

Effect of sensory stimulus on striatal dopamine release in humans and cats: a [¹¹C]raclopride PET study

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Abstract

Background : Sensory stimulation of the forelimb extremities constitutes a well-established experimental model that has consistently shown to activate dopamine (DA) neurotransmission in the mammals' forebrain. **Objectives** : To visualize in vivo this modification of striatal DA release in healthy human volunteers using Positron Emission Tomography (PET) and [¹¹C]raclopride. Experiments in humans were paralleled by experiments in anesthetized cats. Changes in endogenous DA release were assessed through its competition with [¹¹C]raclopride binding (BP_{raclo}), a radioligand probing DA D2-receptors. **Results** : In humans no significant difference of BP_{raclo} in caudate (with sensory stimulation: 2.0 ± 0.3 versus without sensory stimulation: 2.2 ± 0.3; *P* = 0.3) or putamen (2.6 ± 0.3 versus 2.6 ± 0.2; *P* = 0.9) ipsilateral to the stimulus was disclosed as a result of sensory stimulation. Similarly, no change of BP_{raclo} was observed contralaterally to the stimulation in the caudate nucleus (with sensory stimulation: 2.0 ± 0.4 versus without sensory stimulation: 2.1 ± 0.2; *P* = 0.5) and the putamen (2.5 ± 0.4 versus 2.6 ± 0.2; *P* = 0.4). In cats the same results were obtained in the ipsilateral to stimulation striatum (with sensory stimulation: 2.5 ± 0.03 versus without sensory stimulation: 2.4 ± 0.05; *P* = 0.7). No change was also observed contralaterally to the stimulation (2.4 ± 0.04 versus 2.5 ± 0.06; *P* = 0.6). The [¹¹C]raclopride binding remained unchanged by sensory stimuli in both humans and cats. **Conclusion** : This suggests that the DA release induced by sensory stimulus is mostly extrasynaptic whereas the synaptic DA release is probably small, which fits well with the absence of [¹¹C]raclopride displacement. The mechanism of this extrasynaptic DA release could be related to a local action of glutamate on dopaminergic terminals via a thalamo-cortico-striatal loop. Present results also underline homology between cat and human responses to sensory stimuli and validate the use of cat brain to find physiological concepts in humans.

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The quantification of dopamine (DA) neurotransmission in vivo is a crucial challenge in both basic and clinical research. In animals, invasive biochemical methods (such

as microdialysis or voltammetry) provide direct measures of DA concentration in the extracellular space. Due to their invasiveness, such methods cannot be applied in humans and accessing the DA neurotransmission in the human brain has remained a challenge until the recent development of non-invasive techniques such as Positron Emission Tomography (PET) or Single Photon Emission Computed Tomography (SPECT) imaging [5,6,8,13,18,23,24,43]. It has been first demonstrated that [³H]raclopride, a ligand used to measure

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D2-receptor densities, was sensitive to changes in the levels of endogenous DA [44]. Competition between endogenous DA and the radioligand for binding on DA D2-receptors has been proposed as the most important underlying mechanism to explain the changes in [¹¹C]raclopride binding, but other mechanisms such as receptors trafficking also play a role [24]. This gave the opportunity to measure, *in vivo*, using PET and [¹¹C]raclopride, variations of endogenous DA levels under many conditions like glucose deprivation, pharmacological challenges, and cognitive or motor tasks [1,2,5,6,8,11,20,22,23,39,41,45,49]. Pharmacological approaches have also been used with success in animals but are often difficult to transpose in humans [7,13,18,22–24,50].

