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Research report

Motor sequence learning in primate: Role of the D2 receptor in movement chunking during consolidation

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ABSTRACT

Motor learning disturbances have been shown in diseases involving dopamine insufficiency such as Parkinson's disease and schizophrenic patients under antipsychotic drug treatment. In non-human primates, motor learning deficits have also been observed following systemic administration of raclopride, a selective D2-receptor antagonist. These deficits were characterized by persistent fluctuations of performance from trial to trial, and were described as difficulties in consolidating movements following a learning period. Moreover, it has been suggested that these raclopride-induced fluctuations can result from impediments in grouping separate movements into one fluent sequence. In the present study, we explore the hypothesis that such fluctuations during movement consolidation can be prevented through the use of sumanirole – a highly selective D2 agonist – if administered before raclopride. Two monkeys were trained to execute a well known sequence of movements, which was later recalled under three pharmacological conditions: (1) no drug, (2) raclopride, and (3) sumanirole + raclopride. The same three pharmacological conditions were repeated with the two monkeys, trained this time to learn new sequences of movements. Results show that raclopride has no deleterious effect on the well known sequence, nor the sumanirole + raclopride co-administration. However, results on the new sequence to be learned revealed continuous fluctuations of performances in the raclopride condition, but not in the sumanirole + raclopride condition. These fluctuations occurred concurrently with a difficulty in merging separate movement components, known as a "chunking deficit". D2 receptors seem therefore to be involved in the consolidation of new motor skills, and this might involve the chunking of separate movements into integrated motor sequences.

1. Introduction

Activities of daily living such as reaching and grasping an object, writing a letter, or playing golf, always involve sequences of movements grouped together that constitute complex actions. However, the functional and physiological processes underlying such combinations of isolated movements into smooth and coherent motor sequences remain poorly understood. The synergy and kinematic properties of the motor sequence are thought to be progressively learned through practice, until error-based readjustments become minimal [9]. The motor skill is then considered as optimally performed.

Two stages have been commonly identified in the learning process of a motor sequence: a first stage in which rapid improvement takes place within very few trials, and a second stage involving slower but progressive improvement from trial to trial, or from a testing session to another [17,30]. Following this second stage, the motor skill is thought to be consolidated because its optimal performance remains stable, whatever the delay or the interference between each occurrence. This consolidated phase was found to be compromised following the anatomical or pharmacological disturbance of the central dopaminergic systems, in both humans and animals [2,3,16,24,27,38]

Recently, Levesque et al. [22] described persistent fluctuations of motor performance in primates following the administration of raclopride, a selective dopamine D_2 receptor (D_2R) antagonist.

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Although these fluctuations were present throughout learning, they were more particularly evident during the late learning stages, for many weeks, when performances should have been stabilized. However, raclopride did not affect motor sequences that were already consolidated, that is stable before the administration of the drug. Qualitative analyses revealed that the raclopride-induced fluctuations occurred in concomitance with a specific difficulty monkeys had in grouping separate movements into integrated and fluent motor sequences [22].

Graybiel et al. [13] referred to the chunking hypothesis to explain the grouping of movements that takes place during motor sequence learning. This hypothesis, raised first by Miller [27] about episodic memory, may be summarized as the grouping of discrete items into meaningful or categorical chunks, in order to facilitate their retention. The view that such a functional mechanism is also involved in movement learning is concordant with results obtained in rats and primates showing cell activity in the striatum, involved in the re-organization of single movements into integrated sequences [2,3,16,24].

Currently, there is no study showing the systematic induction and reversal of chunking disturbances during movement sequence learning. The present study aimed at further showing the Dopamine dependent mechanism in such a chunking process during motor learning. Two experiments have been conducted in primates for this purpose: one assessing the effects of a systemic injection of a D_2R antagonist, and the second assessing the effects of an injection of D_2R agonist prior to the D_2R antagonist. According to previous studies [22], fluctuations of performance and chunking disturbances are expected with raclopride, especially during the late learning stage, that is during the consolidation process. In the present study, the pre-administration of sumanirole, a selective D_2R agonist, is expected, however, to prevent such a raclopride-induced deleterious effect.

2. Materials and methods

2.1. Animals

Two cebus apella monkeys (2–4 kg), J and L, were used. They were kept in individual cages with food available at all times. A water restriction routine was use to motivate the animals during training periods. Body weight and general health were monitored before and throughout the experiment. All procedures were conducted in accordance with the guidelines of the Canadian Council on Animal Care (CCAC), and approved by both, the UQAM and "Université de Montréal" Animal Research Ethic Boards.

2.2. Drug protocol

S(−)-raclopride (+)-tartrate salt (Sigma–Aldrich, Montréal, Canada) was chosen as D_2R antagonist because of its high affinity and selectivity for this receptor. At low dose, raclopride shows high striatal D_2R occupancy [20,45]. The drug has a short half-life of 3 h, showing complete elimination within 24 h, and allowing a testing session each day. The D_2R agonist (5R)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5,1-ij]quinolin-2(1H)-one(2Z)-2-butenedioate (sumanirole) was chosen for its pharmacokinetic and pharmacodynamic features close to those of raclopride [25,43]. Both drugs were prepared just before testing sessions, by dissolving the pure substance in a 0.9% saline solution.

