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Effect of apomorphine on striatal synaptotagmin 7 mRNA levels in reserpinized rats

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Abstract

Synaptotagmin 7 (Syt 7) is a Ca^{2+} sensor implicated in the regulation of membrane fusion in vesicular transport, but its precise role in neurons is still a matter of controversy. Dopaminergic drugs have been shown to modulate its expression in the striatum. Here we investigate whether dopamine receptor agonist-up-regulation of Syt 7 mRNA is specifically involved in the pathophysiological adaptations of hypersensitive striatum by analyzing other dopaminergic neurons containing brain regions. We treated rats with systemic reserpine injections that rapidly depletes dopamine throughout the brain, but leaves dopaminergic neurons spared from destruction. We analyzed the effects of apomorphine, a D1 and D2 receptor agonist on Syt 7 mRNA expression in caudate putamen, nucleus accumbens, cingulate cortex, substantia nigra compacta, ventral tegmental area and hippocampus. The treatment with reserpine resulted in akinesia, catalepsy and rigidity and up-regulation of proenkephalin and down-regulation of preprotachykinin mRNA in caudate putamen, indicating a severe depletion. By acute treatment with apomorphine proenkephalin mRNA was down-regulated and preprotachykinin mRNA up-regulated in the caudate putamen of reserpinized rats. Apomorphine increased Syt 7 mRNA levels only in striatum (caudate putamen and nucleus accumbens) of reserpinized rats, while in other brain regions it did not have such effect. The reserpinization and/or apomorphine treatment had no effect on Syt 1 mRNA expression in caudate putamen. It may be concluded, that in the striatum depleted of biogene amines, such as occurs after reserpine treatment, the up-regulation of Syt 7 could play a specific role as part of hypersensitive response to dopaminergic agonists.

Keywords: Synaptotagmin VII; Dopaminergic hypersensitivity; Reserpine; Proenkephalin; Preprotachykinin; *In situ* hybridization

Synaptotagmins (Syts) are implicated in the Ca^{2+}-dependent and Ca^{2+}-independent regulation of membrane fusion in vesicular transport through interaction with SNARE proteins and membrane lipids [18]. Syt 7 is a Ca^{2+} sensor but its function in membrane trafficking in neurons appears controversial. Recent data revealed Syt 7 protein participation in the Ca^{2+}-dependent exocytosis of lysosomes [12] and dense-core vesicles [5], while some experiments have implicated Syt 7 acting as positive regulator of endocytosis [21]. Syt 7 is of our special interest since it is known to be involved in adaptive changes of dopaminergic transmission. Syt 7 was induced by repeated injections of cocaine in mice in both parts of striatum: ventral or nucleus accumbens (NAc) and dorsal or caudate putamen (CPu) [22].

In PD a severe depletion of striatal dopamine occurs due to the degeneration of dopaminergic nigrostriatal neurons. The resulting motor deficits could be reversed by the antiparkinsonic drug L-DOPA [20]. One of the adaptations that follow chronic depletion of dopamine is the development of dopaminergic hypersensitivity representing enhanced striatal responsiveness to the dopamine [9,10]. This hypersensitivity could play a role in the development of pharmacological complications of therapy with L-DOPA, such as dyskinesia and psychosis [7]. Based on our previous findings showing that L-DOPA increases Syt 7 mRNA in the denervated dorsal striatum we hypothesized that Syt 7 in PD may be involved in pathophysiologic alterations of synaptic plasticity induced by L-DOPA [8].

The aim of present study was to investigate whether dopamine receptor agonist-up-regulation of Syt 7 mRNA is specifically linked to the hypersensitivity of striatum or it is occurring in other dopaminergic neurons containing regions. To examine this hypothesis we used a reserpine model for PD [7]. On contrary

