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Research Report

Glycine stimulates the release of labeled acetylcholine but not dopamine nor glutamate from superfused rat striatal tissue

*Marina Sorrentino Hernandes, Leandro de Magalhães, Lanfranco Ranieri Paolo Troncone**

Laboratory of Pharmacology, Instituto Butantan, Av. Vital Brasil 1500, São Paulo, SP, 05503.900, Brazil

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ABSTRACT

Glycine is known as an inhibitory neurotransmitter in the spinal cord and forebrain but its precise role in the forebrain is largely overlooked. This investigation evaluated whether glycine alters acetylcholine, glutamate or dopamine release from striatal tissue using an in vitro approach. We observed that while glycine induced a robust ^{3}H-acetylcholine release (^{3}H-ACh) from superfused striatal tissue, it failed at releasing ^{3}H-glutamate or ^{3}H-dopamine. Glycine stimulated ^{3}H-ACh release in a dose- and calcium-dependent manner (EC_{50} = 69 μM). Tetrodotoxin (1 μM) inhibited about 75% of the release demonstrating a predominant dendritic and cell body location of glycine receptors. The prototypical glycine receptor antagonist strychnine at 10 μM completely abolished ^{3}H-ACh release. To further characterize the role of striatal glycine receptors in ^{3}H-ACh release we examined glycine effects after in vivo treatment with Haloperidol-decanoate (HD). Treatment for 30 days or more with HD decreased maximal glycine-stimulated release of ^{3}H-ACh suggesting a non-competitive inhibition. After 30 days of washout release parameters did not return to vehicle-treated levels. The glutamate agonist NMDA also stimulated acetylcholine release but showed slightly different behavior in HD-treated striatal tissue. These effects could be attributed to changes in chloride transporters expressed in the giant striatal cholinergic cell as well as glycine receptor subunit composition and finally, GABA/glycine co-release in this tissue.

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1. Introduction

Beyond its role as an inhibitory neurotransmitter in the spinal cord and its co-agonistic role on NMDA glutamate receptors (Aprison and Werman, 1965; Johnson and Ascher, 1987; Trist, 2000; Betz and Laube, 2006), glycine has been reported to stimulate the release of transmitters from brain structures in a strychnine-dependent manner (Darstein et al., 1997). Glycine can stimulate dopamine release from striatal tissue (Giorguieff-Chesselet et al., 1979) and substantia nigra (Kerwin and Pycock, 1978) and acetylcholine from striatal tissue and also from the solitary tract nucleus and amygdala (Dudeck et al., 2003; Talman et al., 1994). The mechanisms involved in the inhibitory or excitatory actions of glycine may result from reversed chloride currents in susceptible neurons (Darstein et al., 2000).

The basal ganglia are part of a modulatory neuronal loop involved in the regulation of information flow between the cortex and medullar motor neurons. These nuclei are responsible for converging, processing and transferring motor and cognitive information (Tisch et al., 2004). Striatum is the largest structure of the basal ganglia and receives most of their afferent fibers, playing the role of a main processing center of motor information (for a review see: Tepper and Bolam, 2004). Functional studies have revealed strychnine-sensitive glycine

* *Corresponding author*. Fax: +55 11 37267222x2133.
E-mail address: ltroncone@butantan.gov.br (L.R.P. Troncone).

