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THE RELEASE OF AMINO ACIDS FROM RAT NEOSTRIATUM AND SUBSTANTIA NIGRA *IN VIVO*: A DUAL MICRODIALYSIS PROBE ANALYSIS

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Abstract—It has previously been demonstrated, in dual probe microdialysis studies, that stimulation of the neostriatum with kainic acid causes the release of GABA both locally within the neostriatum and distally in the substantia nigra, observations that are consistent with the known anatomy of the basal ganglia. The object of the present study was to further examine the characteristics of GABA release and to determine whether taurine, which has been proposed to be present in striatonigral neurons, has similar characteristics of release, and to examine the release of excitatory amino acids under the same conditions. To this end, dual probe microdialysis studies were carried out on freely-moving rats. The application of kainic acid to neostriatum enhanced the release of GABA, taurine, aspartate and glutamate locally in the neostriatum and distally in the substantia nigra. The distal release of each amino acid in the substantia nigra was sensitive to the administration of 6,7-dinitroquinoxaline-2,3-dione and tetrodotoxin to the neostriatum. Similarly the local release of GABA, aspartate and glutamate but not taurine was sensitive to the intrastriatal application of 6,7-dinitroquinoxaline-2,3-dione or tetrodotoxin.

It is concluded that the release of taurine from the substantia nigra has similar characteristics to that of GABA and may be released from the terminals of striatonigral neurons following the stimulation of their cell bodies in the neostriatum. The release of taurine in the neostriatum however, is likely to be mediated mainly by different mechanisms and not related to neuronal activity. The release of excitatory amino acids is likely to involve indirect effects in the neostriatum and polysynaptic pathways in the substantia nigra.

Key words: basal ganglia, striatonigral, GABA, taurine, glutamate, aspartate.

The basal ganglia are a group of subcortical nuclei involved in a variety of processes including motor, associative, cognitive and mnemonic functions. The major input to the basal ganglia is an excitatory, glutamatergic projection derived from the cortex and carried by the corticostriatal pathways. Virtually the entire cortical mantle projects in a topographical manner to the neostriatum and its ventral homologue the nucleus accumbens.[2,4,32,38,40,43,45,50,58,64,73,83] The main synaptic target of the corticostriatal projection are the medium-size spiny neurons which account for the majority of striatal neurons, are the major projection neuron of the neostriatum, sending their axons to the globus pallidus or the entopeduncular nucleus/substantia nigra and in addition, possess extensive local axonal collaterals that ramify within the neostriatum.[75] This class of neuron utilizes GABA as a neurotransmitter. The neostriatum also possesses small populations of interneurons, one of which has also been identified as a target of the corticostriatal projection and also utilizes GABA as a transmitter.[6,13,14,26,49,51]

In addition to GABA, the amino acid taurine (2-aminoethanesulphonic acid), has been shown to fulfil some of the criteria of a neurotransmitter in the basal ganglia. Thus the neostriatum and substantia nigra contain high levels of taurine and its synthetic enzyme sulfinoalanine decarboxylase (EC 4.1.1.29, commonly referred to as cystein sulfinic acid decarboxylase).[31,53,65,78,82,90] The presence of a high-affinity uptake system for taurine has been detected in both the neostriatum[25,53] and substantia nigra.[28] Furthermore, uptake and release studies of exogenous radiolabelled taurine suggest that neurons identified as medium-size densely spiny striatonigral neurons[24] take up taurine and release it at their terminals in the substantia nigra.[27]

In agreement with anatomical and neurochemical data, stimulation of the corticostriatal system, elicits excitatory postsynaptic potentials in spiny neurons that are mediated by both *N*-methyl-D-aspartate (NMDA) and non-NMDA receptors (see Refs 48

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Abbreviations: ACSF, artificial cerebrospinal fluid; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionate; DNQX, 6,7-dinitroquinoxaline-2,3-dione; KA, kainic acid; NMDA, *N*-methyl-D-aspartate; OPA, o-phthalaldehyde; TTX, tetrodotoxin.