In the present study, another non-invasive experimental model of DA release was evaluated using PET and [¹¹C]raclopride. Indeed, in cats, it has been shown using invasive methods that a lateralized non noxious sensory stimulation of the forelimb induced a long lasting increase of DA release in the striatum ipsilaterally to the stimulation and a contralateral decrease [34,35]. The stimuli-induced alterations in DA release were measured as the efflux of [³H]DA during a local superfusion with [³H]tyrosine (the metabolic precursor of DA) through a push pull canula acutely implanted in the striatum. It was later demonstrated that this effect was mediated through a thalamo-cortico-striatal loop regulating DA striatal terminals through glutamate (GLU) neurotransmission [3,28]. This mechanism of DA release is mainly extrasynaptic. In addition, it does not interfere with post-synaptic DA receptors and reduces DA release via a feedback process involving presynaptic DA receptors [15,37,42]. However, this phenomenon has, to our knowledge, never been studied in humans.

Thus, the main objective of the present study was to analyze using PET and [¹¹C]raclopride, in both cats and humans, the modifications in striatal DA release following sensory stimulation. We hypothesize that, regarding the predominant extrasynaptic DA release demonstrated by microdialysis techniques in cats, no modification of the [¹¹C]raclopride binding should be observed. The same results should be observed in humans if the mechanisms of DA release under sensory stimulation are similar.

Eight normal subjects participated in the study (mean age \pm S.D.: 55.7 ± 9.7 years; range: 41–69; five males/three females). All subjects except one were right handed. In addition, they were all free of psychiatric or neurological disorders and had normal physical examination. Any treatment with neuroleptics, antiparkinsonian or antidepressant drugs, monoamine oxidase inhibitors or alpha-methyl-DOPA meant exclusion. All subjects underwent a standard brain MRI (Siemens Expert 1 T MRI system) with T1 and T2 weighted sequences prior to the PET scan to ensure that no lesion was present. The present study was performed after approval by the Lyon University Hospitals Ethics Committee. All subjects participated after the nature of the procedure had been fully explained and signed an informed consent form according to the declaration of Helsinki.

Four European male cats weighing about 3 kg and obtained from Iffa-Credo (France) were used. Studies were performed by licensed investigators in accordance with French (87-848, Ministère de l'Agriculture et de la Forêt) and European Economic Community (86-60, EEC) guidelines for care of laboratory animals and were approved by the regional ethical animal use committee.

PET studies were performed on a Siemens ECAT Exact HR+ used in three-dimensional mode. The system covers an axial distance of 15.5 cm. The transaxial resolution of the reconstructed images is about 4.1 mm full widths at half-maximum in the center. Transmission scans were acquired with three rotating ⁶⁸Ge–⁶⁸Ga sources and used to correct the emission scans for the attenuation of 511 keV photon rays through tissue and head support.

The human subjects participated in two [¹¹C]raclopride PET scans performed on the same day. The first PET scan was initiated after injection of (mean \pm S.D.) 208 ± 10 MBq [¹¹C]raclopride. The second PET scan was initiated 2–4 h later, after injection of 212 ± 8 MBq [¹¹C]raclopride, and was associated with a non-noxious electrical stimulation of the right wrist, which lasted during all the duration of the PET scan.

Each cat underwent four PET scans. Two were performed without sensory stimulation and the two others under sensory stimulation. Animals were anesthetized by constant insufflation of halothane (1.5%) in medical air through a respiratory mask. Carbon dioxide concentration in expired gases, heart rhythm, and body temperature were continuously controlled throughout the PET experiments. The head was maintained in a fixed position by a stereotactic holding device made with Plexiglas. A canula was inserted in the cephalic vein for radiotracer injection. Time curves–activity were integrated in the same way as in humans but between 40 and 67 min taking because of the lower amount of radioactivity injected (55 MBq).

In humans, the sensory stimulus consisted of an electrical stimulation of the right median nerve at the wrist. Stimulation (pulse duration: 0.5 ms; frequency: 0.2 Hz) was delivered by a constant-voltage stimulator. In cats, sensory stimuli (pulse duration: 0.5 ms; frequency: 0.2 Hz) were delivered through subcutaneously pad-implanted thin needles in one forelimb. In humans and cats, intensity was adjusted just above the threshold for muscular contraction and was not painful.