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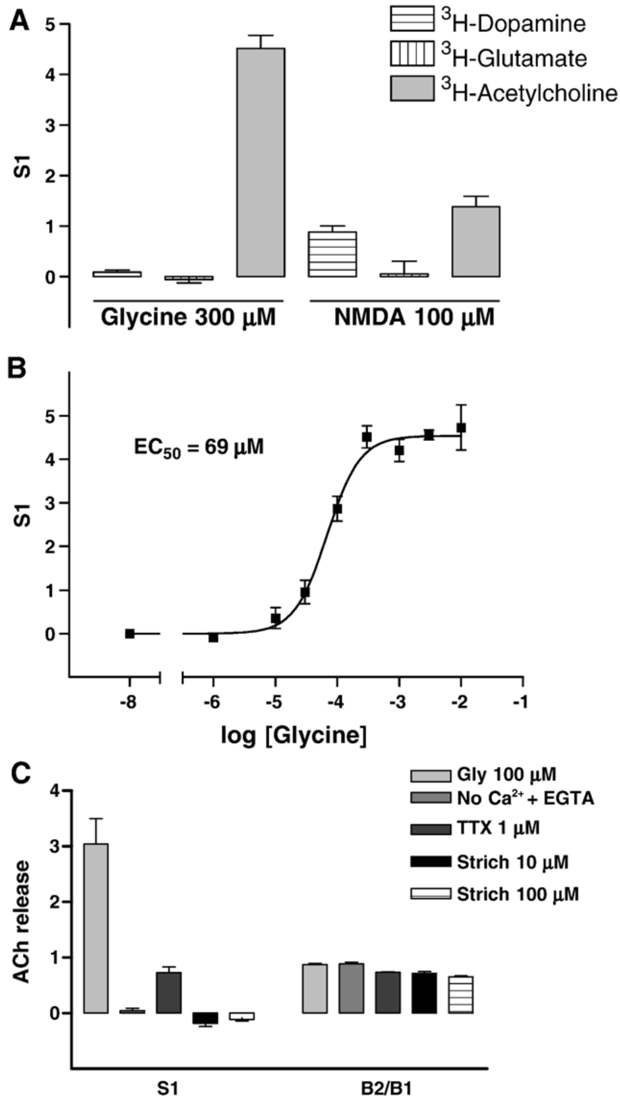

Fig. 1 – A — Glycine stimulates preferentially acetylcholine release. Value of S1 release of the three neurotransmitters under glycine 300 μM or NMDA 100 μM stimulation. Each bar represents the mean ± S.E.M. of 2 to 6 samples; B — Glycine stimulates the release of acetylcholine from striatal tissue in a concentration-dependent manner. Each point represents the mean ± S.E.M. of 2 to 10 samples; C — Characteristics of the glycine-stimulated acetylcholine release: calcium dependence, TTX-dependence and strychnine blockade. The effects of these conditions on glycine-stimulated release (S1) and on basal release (B2/B1) are shown. Each bar represents the mean ± S.E.M. of 4 to 6 samples.

receptors in medium size spiny neurons (GABAergic) as well as in giant aspiny neurons (cholinergic) in striatum (Darstein et al., 2000; Sergeeva, 1998; Sergeeva and Haas, 2001), suggesting a role for glycine in this nucleus. Haloperidol can directly influence striatal cholinergic transmission by disrupting dopaminergic inhibition of striatal cholinergic cells (Guyenet et al., 1975) and consequently increasing acetylcholine release (Scatton, 1982; Sethy and Van Woert, 1974). These effects lead to a behavioral picture involving muscle stiffness, hypokinesia, and tremors (Addonizio et al., 1987) commonly described in rats as catatonia (Kornhuber and Weller, 1994). Extra-pyramidal motor side effects can be produced by prolonged treatments with traditional neuroleptics. Haloperidol is known to block dopamine receptors and lead to an increase in the expression of striatal (and accumbens) dopamine D2 receptors (but not D1) as a compensatory mechanism (MacKenzie and Zigmond, 1985). This super sensitivity has been proposed as the causative factor for the extrapyramidal symptoms mentioned above (MacKenzie and Zigmond, 1985; Duncan et al., 1987). The main objective of the present study was to gather information on the role of glycine in striatum as to understand how could this still unexplored player be exploited in the treatment of motor and affective disorders. In this initial study we investigated, first, the intrinsic factors involved in acetylcholine release induced by glycine; second, how it is modified by prolonged treatments with Haloperidol and, third, compare to the releasing effects of a classical stimulus, the glutamate receptor agonist NMDA.

2. Results

2.1. *Glycine effects on striatal neurotransmitter release*

As can be seen in Fig. 1A glycine stimulated ^{3}H-ACh release but not ^{3}H-glutamate nor ^{3}H-dopamine. Basal unstimulated ^{3}H-