and 85). Furthermore, application of NMDA as well as non-NMDA receptor agonists directly to the neostriatum, stimulates the release of endogenous or pre-loaded GABA from rat striatal slices[34,35,63] and from the neostriatum *in vivo*.[17,19,61,62,94,95] Recent studies using dual probe microdialysis have demonstrated that the intrastriatal application of the non-NMDA excitatory amino acid receptor agonist, kainic acid (KA), enhances the release of endogenous GABA from the local axon collaterals of striatonigral neurons and presumably from GABA interneurons and, at the same time, enhanced release of GABA from the axon terminals of striatal neurons in the substantia nigra.[9] If taurine is also present in striatonigral neurons then one would predict that following stimulation of striatal neurons there would be a simultaneous release of taurine both in the neostriatum and substantia nigra. The first aim of the present investigation was to test this hypothesis using dual probe microdialysis and to compare the release of taurine to that of GABA.

In addition to the excitatory amino acids that are contained within the projections arising in the cortex, other regions including the thalamus and possibly the amygdala and mesopontine tegmentum also give rise to glutamatergic projections.[8,36] Furthermore, immunocytochemical studies indicate that there is a population of neurons in the neostriatum that contain aspartate[69] and the observation that spiny output neurons take up exogenous radiolabelled aspartate in the substantia nigra and globus pallidus and retrogradely transport it to their cell bodies has been taken as evidence that they may be glutamatergic.[89] The second objective of the present study was therefore to examine the basal release of the excitatory amino acids, aspartate and glutamate, from both the neostriatum and the substantia nigra and to determine the effect of stimulation of excitatory amino acid receptors within the neostriatum.

EXPERIMENTAL PROCEDURES

Surgery and microdialysis procedure

All experiments involving laboratory animals were performed according to the Italian Guidelines for Animal Care (D.L. 116/92), which were also in accordance with the European Communities Council Directives (86/609/EEC). The experiments were performed on male Wistar rats (250 g) (Morini, S. Plo d'Enza, Italy). They were housed in groups of five in a 12 h light/dark cycle under controlled conditions of temperature and humidity with free access to food and water. The rats were anaesthetized with chloral hydrate (400 mg/kg, i.p.) and single cannula microdialysis probes were implanted vertically into the right neostriatum (3 mm probe tip) and the ipsilateral substantia nigra reticulata (1 mm probe tip). Stereotaxic co-ordinates, derived from the atlas of Paxinos and Watson,[68] were as follows: neostriatum: AP 0.7, L 3.2, V −5.5 mm; substantia nigra: AP −5.4, L 2.2, V −8.9 mm relative to bregma and dural surface. The animals were allowed to recover and the microdialysis experiments were performed 24 h later.

The dialysis probes of the now freely-moving rats, were perfused with artificial cerebrospinal fluid (ACSF) consisting of (in mM): NaCl 140, KCl 3, $CaCl_2$ 1.2, $MgCl_2$ 1, Na_2HPO_4 1.2, NaH_2PO_4 0.27 and glucose 7.2 (pH 7.4) via polyethylene tubing (i.d. 0.38 mm) connected to a 1 ml syringe mounted on a microinfusion pump (CMA/100, CMA/Microdialysis AB, Stockholm, Sweden), at a rate of 2 µl/min. Following a 1 h stabilization period, perfusates were collected every 20 min over a 4–5 h period. After a collection period of 1 h (three fractions) the neostriatum was exposed to 100 µM KA (Sigma–Aldrich, Milan, Italy) in ACSF for a period of 20 min (one fraction), alone or in the presence of 6,7-dinitroquinoxaline-2,3-dione (10 or 100 µM) (DNQX; TOCRIS Neuramin, U.K) or tetrodotoxin (3 or 10 µM) (TTX; Sigma–Aldrich, Milan, Italy) which were included in the perfusate throughout the experiment. Fractions of the perfusate (20 min) were then collected for up to 3 h after the KA perfusion, after which time a second stimulation was performed by applying 100 mM K^+ for 20 min (one fraction) and collecting two more fractions. Those animals that did not respond to K^+ stimulation at the end of the experiment were discarded.