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to 6-OHDA model where we selectively destroyed dopaminergic nigrostriatal neurons, systemic injections of reserpine cause depletion of dopamine throughout the brain by inhibiting vesicular monoamine transporter responsible for the sequestering of dopamine into storage vesicles [13,15]. In advantage, reserpine leaves dopaminergic neurons spared from destruction. Many studies have suggested that strong reserpinization leads to striatal adaptations very similar to those after 6-OHDA denervation [1]. In addition reserpine could trigger adaptations in dopaminergic neurons in SNc [14]. We found that Syt 7 mRNA is highly expressed in substantia nigra compacta (SNc) and ventral tegmental area (VTA), areas that contain high density of dopaminergic neurons [8]. Therefore, in this study we evaluated Syt 7 mRNA expression after the reserpinization and/or the acute treatment with D1 and D2 dopamine receptor agonist apomorphine in SNc and VTA and in their projections: dorsal striatum (caudate putamen, CPu) and ventral striatum (nucleus accumbens, NAc) [4]. CPu and NAc are the regions that are known to become hypersensitive after dopamine depletion or repeated treatment with dopaminergic drugs [22,9,10]. We also analyzed Syt 7 mRNA in other projections of dopaminergic neurons: cingulate cortex (cCo) and hippocampus [4]. In addition, we examined the preprotachykinin (PPT), proenkephalin (PENK) mRNA expression to evaluate the level of reserpinization in experimental animals and synaptotagmin 1 (Syt 1) to eliminate the influence of possible treatment-induced neuronal stress.

We used male Wistar rats maintained on a 12:12 h light:dark cycle (lights on 07.00–19.00 h) in a temperature-controlled colony room at 22 °C with free access to rodent pellets and tap water. They were handled according to the NIH Guide for the Care and Use of Laboratory Animals. The following drugs were used: reserpine (Sigma, St. Louis, MO, USA) was dissolved in vehicle (propylene glycol and dimethylsulfoxide (1:1)), apomorphine hydrochloride (Sigma, St. Louis, MO, USA) was dissolved in 0.9% saline containing 0.02% ascorbic acid.

Twenty-four rats were divided into four groups of six animals. First two groups of rats received three injections of reserpine (10 mg/kg; s.c.) every 3 days. Three days after the last injection of reserpine, the group Res/APO received the injection of apomorphine (0.5 mg/kg, s.c.), while the group Res/Sal received the injections of saline (i.p.). The last two groups Veh/APO and Veh/Sal received three injections of vehicle every 3 days. Three days after the last injection of vehicle, the group Veh/APO received the injection of apomorphine (0.5 mg/kg, s.c.), while the group Veh/Sal was injected with saline (i.p.). For the behavioral testing we placed rats in plastic cylindrical chambers 15 min before receiving the last injection in order to adapt. After receiving the injection, rats were filmed with camera for 1 h. Locomotor activity for individual rats was measured as distance traveled in 15 min period using video tracking system for automation of behavior experiments Noldus Ethovision Pro Version 3.0 (Noldus Information Technology, Wageningen, Netherlands). The measurements of locomotor activity were statistically analyzed with unpaired Student *t*-test for comparing the groups Veh/Sal versus Res/Sal and Veh/APO versus Res/APO ($p < 0.05$).

All the animals were killed 8 h after the last treatment. The brains were rapidly removed and quickly frozen on dry ice. Coronal sections (10 μm) were cut through the striatum (between 2.2 mm and −0.3 mm from bregma). The sections were fixed in 4% phosphate-buffered paraformaldehyde, washed in phosphate-buffered saline, dehydrated in 70% ethanol and stored in 95% ethanol at +4 °C until processed for *in situ* hybridization histochemistry.

The standard procedure of *in situ* hybridization histochemistry described in detail by Zivin et al. [23] was performed. We used 3′ end ^{35}S-labeled oligodeoxyribonucleotide antisense probes (45 bases long) complementary to the rat Syt 7 mRNA (bases encoding 300–344, sequence 5′-CCG AGT CTG GCG TGC CCA CCG TCT CCA AGG AGT TCT TGT AGC GTT-3′), rat PPT mRNA (bases encoding 136–180, sequence 5′-TCG GGC GAT TCT CTG AAG AAG ATG CTC AAA GGG CTC CGG CAT TGC-3′), rat PENK mRNA (bases encoding 153–109, sequence 5′-GTA GCT GCA TTT AGC GCA GTC CTG GCT GCA GTC TGC CTG CAC TGT-3′) and rat Syt 1 mRNA (bases encoding 601–645, sequence 5′-GGA AAA GGC ATC TTC CTT CCC TTC CCC AGG ACT GGC TGG CTC AGT-3′). GenBank accession numbers used to design the probes were as follows: Syt 7 U20106, Syt I X52772, PPT M14312 and PENK M28263. For each labeled probe the control sections were hybridized in the presence of 100-fold excess of the unlabeled probe. Air dried hybridized sections were exposed to X-ray film (Scientific Imaging Film X-Omat^{TM} AR, Kodak, Rochester, NY) at room temperature for 2–3 weeks and developed using standard darkroom techniques.