The stimulation began at the injection time and lasted the whole duration of the scan (90 min and 67 min, respectively, in human and cat).

The 3D emission data were reconstructed by 3D filtered back projection (Hanning filter; cut-off frequency, 0.5 cycles/pixel), giving a transaxial resolution of 6.5 mm full-width half-maximum. Radioactivity was measured in a series of sequential time frames of increasing duration (from 30 s to 10 min) corrected for decay and plotted versus time. The total time for measurement of radioactivity in the brain was 90 min for [¹¹C]raclopride (67 min in cats) studies.

In human subjects, one elliptical region of interest (ROI) of $2.5 \pm 0.3 \text{ cm}^2$ was placed along the axis of each putamen and one circular ROI of $1.3 \pm 0.1 \text{ cm}^2$ was positioned on each head of caudate nucleus. These ROIs were placed on five consecutive planes according to a human brain atlas. The non-specific background activity was averaged from a single elliptical ROI of $5 \pm 0.5 \text{ cm}^2$ drawn over the cerebellum on two consecutive planes. The BP_{raclo} was determined using a graphical approach and a tissue input function as previously described [21].

In cats, ROI for the right and left caudate nuclei and the cerebellum were drawn on the reconstructed PET images according to a cat brain atlas. Due to the small area of occipital cortex in the reconstructed images, the cerebellum was preferred as reference. Radioactivity in the cerebellum was used as an estimate of free radioligand concentration and non-specific binding in brain (F). Specific ligand binding (B) was defined as the difference between the total regional radioactivity and that of the cerebellum. The time curves for B ($B(t)$) and F ($F(t)$) were integrated and the specific binding ratio (B/F) which is also referred as the BP_{raclo} was calculated with the same method as in humans [21].

The mean [^{11}C]raclopride binding values for both the ipsilateral and contralateral caudate nucleus and putamen without sensory stimulation were compared with those under sensory stimulation using paired Student two-tailed t test with Bonferroni correction for multiple comparisons ($P < 0.05$).

In humans no significant difference of BP_{raclo} in the caudate (with sensory stimulation: 2.0 ± 0.3 versus without sensory stimulation: 2.2 ± 0.3 ; $P = 0.3$) or putamen (2.6 ± 0.3 versus 2.6 ± 0.2 ; $P = 0.9$) ipsilateral to the stimulus was disclosed as a result of sensory stimulation. Similarly, no change of BP_{raclo} was observed contralaterally to stimulation in the caudate nucleus (with sensory stimulation: 2.0 ± 0.4 versus without sensory stimulation: 2.1 ± 0.2 ; $P = 0.5$) and the putamen (2.5 ± 0.4 versus 2.6 ± 0.2 ; $P = 0.4$). These data are presented in Fig. 1.

As in humans, no change in the BP_{raclo} was obtained in the striatum ipsilateral to stimulation (with sensory stimulation: 2.5 ± 0.03 versus without sensory stimulation: 2.4 ± 0.05 ;

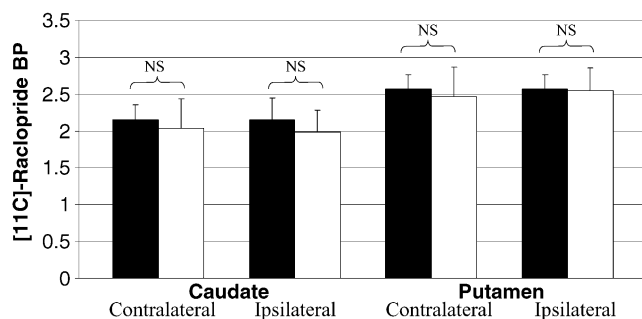


Fig. 1. [^{11}C]Raclopride binding in humans in the caudate nucleus and putamen, contralateral and ipsilateral to the sensory stimulation (mean \pm S.D.). (In black) [^{11}C]Raclopride binding without sensory stimulation. (In white) [^{11}C]Raclopride binding under sensory stimulation. NS: not significant; BP: binding potential.