The mean membrane recovery for the four amino acids was 25–30 ± 4% and 6–8 ± 1% for neostriatum and substantia nigra, respectively. However, data were not corrected for the recovery rate. At the end of the experiment the rats were anaesthetized with chloral hydrate and killed by decapitation. The brain was removed and placed in 4% phosphate-buffered formaldehyde solution. Three to four days later 50 µm-thick coronal sections were cut using a microtome (Polaron, U.K.) and the position of the probes was checked by light microscopy. There was a rate of 100% success in the striatal placement of the probe, whereas there was a 30% failure in placing the probe within the substantia nigra. Misplacement of the probe in this area was associated with an undetectable basal GABA output; in these cases the nigral data were discarded.

Measurement of amino acids

The perfusion fractions were frozen and stored at −20°C for up to six months before analysis. The amino acid levels were stable for up to six months, but a 30% loss was observed after one year. The content of GABA, taurine, aspartate and glutamate in microdialysis perfusates was measured by high-performance liquid chromatography with fluorimetric detection as described by Bianchi *et al.* (submitted for publication). Briefly, the amino acids were derivatized with mercaptoethanol and o-phthalaldehyde (OPA). The OPA derivatives were then separated on a 5 µm reverse-phase Nucleosil C18 column (250 × 4 mm; Machery–Nagel, Duren, Germany) kept at room temperature, using a mobile phase consisting of methanol and potassium acetate (0.1 M, pH adjusted to 5.52 with glacial acetic acid) at a flow rate of 0.9 ml/min in a three linear steps gradient (from 25% to 90% methanol).

The levels of amino acid in the perfusate fractions were expressed as fmol or pmol of amino acid/µl of perfusate (nM or µM) or as the area under the concentration–time curve normalized to the time corresponding to one fraction (20 min). The basal value was obtained from the area under the curve between −40 and 0 min, since it was found to remain unchanged up to 100 min after mock stimulation (control curves not shown). The stimulated area was obtained from the area under the curve between 0 and 100 min. Data were evaluated by analysis of variance of the actual area values, as described previously.[9]

RESULTS

Basal levels of taurine, GABA, aspartate and glutamate in neostriatal perfusates were 1082 ± 76, 31 ± 4, 221 ± 24 and 556 ± 34 nM (n = 21), respectively, and 1074 ± 109, 31 ± 2, 214 ± 18 and 684 ± 75 nM (n = 20), respectively, in nigral perfusates. In

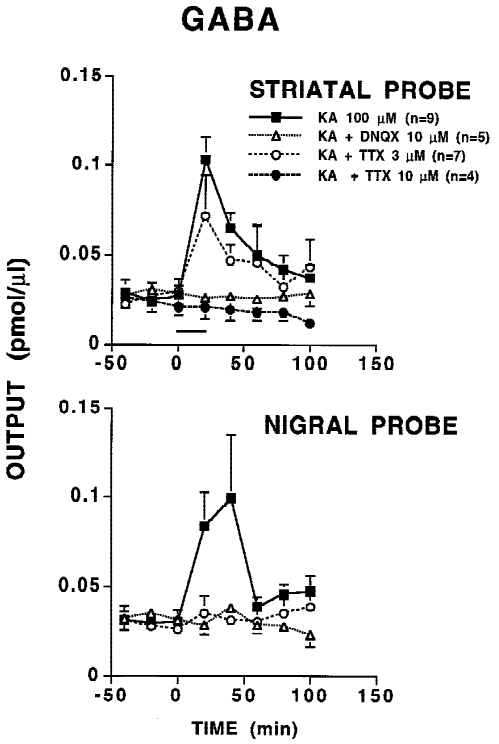

Fig. 1. Time-course of the release of endogenous GABA from the neostriatum (upper panel) and the substantia nigra (lower panel) in response to intrastriatal administration of KA (100 μM). Data are expressed as pmol of amino acid/μl of perfusate in 20 min fractions and presented as mean ± S.E.M. of the number of samples indicated by *n*. The curves show the effect of KA alone, administered at time 0 for 20 min (one fraction), KA administered in the presence of DNQX (10 μM) or TTX (3 or 10 μM). TTX and DNQX were present throughout the experiment.