The hybridization signals of all probes were analyzed densitometrically with MCID, M4 image analyzer (Imaging Research Inc., Canada) in the region of CPu using 3 mm diameter circle template. The levels of Syt 7 mRNA signal were measured also in NAc, SNc, VTA, cCo and hippocampal subregions CA1, CA3 and dentate gyrus (DG) using circle templates with different diameters depending on the region size. Relative optical density (ROD) measurements were performed on three sections of each animal. Nonspecific background signal, defined as the ROD of parts of the film without hybridization signal, was subtracted from the ROD measurements. The comparisons of the effects of treatments on gene expression between experimental groups were performed by use of one-way ANOVA followed by Scheffe's multiple-comparison test. All data are expressed as means ± S.E.M. Statistical significance was set at $p < 0.05$.

Animals treated with reserpine (Res/Sal) displayed significantly decreased locomotion as compared to the vehicle counterparts (Veh/Sal) (Fig. 1). Reserpinized rats were displaying akinesia, catalepsy and rigidity. The injection of apomorphine induced enhanced locomotor activity in reserpinized rats as shown as a greater distance traveled (Res/APO) compared to the reserpinized saline-treated rats (Res/Sal). Apomorphine also induced stereotypic behavior in reserpinized rats (Res/APO) that was not observed in non-reserpinized rats treated with apomorphine (Veh/APO). The administration of apomorphine did not produce the significant difference in the locomotor activity between the reserpinized (Res/APO) and non-reserpinized rats (Veh/APO).

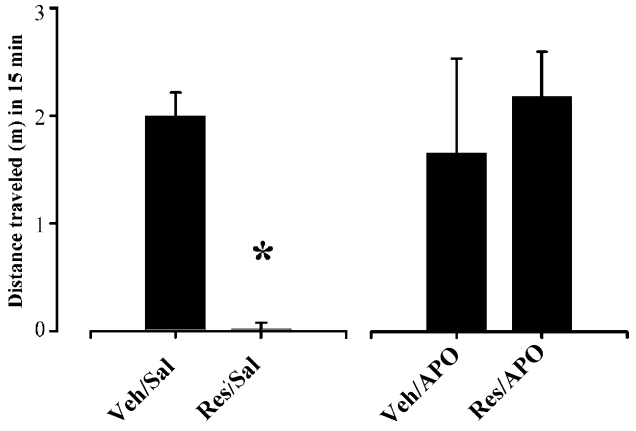

Fig. 1. The effect of reserpine (Res) and apomorphine (APO) on motor activity of the rats. The motor activity was measured as distance traveled in the first 15 min after injection. The animals were pretreated with three doses of reserpine (10 mg/kg; s.c.) or vehicle (Veh). The last injection was apomorphine (0.5 mg/kg, s.c.) or saline (Sal; i.p.). *Significantly different as compared to group Veh/Sal ($n = 6$ for each group, unpaired Student's t-test, $p < 0.05$). Error bars indicate S.E.M.

The pattern of distribution of Syt 7, PPT, PENK and Syt 1 mRNAs (Figs. 2 and 3) obtained by the probes we used matched to that described by our and other previous studies for the rat brain [8,6]. The specificity of all the probes used in this study was confirmed also by the almost complete disappearance of the autoradiographic signal when radiolabeled probes were hybridized in the presence of 100-fold excess of unlabeled probes (not shown). In animals that were reserpinized (Res/Sal) there was a significant 55% up-regulation of PENK mRNA (Fig. 2c and e; $n = 6$, ANOVA, $p < 0.05$) and 31% down-regulation of PPT mRNA (Fig. 2h; $n = 6$, ANOVA, $p < 0.05$) in the CPu compared to the non-reserpinized rats (Veh/Sal). Administration of reserpine had no effect on the expression of Syt 7 mRNA in the CPu (Fig. 3a–c; $n = 6$, ANOVA, $p > 0.05$). In the CPu and NAc of reserpinized animals (Res/APO) the injection of apomorphine caused a significant elevation of the Syt 7 hybridization signal compared to animals that received saline (Res/Sal) (Fig. 3a–c; $n = 6$, ANOVA, $p < 0.05$). In the CPu of reserpinized rats injected with apomorphine (Res/APO) PENK mRNA levels were significantly reduced (−25%) whereas PPT mRNA levels were up-regulated (+130%) as compared to the striatum of saline-treated reserpinized rats (Fig. 2; $n = 6$, ANOVA, $p < 0.05$). The reserpine and apomorphine treatments did not significantly affect Syt 1 mRNA levels in the CPu (Fig. 2i–k) or Syt 7 mRNA levels in cCo, SNc, VTA and hippocampal subregions DG, CA1 and CA3 (Fig. 3) ($n = 6$, ANOVA, $p > 0.05$).

