Role of D1 and D2 Receptors in the Regulation of Voluntary Movements

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The effect of dopamine receptor agonist cabergoline on muscle tone and contractility was studied in healthy volunteers. Variations in muscle tone were evaluated by means of transcranial magnetic stimulation under resting conditions. Muscle contractility was estimated from kinematic parameters of voluntary movements. Oral administration of cabergoline in a dose of 2 mg was followed by a decrease in muscle tone and increase in muscle contractility. Our findings indicate that the brain dopaminergic system regulates voluntary movements by decreasing the tone and increasing contractility of skeletal muscles. Under resting conditions, prolonged exposure of D1 receptors to dopamine in a low concentration decreases excitability threshold of the motor cortex and reduces muscle tone. During voluntary movements, short-term stimulation of D2 receptors with dopamine in a high concentration increases excitability of the motor cortex and induces muscle contraction. The movement occurs when D2 receptor-mediated excitation of the cortex and induced muscle contraction exceed the decrease in muscle tone and excitability threshold caused by stimulation of D1 receptors.

Key Words: *dopamine; dopamine receptor; regulation of movements; muscle fiber; model*

The brain dopaminergic system is involved in the regulation of movements [2]. The nigrostriatal dopaminergic system of the brain regulates voluntary movements by decreasing the tone and increasing contractility of skeletal muscles. The dopaminergic regulation of muscle tone and contractility is realized via postsynaptic D1 and D2 dopamine receptors in nigrostriatal synapses [6]. The regulation of muscle tone and contractility in vertebrates involves both types of dopamine receptors in the nigrostriatal system [17]. D1 and D2 receptors differ in the chemical structure, activate various intracellular signal systems, and have different evolutionary origin. This conclusion is derived from significant differences in the structure of genes encoding D1 and D2 receptors [2]. Evolutionarily, D1 and D2 receptors gain the ability to bind dopamine independently of each other. Selective modulation of D1 and D2 receptors is associated with different sensitivity of these structures to various concentrations of dopamine. D1 and D2 receptors are sensitive to dopamine in low and high concentrations, respectively [18]. Colocalization of both receptors on the neuronal membrane contributes to regulation of the tone and contractility in agonistic and antagonistic muscles, which are involved in the realization of certain movements [1].

Here we studied the effect of dopamine receptor agonist cabergoline on the amplitude of the compound muscle action potential induced by focal transcranial magnetic stimulation under resting conditions. Kinematic parameters of standard repeated voluntary movements were recorded. This work was designed to evaluate the role of D1 and D2 receptors in the regulation of the tone and contractility of striated muscles.

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MATERIALS AND METHODS

We examined 8 healthy volunteers. The scheme of our study was approwed by the Ethical Committee of the Frankfurt am Main University. The trial was performed with right-handed individuals (5 men and 3 women of 24-36 years, average age 29.2± 2.3 years). D1 and D2 receptor agonist cabergoline was given orally in a single dose of 2 mg. The half-life period of cabergoline is 24 h. The dissociation constants of cabergoline for various types of dopamine receptors are similar to those of physiological dopamine [8]. The tone was estimated before and 2, 6, and 24 h after administration of cabergoline.

Muscle tone was evaluated from the compound muscle action potential in the short adductor muscle of thumb (*M. adductor pollicis brevis*). It was induced by focal transcranial magnetic stimulation (TMS) under resting conditions. The potential was recorded on a Dantec electromyograph equipped with 0.05-2.00-kHz filters (digitization frequency 4 kHz). TMS was performed using a BiStim module device (Magstim Co). The potential of resting muscle was induced by TMS of increasing intensity. The strength of stimulation progressively increased from the threshold level (minimal stimulation, 50-μV potential in resting muscle) to a level at which further increase in stimulation was accompanied by maximum increase in muscle resting potential. Further increase in the strength of TMS was not followed by the increase in the potential. The pulses of different power (threshold-to-maximum stimulation) were randomly delivered at 20-sec intervals. A total of 50 pulses of 10 powers were delivered (5 pulses of each power).

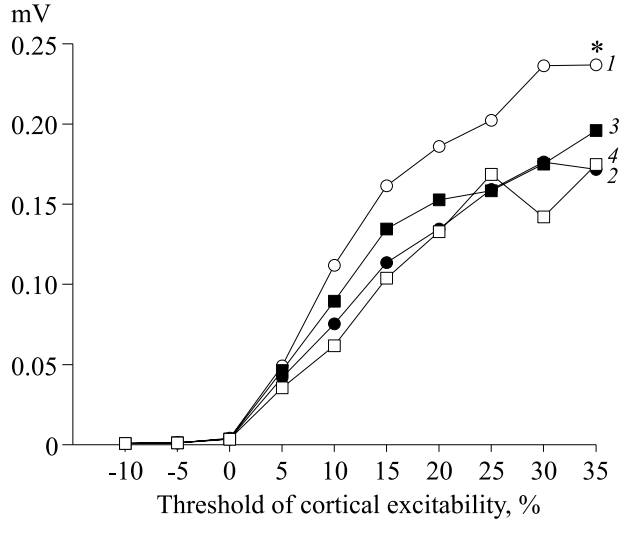

Fig. 1. Decrease in cortical excitability at increasing stimulation. Before (*1*) and 2 (*2*), 6 (*3*), and 24 h after administration of cabergoline. *$p<0.05$ compared to the baseline value.