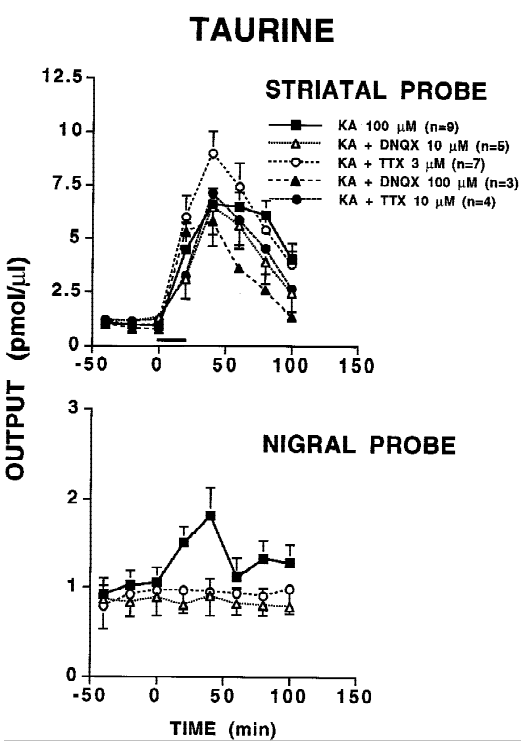

Fig. 2. Time-course of the release of endogenous taurine from the neostriatum (upper panel) and the substantia nigra (lower panel) in response to intrastriatal administration of kainic acid (100 μM). Data are expressed as pmol of amino acid/μl of perfusate in 20 min fractions and presented as mean ± S.E.M. of the number of samples indicated by *n*. The curves show the effect of KA alone administered at time 0 for 20 min, KA administered in the presence of DNQX (10 or 100 μM) or TTX (3 or 10 μM). TTX and DNQX were present throughout the experiment.

both regions the output of the four amino acids was stable for several hours.

Consistent with previous observations[9] inclusion of KA (100 μM) in the perfusate of the probe in the neostriatum induced a statistically significant ($P<0.05$) increase of the output of GABA and taurine from both the neostriatum and the ipsilateral substantia nigra (Figs 1, 2; Table 1). The enhanced release of GABA was of a similar magnitude locally in the neostriatum and distally in the substantia nigra (206% and 200% of basal values, respectively; area under curve see Table 1). In contrast, the enhanced release of taurine was of a greater magnitude in the neostriatum than in the substantia nigra (517% and 134% of basal values, respectively; area under curve see Table 1) which resulted in an apparently longer time-course (compare Figs 1 and 2).

The intrastriatal application of KA also induced a statistically significant increase ($P<0.05$) in the local output of both glutamate (158% of basal output) and aspartate (216% of basal output) and in both cases the time-course was similar to that of the enhanced release of GABA, see Figs 3 and 4). The intrastriatal application of KA also induced a statistically significant increase (199% of basal value) in the output of aspartate at the distal site in the substantia nigra. In contrast the increased output of glutamate induced in the distal probe in the substantia nigra (140% of basal values) was not statistically significant.

In order to determine the specificity of the increase in the output of the four amino acids induced by KA, the stimulation was also performed in the presence of a selective non-NMDA receptor antagonist, DNQX (10 or 100 μM) or the Na^+ channel blocker, TTX (3 or 10 μM) (Figs 1–4; Table 1). As shown previously,[9] both the local and the distal release of GABA was abolished when KA was applied to the neostriatum in the presence of 10 μM DNQX. The presence of 3 μM TTX abolished the KA-stimulated release of GABA at the distal site, whereas locally, the KA-stimulated GABA output was reduced only partially (50%), but it was abolished in the presence of 10 μM TTX. The enhanced release of taurine in the neostriatum was not affected by the presence of either DNQX (10 or 100 μM) or TTX (3 or 10 μM) in the perfusion fluid (Fig. 2; Table 1). However, the presence of 10 μM DNQX or 3 μM TTX in the neostriatal perfusion fluid completely abolished the KA-stimulated