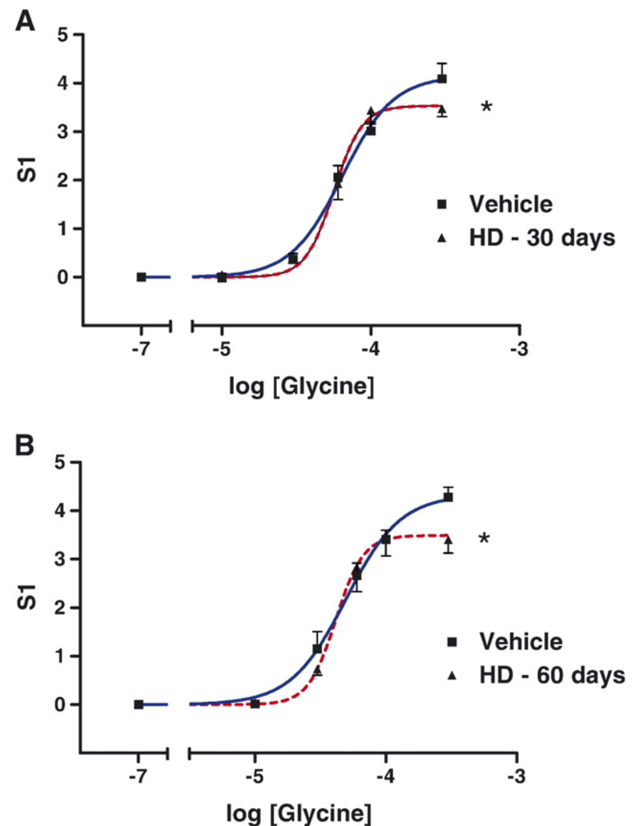

Fig. 2 – A — Glycine-stimulated acetylcholine release from striatal tissue of vehicle-treated and HD-treated rats. Treatment lasted for 30 days. Each point represents the mean ± S.E.M. of 4 to 11 samples.; B — Same as A but treatment lasted for 60 days. Each point represents the mean ± S.E.M. of 6 samples.

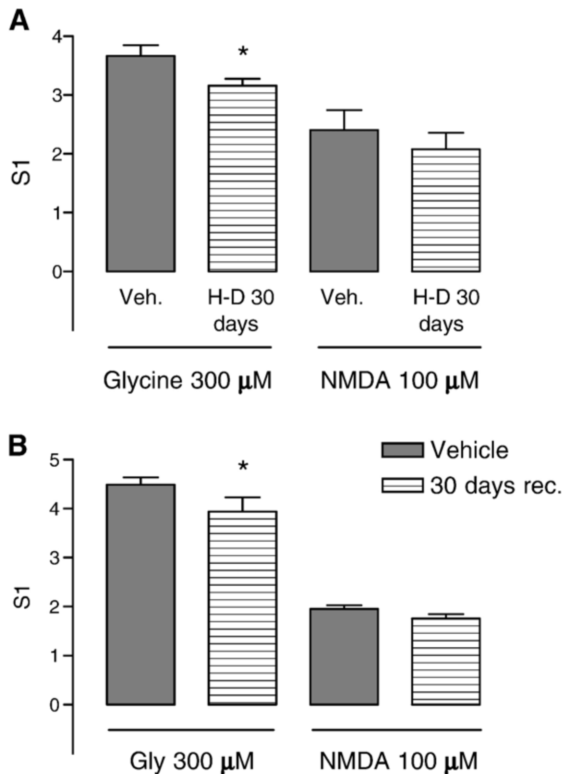

Fig. 3 – A — Assessment of the striatal acetylcholine release in vehicle- or HD-treated rats under stimulation by glycine or NMDA. Each bar represents the mean ± S.E.M. of 8 to 22 samples. * = $p \leq 0.05$ by ANOVA followed by Bonferroni's multiple comparisons test; B — Recovery of the striatal acetylcholine release in vehicle- or HD-treated rats under stimulation by glycine or NMDA. Experiments were performed 45 days after the last of two injections of HD or vehicle to allow for a washout of the drug. Each bar represents the mean ± S.E.M. of 13 to 28 samples. * = $p \leq 0.05$ by ANOVA followed by Bonferroni's multiple comparisons test.

ACh release was only of 1.5–2% of the total content of label at the time of release (fractional release). Under glycine perfusion (300 μM) fractional release reached between 5% and 7%. Fig. 1B shows the concentration vs. response curve of glycine on ^{3}H-ACh release expressed by the value of S1 (as described in Experimental procedures). Calculated EC_{50} was 69 μM. Fig. 1C shows that glycine-stimulated ^{3}H-ACh in the absence of Calcium and presence of 1 mM EGTA was completely abolished but basal release seems not to be affected. The addition of strychnine to the perfusion medium also completely blocked the stimulated release of radiolabel with no changes in basal release. Both doses of 1 and 10 μM of strychnine yielded complete blockade. Tetrodotoxin, the classical sodium channel blocker, inhibited up to 75% of S1 at a dose of 1 μM.