By reserpinization we achieved severe dopamine depletion as indicated by akinesia, catalepsy and rigidity. As expected, dopamine receptor agonist apomorphine induced locomotor activity in control and in reserpinized rats. One could pre-

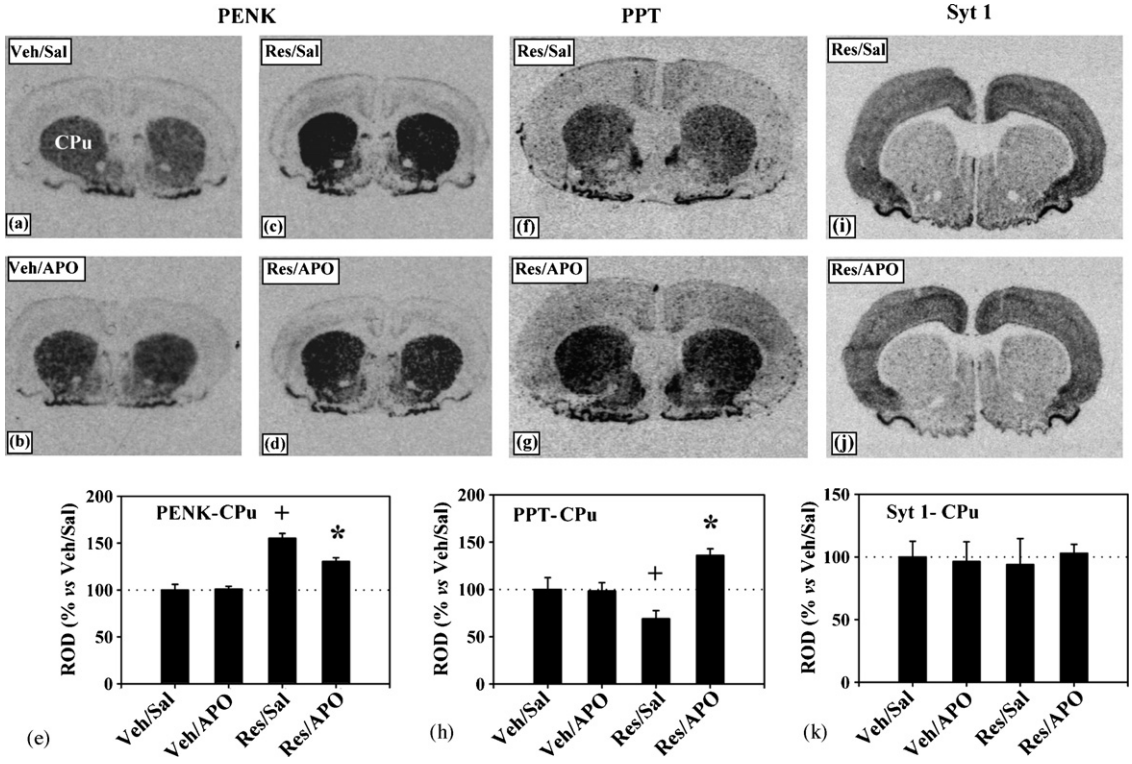

Fig. 2. The effect of reserpine (Res) and apomorphine (APO) on caudate putamen (CPu) PENK ((a)–(e)), PPT ((f)–(h)) and Syt 1 ((i)–(k)) mRNA levels. The animals were pretreated with three doses of reserpine (10 mg/kg; s.c.) or vehicle (Veh). The last injection was apomorphine (0.5 mg/kg, s.c.) or saline (Sal; i.p.). Animals were killed 8 h after the last injection. (a)–(d) and (f), (g) Representative autoradiograms of brain sections of rats treated with different drug combinations. (e) and (h) Bar charts of average relative optical density (ROD) of the CPu expressed in the % of ROD of striatum of group Veh/Sal. $^{+}$Significantly different from ROD of the CPu of groups Veh/Sal and Veh/APO. *Significantly different from ROD of the CPu of group Res/Sal ($n = 6$ for each group, one-way ANOVA followed by Scheffe's multiple-comparison test, $p < 0.05$). Error bars indicate S.E.M.