For each monkey, doses of raclopride were determined from the criteria of Levesque et al. [22] allowing to reach the highest tolerated doses showing no sedation, or extrapyramidal side effect. This corresponded to 0.01 mg/kg for monkey L and 0.005 mg/kg for monkey J. Raclopride is known to reach its peak concentration time (T_{max}) at 30 min post-injection [20]. The testing sessions took place at this time, and lasted 15 min. Sumanirole doses were those suggested by Stephenson et al. [43] to obtain the maximum antiparkinsonian effect. This corresponds to 1 mg/kg in each monkey. Sumanirole is known to reach its T_{max} at 60 min post-injection, and has an elimination half-life of 2 h, allowing daily administration without accumulation. In the sumanirole + raclopride condition, sumanirole was first injected followed 15 min later by the raclopride injection. This procedure allowed us to reach the T_{max} at approximately the same time for both drugs, and assured adequate drugs exposure of monkeys during testing (which occurred in a window of 45–60 min post-sumanirole injection).

Potential extrapyramidal side effects of raclopride, or sumanirole + raclopride, were assessed prior to the experimental conditions. During these pre-experimental sessions, two injections were always given to each monkey, in order to eliminate the potential distinction between the raclopride and the raclopride + sumanirole conditions, which involve respectively one and two drugs. We tested four conditions including: (1) raclopride 0.005 mg/kg + a vehicle, (2) raclopride 0.01 mg/kg + a vehicle, (3) raclopride 0.005 mg/kg + sumanirole 1 mg/kg, and (4) two vehicle injections. These conditions were randomized, and occurred at a 3-day interval. Monkeys' movements and postures were evaluated during the 2 h following injection, by using an adapted version of the ≪Abnormal Involuntary Movements Scale≫ (AIMS) [36]. The scale was administered by an experienced neurologist (P.B.) familiar with the extrapyramidal symptoms in monkeys, and blind to the injections. The monkey's overall activity was also monitored with a digital camera connected to a computer equipped with custom-made software. This allowed identifying any symptom of bradykinesia, or sedation that may have appeared outside the 2 h observation window. The two monkeys showed no evidence of sedation or extrapyramidal symptoms following the administration of the doses used for this study.

2.3. Behavioral task

The movement sequence learning task was similar to the one described by Levesque et al. [22], and will only be summarized here. The two primates were trained to sit in a monkey chair facing a 25 cm × 25 cm box placed 30 cm in front of them, and on which could be found six light-emitting push-buttons (3 cm × 3 cm) that could be lit independently (Fig. 1). Monkeys were required to press push-buttons to obtain a reward (drop of water). Button illumination and data acquisition were controlled by a computer equipped with custom-made software (DOCO Microsystems Inc. Montréal, Canada). Movement sequences consisted in successively pressing three lit push-buttons. Monkeys had to press the push-button before illumination of the next. All sequences covered the same spatial length, and the same number of buttons. For each correct sequence, reward was given after the press of its third push-button. If the monkey did not press a push-button after 4 s, or pressed on an incorrect push-button, the trial was cancelled and a new trial began. Trials were administered at a random interval between 1 and 3 s. Monkeys were able to complete 100–150 trials per day, within a testing session of approximately 15–20 min.

Before learning any sequence, monkeys were required to press on push-buttons randomly lit one at the time, in order to explore the entire box. When monkeys were able to press on each push-button with a success rate of at least 80%, sequence learning began. Monkey L was left-handed and was trained to learn the sequences clockwise, while monkey J was right-handed and learned the sequences counterclockwise.

The first portion of each motor sequence (1st and 2nd push-button) was kept the same for all sequences used in this study, while the second portion (2nd and 3rd push-button) changed according to the experimental condition (Fig. 1b). By distinguishing the two portions of the sequences, we aimed at better defining the chunking process of a new motor component (push-buttons 2–3) to a well established one (push-buttons 1–2).

2.4. Training protocol

The protocol is illustrated in Fig. 1b. Four different sequences were used depending on the experimental conditions. In the first condition, monkeys had to learn a first motor sequence, and execute it for over 2000 trials, corresponding to 20 days of testing. This over-learned sequence was considered as the baseline condition, that is a well established movement sequence. In the second condition, monkeys had to learn a new sequence without drugs (no drug condition). Thereafter, monkeys had to learn again a new sequence under the effect of an acute injection of raclopride (raclopride condition). Finally, a fourth sequence had to be learned by the monkeys, following the co-injection of sumanirole and raclopride (sumanirole + raclopride condition). Each of these learning conditions required the primates to successfully complete 1500 trials, corresponding to 15 days of testing. Before any change from one condition to another, a recall of the over-learned sequence was done to assess the effect of drugs on such a well established motor sequence. This recall condition of the over-learned sequence spanned over 500 trials, corresponding to 5 days of testing. Between each of the four experimental conditions, monkeys were not taken out of their home cage for a 5 day period, in order to avoid a possible carry on effect of the drug used in previous experimental condition.

2.5. Movement learning measurements

2.5.1. Raw data

Each sequence performed within a trial can be divided into a first portion (spreading from the 1st push-button release to the 2nd push-button press), and a second portion (spreading from the 2nd push-button release to the 3rd push-button press). Reaction time (RT), and movement time (MVT) were recorded separately for these two portions. RT was defined as the time between a push-button illumination, and the release of the preceding push-button. MVT was defined as the time between the release of a push-button, and the pressing on the next one. Therefore,