Muscle contractility was estimated from kinematic parameters of standard repeated voluntary movements before and 6 h after drug treatment. Standard repeated voluntary movements were manifested in adduction and abduction of the thumb in the right (dominant) hand. Adduction and abduction should be performed 100 times at the maximum frequency in response to the metronome signal (1 Hz). Two uniaxial accelerometers (Model 2256A-100) were fixed to the thumb. Kinematic parameters of abduction-adduction and flexion-extension were measured with sensitivity of 100 mV/g (Endevco corp.). We recorded induced movement acceleration, maintenance of movement direction, and variations of each movement from the specified direction (dispersion). The percentage of movements that corresponded to ±15% range of the specified direction was calculated.

Muscle tone and contractility in each volunteer were measured twice (cabergoline and placebo presented at random) with 1-week interval.

The results were analyzed by ANOVA for repeated measurements (SPSS software). The mean values were compared before and after cabergoline administration. Variations of parameters were also evaluated in the placebo group. The differences were significant at $p<0.05$.

RESULTS

The compound muscle action potential induced by TMS of resting muscle was much lower 2, 6, and 24 h after cabergoline administration ($p<0.05$, Figs. 1 and 2). Cabergoline-induced decrease in the amplitude was observed during TMS of any suprathreshold intensity. After drug treatment, the curve for the increase in the compound muscle action potential reached a plateau and remained unchanged at lower TMS intensity (compared to the pretreatment level). These changes reflect the decrease in motor cortex excitability. In patients with Parkinson's disease, the increase in muscle tone (rigidity) correlates with high amplitude of the potential and elevated excitability of the cortex [8]. TMS in patients with Parkinson's disease was performed before and after switching on the bilaterally implanted subthalamic electrodes. A simultaneous decrease in cortical excitability and muscle tone was revealed [4,5]. This treatment is similar to pharmacological stimulation of dopamine receptors under the influence of cabergoline. The decrease in the amplitude of muscle contraction can be considered as an electrophysiological criterion for the reduction of muscle tone.

Cabergoline significantly improved kinematic parameters of voluntary movements. Movement

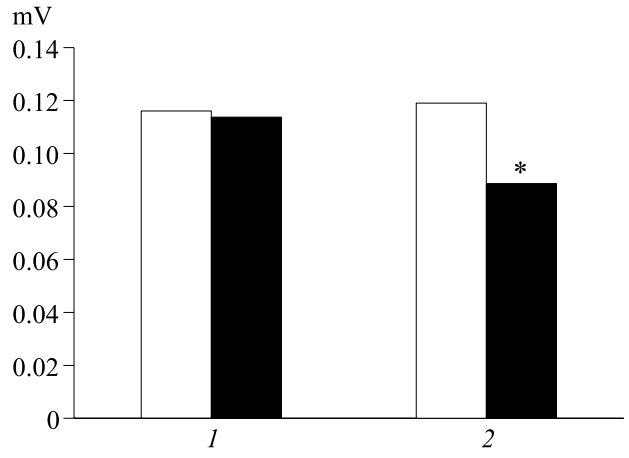

Fig. 2. Decrease in the amplitude of the compound muscle action potential at increasing stimulation after administration of cabergoline (compared to placebo). Here and in Fig. 3: light bars, baseline parameters; dark bars, after administration of placebo (*1*) and cabergoline (*2*). *$p<0.05$ compared to placebo.

acceleration increased from 28.3 to 46.2 m/sec^2 ($p<0.05$). The direction of movement was preserved in 77% kinematic tests (*vs*. 45% under basal conditions, $p<0.05$, Fig. 3). Kinematic parameters of voluntary movements depend on contractility of striated muscle [7,11]. Muscle contractility is determined by the strength of nigrostriatal dopaminergic stimulation. Hence, the increase in nigrostriatal dopaminergic stimulation can improve contractility. This phenomenon manifested in reduction of bradykinesia in patients with Parkinson's disease after treatment with dopaminergic drugs. Our results indicate that the improvement of kinematic parameters may occur in healthy people after administration of the dopamine agonist.