2.2. Glycine- or NMDA-stimulated ^{3}H-ACh release after haloperidol treatments

Fifteen days after a single i.m. injection of 21 mg/kg of Haloperidol-decanoate (controls with vehicle) striatal tissue already presented an impairment in the maximal release of ^{3}H-ACh stimulated by glycine or NMDA (data not shown). Fifteen days after the second of two identical injections (meaning 30 days of treatment) and after the fourth of four injections (meaning 60 days of treatment) striatal tissue responded already with the same decreased release of ^{3}H-ACh (Figs. 2A and B). Maximal calculated values of S1 were of 4.2 ± 0.22 (Mean ± S.E.) and 3.5 ± 0.13 for 30 days vehicle- and HD-treated rats, respectively and considered significant with p value of 0.02. For 60 days of treatment maximal S1 values were 4.3 ± 0.27 and 3.8 ± 0.24 for vehicle- and HD-treated samples and considered significant with $p = 0.024$. In addition, the Hill slope of the vehicle- and HD-treated curves are remarkably different although the Confidence Interval 95% (CI_{95}) are still overlapping. The difference points towards a steeping of the curve obtained in HD-treated animals. Hill slope after 30 days vehicle were 2.519 ± 0.582 (CI_{95} = 1.090 to 3.948), HD were 4.569 ± 1.343 (CI_{95} = 1.318 to 7.820) with $p = 0.17$. For 60 days of treatment, values are 2.068 ± 0.365 (CI_{95} = 1.235 to 2.900) for vehicle-treated samples and 3.533 ± 1.19 (CI_{95} = 1.183 to 5.884) for HD-treated samples with $p = 0.10$. In a similar way, NMDA also showed a reduced capacity to release ^{3}H-ACh but our results did not reach statistical significance (Fig. 3A). Forty-five days after the last injection of HD, meaning roughly 30 days of recovery, the release of ^{3}H-ACh stimulated by glycine have not returned to control vehicle-treated levels, as represented in Fig. 3B.

3. Discussion

The correct balance between cholinergic and dopaminergic function in striatum is crucial for the execution of motor tasks (Di Chiara et al., 1994). Parkinson's disease arises after a major loss of dopaminergic input to striatum leading to an imbalance in this system. In order to correct or compensate for this striatal imbalance therapeutic interventions are based on drugs that exacerbate dopaminergic transmission (L-DOPA) or impair cholinergic transmission (muscarinic antagonists). To broaden our knowledge of the basal ganglia physiology and the challenging controversial excitatory vs. inhibitory roles of glycine in neural systems, we investigated the effects of this simple amino acid on striatal cholinergic function. The "in vitro" neurotransmitter release method employed here is particularly useful to determine the functioning of local circuits without the confounding effects of long feedback loops and yet evaluates a functional parameter as the exocytotic neurotransmitter release.

In this study, our main finding was a stimulating effect of glycine on ^{3}H-ACh release in a concentration-dependent manner and obeying the rule of calcium-dependence. The use of tetrodotoxin, a sodium channel blocker commonly used to determine the sub-cellular localization of receptors in this kind of experiments, revealed that glycine receptors are predominantly found on the cholinergic cell body or dendrites and possibly on neuronal endings to. Since glycine failed at stimulating glutamate release, it seems unlikely that an interposed glutamatergic step would be operating in the described effect. Finally, the glycine receptor antagonist strychnine completely blocked the glycine effects in concentrations as low as 10 μM. Therefore these characteristics strongly resemble that of other classical excitatory neuro-

transmitter, glutamate, impinging on cholinergic cells (Paes et al., 2004). In addition, and arguing against a non-specific effect, glycine failed at inducing releases of labeled dopamine and glutamate in the same tissue.