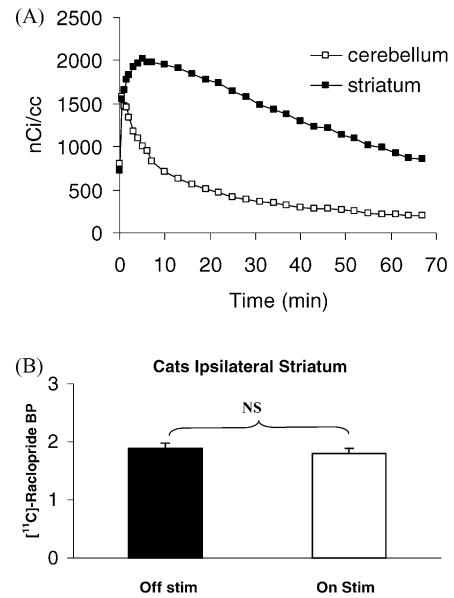


Fig. 2. (A and B) [^{11}C]Raclopride binding in 1.5% halothane anesthetized cat. Time-activity curves obtained in striatum ipsilateral to the stimulation and cerebellum after intravenous injection of the radioligand (A). BP_{raclo} values are presented on histogram (B). No significant difference was induced by the stimulation. (In black) The mean [^{11}C]raclopride binding value without sensory stimulation. (In white) The mean [^{11}C]raclopride binding value under sensory stimulation. BP: binding potential; NS: not significant.

$P = 0.7$). No change was also observed contralaterally to the stimulation (2.4 ± 0.04 versus 2.5 ± 0.06 ; $P = 0.6$). These data are presented in Fig. 2A and B.

During the two last decades, the mechanisms underlying the increase in DA neurotransmission induced by sensory stimuli have been progressively characterized in animals. The present study suggests that the striatal DA release induced by sensory-stimulus does not modify the [^{11}C]raclopride binding, which is compatible with an extrasynaptic DA release previously measured by microdialysis.

Sensory stimuli have been consistently reported to increase DA release in the cat striatum on the side corresponding to the stimulated forelimb [3,28,34,35]. However, no reduction in BP_{raclo} was detected using this experimental paradigm, whereas several experimental situations producing putative increases of DA neurotransmission such as complex cognitive tasks, stress, motor tasks as well as pharmacologic challenge have shown a decrease [^{11}C]raclopride binding by a competitive effect with endogenous DA [1,2,5,6,20,22,23,44,49].

In cats, halothane anesthesia could have played a role in this lack of [^{11}C]raclopride displacement. The effects of anesthetics on [^{11}C]raclopride uptake have been assessed in numerous studies. It has been shown that isoflurane enhances the displacement of [^{11}C]raclopride induced by nicotine [44]. Other experiments demonstrated that ketamine, another anesthetic drug, decreases the striatal binding of [^{11}C]raclopride [45]. Halothane can potentiate the effect of a dopamine transporter inhibitor leading to a further reduction

of striatal dopamine release [10]. The physiological basis of the modification of [^{11}C]raclopride binding induced by anesthetic drugs remains debated but modifications of dopaminergic D2 receptors affinity and dopamine turn-over and not only changes of synaptic dopamine concentration have to be considered [47]. We recently showed that no [^{11}C]raclopride displacement could be obtained after drug or depolarisation-induced DA release under halothane when it was possible under ketamine [14]. This difference has been interpreted as a reduction of D2 receptors affinity under halothane but not ketamine [14]. However, for the purpose of our present study, it has been verified in another experiment that, under sensory stimulation, no change in BP_{raclo} occurred even under ketamine anesthesia [16]. To summarize, the role of anesthesia cannot be completely ruled out in cats, but obviously cannot explain the results in humans.