The TMS potential amplitude and kinematic parameters remained unchanged in the placebo group ($p>0.05$, Figs. 2 and 3). The decrease in cortical excitability and improvement of kinematic parameters were significant in cabergoline-treated patients ($p<0.05$ compared to placebo).

The observed changes in muscle tone and contractility are probably associated with the ability of nigrostriatal dopamine to regulate both types of muscle fibers in striated muscles, including red fibers (slow or tonic fibers for maintenance of muscle tone) and white fibers (rapid or phasic fibers for muscle contraction) [15]. Dopamine can produce a selective effect on the tone and contractility, which depends on the type of activated receptors. Locomotor disorders differ in genetically modified muscles that do not express the D1 or D2 receptor [14].

The presence of dopamine in high concentration that activates D2 receptors is observed during activation of voluntary movements (*i.e.*, muscle contraction) [13]. The tone of striated muscles remains unchanged at rest. Dopamine concentration in the synaptic gap is low, which contributes to activation of only D1 receptors [18]. It should be emphasized that dopamine acts diffusely in rest (volume mediator) [9]. These data suggest that activation of D2 receptors is related to function of white muscle fibers (phasic or rapid fibers) and results in muscle contraction. Activation of D1 receptors regulates the state of red fibers (tonic or slow fibers) and, therefore, affects muscle tone. Colocalization of both receptors on the membrane of the same striatal neurons [1] allows simultaneous topic regulation of the tone and contractility in agonistic and antagonistic muscles, which are involved in the realization of certain movements. Modulation of the tone and contractility is realized via the motor cortex [10] and descending reticulospinal tract [16]. Under resting conditions, prolonged exposure of D1 receptors to dopamine in low concentration is followed by a decrease in the excitability threshold

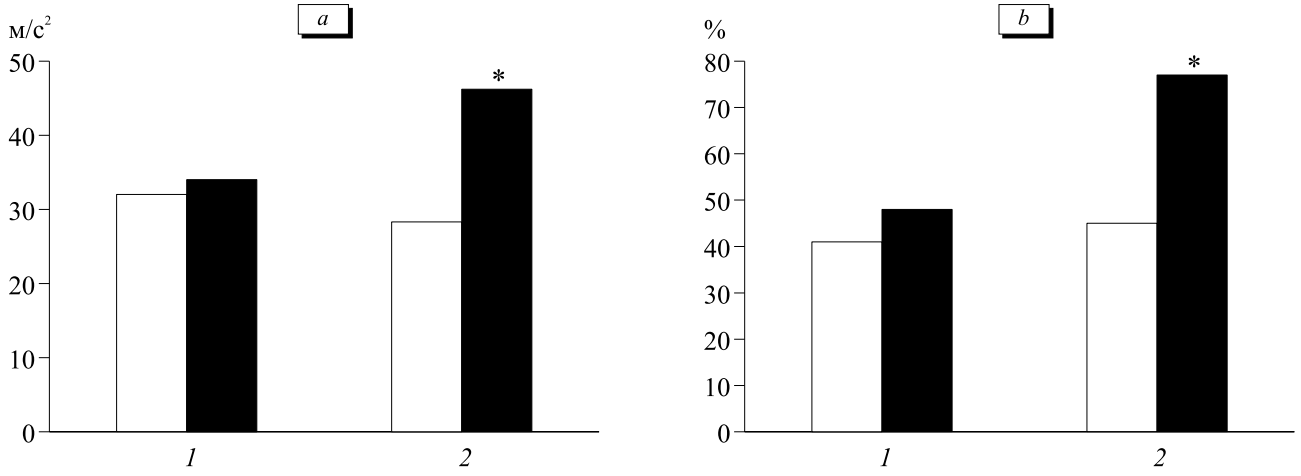

Fig. 3. Variations in kinematic parameters: acceleration (*a*) and maintenance of movement direction (*b*) after administration of cabergoline.

of the motor cortex and decrease in activity of the reticulospinal tract [16]. The decrease in the excitability threshold of the motor cortex prevents the increase in muscle tone. Short-term stimulation of D2 receptors with dopamine in high concentration is followed by an increase in motor cortex excitability and causes muscle contraction due to corticospinal influences. The movement occurs when D2 receptor-mediated excitation of the cortex and induced muscle contraction exceed the decrease in muscle tone and excitability threshold due to D1 receptor stimulation. Nigrostriatal dopamine deficiency during hypokinetic rigid syndrome (*e.g.*, Parkinson's disease) is accompanied by an increase in the tone (rigidity) and decrease in contractility (hypokinesia).

Variations in the tone and contractility under the influence of cabergoline are probably associated with a similar neurochemical profile of this drug and physiological dopamine. Our results can be used to evaluate the regulation of voluntary movements and to develop new pharmaceutical preparations for the therapy of locomotor disorders.

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