Haloperidol is a classical dopamine antagonist largely employed as antipsychotic. Acute effects of Haloperidol include some of the Parkinsonian symptoms like stiffness and immobility. The prolonged use of this drug leads to extrapyramidal motor dysfunctions known as dyskinesia and is known to induce an up regulation of dopamine receptors as an attempt to overcome the pharmacological blockade (Turrone et al., 2003; Burt et al., 1977; Tarazi et al., 1997). In the present study we observed that striatal tissue from rats submitted to a constant Haloperidol treatment during at least 15 days, show an impaired capacity to release acetylcholine when challenged with glycine. Concentration vs. response curves suggest an increased Hill slope but the maximal release obtained in control vehicle-treated tissue is never reached indicating that the modifications imposed to the cholinergic cells are rather complex and multi-factorial and could possibly be explained by chemical changes in the release machinery like phosphorylation states of proteins (SNARE, voltage-dependent calcium channels, etc.) (MacDonald et al., 2005; Alimohamad et al., 2005; Turalba et al., 2004) in the cholinergic cell, an issue that remains to be studied. These changes are not reverted after 30 days of "washout". One could raise the question of whether Haloperidol could still be present in the superfused tissue but we strongly believe that a 1-h stabilization perfusion that precedes the assay procedure (it means changing the whole chamber volume 60 times) is enough to wash off any significant amount of drug eventually present in the sample.

The presence of glycine receptors on striatal giant aspiny cholinergic neurons (GAN) has been demonstrated by others (Darstein et al., 2000; Sergeeva, 1998; Sergeeva and Haas, 2001). Since glycine has been known as an inhibitory amino acid Darstein and collaborators (Darstein et al., 2000) suggested that GlyR from medulla and forebrain differ about inhibitory/excitatory functions by an inversion in chloride currents. According to Jentsch and collaborators (Jentsch et al., 2002) the intracellular chloride concentration determines the response to glycine and GABA. Activation of GlyR, GABA-A and C receptors lead to a passive inward chloride current in accordance to the equilibrium potential for this ion. Therefore, high intracellular chloride concentration may turn the usual inhibitory current into a depolarizing current (Lynch, 2004). In normal conditions, the equilibrium potential for chloride ions is more negative than the membrane resting potential and the activation of glycine receptors lead to an inward chloride current. During embryonic development though, intracellular chloride is considerably higher and the activation of GlyR lead to a depolarization. Also, besides the changes in GlyR sub-unit composition from immature homomeric alpha or heteromeric alpha2-beta to mature alpha1-beta, mature neurons start expressing K^+/Cl^- co-transporters that reduce intracellular chloride and consequently change the equilibrium potential for this ion converting chloride currents from excitatory to inhibitory (Rivera et al., 1999). A few chloride transporters have been described in the CNS: $Na^+/K^+/2Cl^-$ (NKCCs) and K^+/Cl^- (KCCs). Another transporter Na^+/Cl^- (NCCs) was described but it is absent from the CNS. Under physiological conditions, NCC and NKCC promote intracellular accumulation of chloride (Gamba et al., 1994). These transporters may be involved in the generation of the results here reported and deserve a careful description. According to Login and collaborators, the activation of GABA-A receptors from enzymatically isolated GANs can lead to depolarization (Login et al., 1998). Szabadics and collaborator showed similar results with cortical neurons (Szabadics et al., 2006). In this case the absence of KCC transporters in parts of the axonal membrane may contribute to this effect. Our results could be explained by such absence of transporters as well but more experiments are needed to explore this hypothesis.

Following another line of thought, Wojcik and collaborators showed recently that GABA and glycine could be transported into striatal and spinal cord synaptic vesicles (Wojcik et al., 2006). By using a knockout mouse lacking the vesicular inhibitory amino acid transporter (VIAAT) these authors showed that GABA and glycine are effectively stored and co-released by these cells. It would be interesting to examine whether these inhibitory transmitters are indeed co-released in our superfusion model and then conclude that, among the neurotransmitters assayed in our present study, only cholinergic cells respond to glycine because only them express glycine receptors. We consider the co-release of GABA and glycine the most likely hypothesis and this will be a subject of our future investigations.

4. Experimental procedures

4.1. *Animals*

Male Wistar rats weighing between 200 and 250 g were employed in all experiments. Animals were breed in the Instituto Butantan animal facility and kept in our temporary animal facility at the Pharmacology department with water and standard pelleted chow *ad libitum*. Animal facilities were maintained at constant temperature 24 °C, forced ventilation and controlled light/dark cycle. All the procedures involving animals were previously approved by the Butantan committee for animal experimentation and found in accordance with the National rules on animal experimentation (CEUAIB No. 068/2002).

4.2. *Drugs and reagents*

Strychnine, hydrochloride, N-methyl-D-aspartate and Tetrodotoxin tartrate were from Tocris (USA) — Haloperidol, decanoate from Jahnsen Pharmaceuticals (Brazil) — ^{3}H-dopamine–^{3}H-choline–^{3}H-glutamate were from Amersham Bioscience, salts were of analytical grade from Sigma and Merck.