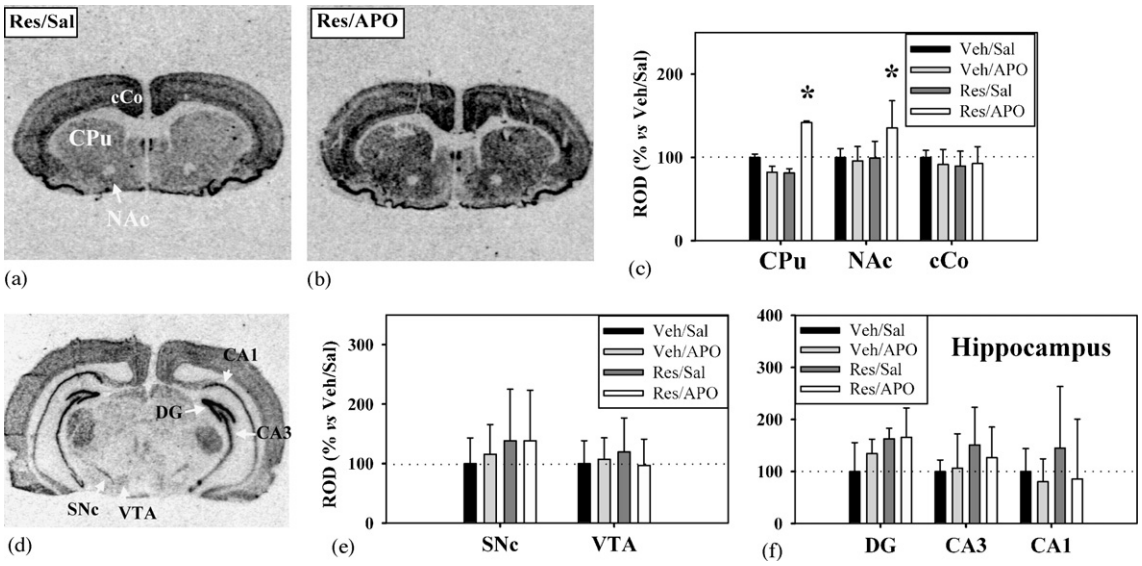

Fig. 3. Apomorphine elevated Syt 7 mRNA levels in the caudate putamen (CPu) and nucleus accumbens (NAc) of reserpine treated rats. Reserpine or apomorphine treatment had no effect on Syt 7 mRNA levels in cingulate cortex (cCo), substantia nigra compacta (SNc), vental tegmental area (VTA) or hippocampal regions. The animals were pretreated with three doses of reserpine (Res, 10 mg/kg; s.c.) or vehicle (Veh). The last injection was apomorphine (APO, 0.5 mg/kg, s.c.) or saline (i.p.). Animals were killed 8 h after the last injection. (a) and (b) Representative autoradiograms of brain sections illustrating the areas of CPu, NAc and cCo of rats treated with different drug combinations. (d) Representative autoradiogram of brain section showing SNc, VTA and hippocampus. (c), (e) and (f) Bar charts of average relative optical density (ROD) of Syt 7 mRNA signal of brain region expressed in the % of ROD of brain region of group Veh/Sal. *Significantly higher from ROD of the CPu or NAc of groups Veh/Sal, Veh/APO and Res/Sal ($n = 6$ for each group, one-way ANOVA followed by Scheffe's multiple-comparison test, $p < 0.05$). Error bars indicate S.E.M. Hippocampal regions: DG, dentate gyrus, CA1 and CA3.

dict that after apomorphine enhanced locomotor activity due to dopaminergic striatal supersensitivity may be observed in reserpinized as compared to non-reserpinized controls [19]. However, our results revealed no difference in locomotor activity in the open field between these two groups. This may be because of markedly high influence of stereotypic behavior on locomotion in reserpinized rats by the relatively high dose of apomorphine (0.5 mg/kg).