The first explanation for the lack of effect of sensory stimulation on [^{11}C]raclopride binding and for the discrepancy between microdialysis and PET data may be the relatively poor sensitivity of [^{11}C]raclopride to moderate changes in DA release [33,48]. Indeed, the alterations in the DA release produced by sensory stimuli were reported to be of low amplitude. When measured using *in vivo* local superfusion methods an increase of only about 50% of the extracellular level was reported [28]. Also the test-retest variability of BP_{raclo} in healthy control volunteers has been reported to vary between 7 and 13% [43,49]. On the other hand it has been demonstrated after amphetamine that an increase by 44% DA release, assessed by microdialysis, results in only a 1% decrease in [^{11}C]raclopride binding [2]. This shows that, although amphetamine induces a 400–1500% increment in DA release, the BP_{raclo} is only reduced by 10–38%. It therefore might be possible that the failure to detect significant changes in BP_{raclo} following sensory stimulation could be due to the fact that such changes, if they exist, may have been within the range of test-retest variability or were very small and therefore undetectable.

However, the problem is likely more complex. Indeed, direct electrical stimulation of DA axons in the cat and the rat also produces a moderate increase of the DA release, but this also leads to a clear displacement of the [^{11}C]raclopride [14,29,32,38]. This shows that a small synaptic DA release can induce a significant [^{11}C]raclopride displacement.

We therefore think that the discrepancy between the lack of BP_{raclo} modifications and the measured DA release induced by sensory stimulation is more likely due to the type of DA release under this specific sensory stimulation. Indeed, two major mechanisms contribute to the striatal DA release. Discharge of the neurons in a bursting way induces a major increase of intrasynaptic DA release (phasic), which interferes with the postsynaptic receptors. By contrast, glutamatergic inputs to the DA cells regulate a lower tonic DA release, which does not trigger intrasynaptic receptors, and reduce the DA release via the stimulation of presynaptic DA receptors [15,26,37,42]. The signal that initiates DA release in the striatum after sensory stimuli was proposed for a long

time to result from a local action of GLU on DA terminals via a thalamo-cortico-striatal loop [3,27]. The way by which GLU interferes with DA release in the striatum is complex and highly dependent on the experimental conditions [3,5,9,30,31]. However, a large set of evidence obtained in animals support the hypothesis that GLU facilitates the reverse transport of the amine, and reduces the natural uptake [12,26]. Finally, GLU inhibits DA synthesis [4]. This mode of release involves the DA-transport protein, known to be located extrasynaptically [17,36,40]. Thus this kind of DA release occurs in large part outside the synapses and [^{11}C]raclopride binding is likely much more sensitive to events occurring intrasynaptically than to alterations of extracellular DA level. This is attributable to a major intrasynaptic location of the DA D2 receptors [19,25]. It follows from this that sensory stimuli increase extrasynaptic DA release and thus does not affect BP_{raclo} .

Another mechanism related to complex modifications of dopamine synthesis, dopamine transporter availability or dopamine receptors affinity could also explain the discrepancy between the previously demonstrated increase of extracellular dopamine release under sensory stimulation and the lack of [^{11}C]raclopride uptake reduction. This has been well illustrated by Tsukada et al. who showed in conscious monkeys that scopolamine, a cholinergic antagonist, or ketamine, reduced striatal [^{11}C]raclopride binding without increasing extracellular striatal dopamine concentration [46,47]. The absence of increase of extracellular dopamine concentration was attributed to the opposite effects of an increase of dopamine synthesis and of dopamine transporter availability, while the reduction of [^{11}C]raclopride binding was due to a lower affinity of D2 receptors. In our experiment we cannot exclude that modifications of dopamine receptors affinity or of dopamine turnover may have participated to the absence of [^{11}C]raclopride binding changes.

In conclusion, the present study showed no modification of the striatal [^{11}C]raclopride binding due to a sensory stimulus, in both humans and cats. According to the microdialysis animals' data, this suggests in both animals and humans a mostly extrasynaptic mechanism of dopamine release.

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