4.3. *Treatments*

Haloperidol-decanoate (Haldol-®) was injected i.m. in the thigh in a dose of 21 mg/kg equivalent to a daily dose of at least 1 mg/kg and corresponding to a plasma concentration higher than that obtained in humans under clinical treatment (Turrone et al., 2003). In these experiments control animals were injected with sesame oil, the same vehicle of (Haldol-®),

in the same way as experimental rats. Two animals were used in each group with the respective striata removed and processed separately and always in parallel.

4.4. *Neurotransmitter release*

Labeled neurotransmitter release experiments were carried out as described elsewhere (Paes et al., 2004; Troncone et al., 1995; Camillo et al., 2001). Briefly, in each experiment three adult male Wistar rats were killed by decapitation and the striata were dissected and placed in ice-cold Krebs–Ringer bicarbonate buffer (KRB) with the following mM composition: NaCl 118, $NaHCO_3$ 25, KCl 4.8, $CaCl_2$ 1.2, KH_2PO_4 1.2, and glucose 10, pH 7.3 and constant gassing with CO_2/O_2 (5/95%) was maintained throughout the experiment. Striatal tissue was then chopped twice in a McIlwain tissue shopper set to cut at 250 μm to form prisms and pooled to achieve enough tissue for the 10 chambers. In experiments with HD pre-treatment tissue from two rats equally treated was pooled (as described above). Chopped tissue was dispersed with a pipette and washed twice in 20 ml ice cold KRB and transferred to a beaker containing 3 ml KRB with 0.055 μM of [^{3}H]methyl choline and maintained at 37 °C for 20 min to allow for the uptake. In a few experiments a double labeling procedure was employed using 0.25 μM [^{14}C]-Methyl-choline together with 0.05 μM [^{3}H]dopamine with Kreb's solution supplemented with 1 μM pargiline during the radiolabel loading procedure. For [^{3}H]glutamate release experiments a concentration of 0.05 μM label was used. Tissue was then filtered and washed twice with normal ice cold KRB and distributed in 10 superfusion chambers with internal volume of 0.25 ml. Superfusion was performed at a rate of 0.25 ml/min with a 10-channel peristaltic pump, during 60 min in order to achieve a stable baseline of [^{3}H]ACh release. After this time, three successive baseline samples were collected from each chamber at 3-min intervals with an adapted custom-made sample collector. Superfusion with test agents (TTX, no Ca^{2+}+EGTA 1 mM, strychnine, according to the test protocol) followed in the 4th interval and lasted until the end of the experiment. A stimulus perfusion was performed in the 7th interval and lasted for 2 min and allowed to collect most of the label in a single sample. In the 10th interval, tissue was perfused with 0.1 M HCl for 6 min to induce release of the total amount of labeled transmitter still present in the tissue. $MgSO_4$ 1.2 mM was omitted from the Kreb's solution in specific experiments where NMDA stimulation was employed. Results are expressed as fractional release, i.e., percent of labeled neurotransmitter released over the total contained in the tissue at the time of release. The effects of drugs were evaluated initially by the fractional release profile compared to the control sample profile. S_1 is the release obtained by stimulation in control conditions. Spontaneous releases in the presence of test drugs (B_2) and control spontaneous release (B_1) were used to evaluate the effects of antagonists on spontaneous release using the B_2/B_1 ratio. S_1 was calculated subtracting $B(_1$ or $_2)$ from the total release obtained under stimulation. B_1 and B_2 corresponded to the mean of three consecutive samples. Radioactivity was measured by scintillation spectrometry corrected by external standard counting performed in a Beckman 6500 Scintillation counter and ACS (Amersham) or Ecolume (ICN) scintillation cocktails.

4.5. *Statistics*

Statistical analysis was performed with the software GraphPad Prism. EC_{50} and CI_{95} values were obtained fitting the values to a sigmoidal dose–response curve with variable slope, identical to the four-parameter logistic equation (Top, Bottom, Log EC_{50} and Hill Slope). Sigmoidal curves obtained with vehicle and HD-treated samples were compared using a two-tailed *t*-test. To evaluate the experiments of single doses of glycine and NMDA (Fig. 3) ANOVA followed by Bonferroni's multiple comparisons test was employed. A value of $p \leq 0.05$ was assumed for significance limit.

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