Thus, we used additional controls to estimate the level of CPu dopamine depletion by monitoring the expression of PENK and PPT mRNAs. It is well known that at least 90% of CPu dopamine depletion is necessary to establish postsynaptic changes in gene expression, such as increased levels of PENK mRNA or decreased levels of PPT mRNAs [11,17]. Our results confirmed the strong reserpinization since reserpine treatment significantly up-regulated PENK and down-regulated PPT mRNA in the CPu. We show a partial reduction of the up-regulated striatal PENK mRNA in apomorphine-treated reserpinized rats. The reduction of PENK mRNA could be due to agonistic effect of apomorphine on D2 dopamine supersensitive receptors, although it is indicated from the literature that the up-regulation of CPu PENK mRNA could be reversed only by chronic treatment with D2 agonists [6,16]. The strong reserpinization of Res/APO group was proved by the up-regulation of CPu PPT mRNA in these animals as compared to the reserpinized rats treated with saline.

Apomorphine induced a significant up-regulation of CPu Syt 7 mRNA levels in reserpinized rats as compared to CPu of non-reserpinized controls. By our previous experiments with 6-OHDA rats the treatment with a selective D1 dopamine receptor agonist SKF82958 and L-DOPA induced a transient increase in VII mRNA levels in denervated CPu [8]. This up-regulation was prevented only by D1 antagonist but not D2 antagonist. This indicated that the up-regulation of Syt 7 mRNAs in the dopamine-depleted CPu could be induced only by the stimulation of D1 receptors. This was in agreement with reports from the literature that clearly show that in models of dopaminergic denervational supersensitivity the D1 receptor agonists induce a robust up-regulation of CPu mRNAs, such as PPT while having only minor effects in intact CPu [6,2,10]. By contrast, it is not known that the stimulation of D2 receptors have any such effects since is known that D2 receptor stimulation inhibits adenylyl cyclases [6]. It maybe therefore speculated that the effects of apomorphine on the up-regulation of CPu Syt 7 mRNA in reserpinized rats may depend on the stimulation of dopamine D1, but not D2 receptors by apomorphine. The up-regulation of CPu Syt 7 mRNA levels in reserpinized rats most probably occurred within the neurons of the direct striatonigral pathway, since these neurons represent the majority of CPu neurons that express dopamine D1 receptors [6].

We found that apomorphine up-regulates Syt 7 mRNA in the NAc of resepinized rats probably indicating the development of hypersensitivity. Zhang and Xu [22] confirmed up-regulation of Syt 7 mRNA in NAc after repeated cocaine administration. In addition, reserpine treatment up-regulates Fos-like immunoreactivity in NAc signifying the development of denervation dopaminergic hypersensitivity in this region [3]. In 6-OHDA animals, we observed that the D1 receptor-mediated up-regulation of Syt 7 mRNA in NAc on denervated side paralleled the up-regulation in CPu only in animals where the injection of 6-OHDA destroyed not only SNc, but also VTA (unpublished data). In present study reserpine that was injected

systemically caused dopaminergic depletion probably also in VTA. We predict that similar to nigrostriatal system one must achieve a sufficient depletion of VTA dopaminergic neurons to induce Syt 7 mRNA up-regulation in NAc.

The reserpinization and/or apomorphine treatment did not change the expression of Syt 7 mRNA in SNc and VTA regions. The adaptive changes are taking place in SNc after the interruption by reserpine, evident from the reduced levels of neuropeptide neurotensin that is regulated by tonic dopamine release [14]. These results indicate that Syt 7 is probably not involved in possible adaptations in these neurons that could take place after reserpine-induced dopaminergic depletion.

In conclusion, our results support our previous studies implicating the involvement of Syt 7 in the striatal neuronal alterations in response to antiparkinsonic drugs. The evidence that the changes of Syt 7 mRNA are striatum specific is further supported by our results showing no change in Syt 7 mRNA expression in non-striatal projection areas of dopaminergic neurons, cingulate cortex and hippocampus. The levels of Syt 7 expression could be affected by possible apomorphine and/reserpine-produced neuronal stress. To exclude this possibility we analyzed the expression of Syt 1 mRNA in CPu. To address this question we found Syt 1 very useful since in 6-OHDA model the dopaminergic depletion or acute treatments with dopamine agonists had no influence on its mRNA levels [8]. The reserpine and/or apomorphine treatments did not change the expression of Syt 1 mRNA in CPu. The invariability of Syt 1 in this particular model for PD is thus even strongly supporting the specific role of Syt 7 in the striatal plasticity accompanying the dopaminergic hypersensitivity.

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