic receptor occupancies during the resting and burst states under each condition as below.

2.2. Model for postsynaptic dopamine 2 receptors

The postsynaptic dopamine 2 receptors were assumed to be a mixture of high-affinity receptors (D2H, Kd = 10 nM) and low-affinity receptors (D2L, Kd = 1000 nM). In the normal state, the proportion of D2H is 20%. The composite postsynaptic receptor occupancy is the sum of occupied D2H and D2L receptors among total receptors (Kang, 2012).

2.3. Model for mania

The model for mania consisted of normal postsynaptic receptors with an increased ECF dopamine concentration. This model was based on the acute effects of psychostimulants (Johanson and Uhlenhuth, 1980; Lyon, 1991; Silverstone et al., 1983). Concentrations of resting and burst dopamine under normal and psychostimulant-treated conditions were estimated as shown below.

1) Cocaine induces dose-dependent increases in dopamine levels and locomotor activity (Hurd and Ungerstedt, 1989; Lau et al., 1991). Thus, an increased dopamine concentration is related to an increase in locomotor activity, which is a model behavior in mania.
2) A simulation based on actually measured data indicated the ECF dopamine levels during the tonic (resting) and the phasic (burst) release (Venton et al., 2003). The tonic state was defined as non-synchronized firing of neurons at an average rate of 5 Hz, while phasic firing was defined as four synchronized action potentials at 20 Hz. The average tonic dopamine level was 30 nM. When DAT was blocked with 10 mg/kg cocaine, the level rose to 110 nM. Although the numerical value of the phasic dopamine level was not indicated in this report, it was around 100 nM after the first firing and rose to 200 nM after the last firing. We averaged these levels to 150 nM for the simulation. Similarly, the phasic concentration after cocaine treatment was averaged to 200 nM.
3) The resting and burst concentrations without cocaine were grossly compatible with those previously used (Kang, 2012).
4) In the paradigm of cocaine self-administration, when a stable steady state was established, the striatal dopamine concentration was 78 nM (Pettit and Justice, 1989), which is a 355% increase from the pre-treatment level of 22 nM. Because the microdialysis data were averaged over 5 min in stably habituated animals, the data represent the resting level. The proportion of increase by cocaine was fairly consistent with the present model (110/30 = 367%).
5) The peak value of electrically elicited dopamine release in the brain slice decreased with increasing concentrations of uptake inhibitors (cocaine) or releasers (amphetamine) (John and Jones, 2007). The reduced effect of burst was compatible with the present model. The burst/resting ratio decreased from normal (3.7) to cocaine (1.8) conditions with the present parameters. This means that the dynamic range of dopamine signaling was decreased by DAT blockade.

In short, in the model of mania, the normal range of dopamine, which was between 30 and 150 nM, was changed to 110–200 nM (Fig. 1) and the dynamic range of dopamine signaling was decreased.

2.4. Model for psychosis

The model for psychosis consisted of an increased responsiveness of postsynaptic dopamine 2 receptors to normal ECF dopamine concentrations. This increase was caused by an increase in the proportion of high-affinity receptors. This model was based on the postsynaptic sensitization hypothesis (Seeman, 2011), which was adopted previously

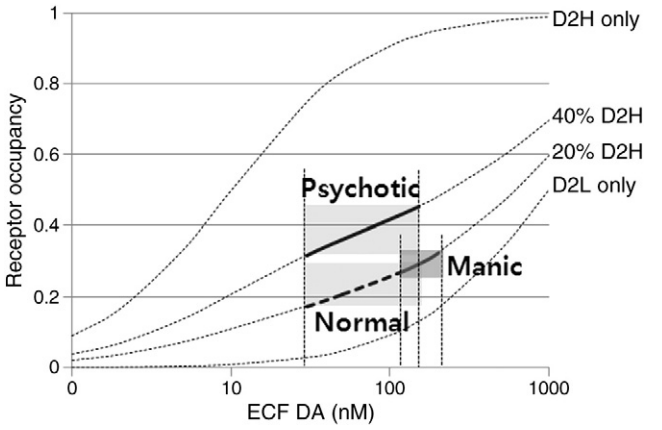

Fig. 1. Hypothetical ranges of dopamine concentration (abscissa, logarithmic) and postsynaptic dopamine 2 receptor composite occupancy (ordinate) in normal, psychotic, and manic models. The normal state is defined as 20% D2H and 30 (resting) to 150 nM (burst) dopamine. Psychosis is defined as 40% D2H and 30 (resting) to 150 nM (burst) dopamine. The manic state is defined as 20% D2H and 110 (resting) to 200 nM (burst) dopamine. The curve was adopted from the previous report (Kang, 2012).