Table 1. Basal and stimulated levels of GABA, taurine, glutamate and aspartate monitored by *in vivo* double probe microdialysis in neostriatum and substantia nigra pars reticulata of freely-moving rats

Area			Amino acid output (pmol/μl/20 min)			
Treatment	(*n*)		GABA	Taurine	Glutamate	Aspartate
Neostriatum						
KA 100 μM	(9)	Basal	27 ± 4	1019 ± 113	501 ± 30	238 ± 57
		Stimulated	58 ± 6	5266 ± 627	811 ± 55	491 ± 74
		Net output	31 ± 7*	4247 ± 572*	310 ± 67*	253 ± 66*
KA+DNQX 10 μM	(7)	Basal	29 ± 7	1198 ± 154	515 ± 49	200 ± 33
		Stimulated	27 ± 4	4240 ± 730	487 ± 31	216 ± 35
		Net output	−2 ± 5	3042 ± 674*	−28 ± 26	16 ± 11
KA+TTX 3 μM	(5)	Basal	30 ± 7	1032 ± 113	690 ± 123	227 ± 32
		Stimulated	47 ± 11	6068 ± 730	706 ± 90	257 ± 46
		Net output	17 ± 4*	5036 ± 587*	16 ± 39	30 ± 32
KA+DNQX 100 μM	(3)	Basal		797 ± 192		
		Stimulated		3440 ± 192		
		Net output		2643 ± 1023*		
KA+TTX 10 μM	(4)	Basal	13 ± 5	1192 ± 180		334 ± 42
		Stimulated	14 ± 5	5168 ± 1152		329 ± 71
		Net output	1 ± 1	3988 ± 999*		−5 ± 44
Substantia nigra pars reticulata						
KA 100 μM	(8)	Basal	31 ± 4	1068 ± 168	658 ± 92	174 ± 30
		Stimulated	62 ± 9	1423 ± 203	841 ± 128	415 ± 118
		Net output	31 ± 7*	355 ± 99*	183 ± 80	241 ± 91*
KA+DNQX 10 μM	(7)	Basal	31 ± 5	894 ± 167	684 ± 111	243 ± 42
		Stimulated	30 ± 4	840 ± 174	675 ± 133	270 ± 44
		Net output	−1 ± 4	−54 ± 70	−9 ± 42	27 ± 23
KA+TTX 10 μM	(5)	Basal	26 ± 2	968 ± 274	590 ± 101	203 ± 39
		Stimulated	33 ± 6	958 ± 244	603 ± 96	200 ± 33
		Net output	7 ± 4	−10 ± 31	13 ± 28	−3 ± 27

Statistical analysis was performed on values of the area under the concentration time curve/20 min (basal area, from −60 to 0 min/3 and stimulated area, from 0 to 100 min/5).

*Net output significantly different from 0 (stimulated area higher than basal area, $P<0.05$, MANOVA). *n*, number of animals.

release of taurine observed distally in the substantia nigra. The presence of 10 μM DNQX or 3 μM TTX abolished the KA-stimulated release of aspartate, both locally and distally, and the distal release of glutamate (Figs 3, 4; Table 1). In contrast, the local release of glutamate was only partially blocked by 3 μM TTX.

DISCUSSION

Consistent with previous findings, the administration of KA to the neostriatum caused a DNQX-sensitive release of endogenous GABA both within the neostriatum and, simultaneously, from the distal probe located in the substantia nigra.[9] These characteristics imply that the release of GABA in response to KA occurs as a result of stimulation of α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA)/kainate receptors at postsynaptic sites within the neostriatum causing the release from the local axon terminals of medium spiny projection neurons and GABA interneurons. The release of GABA in the substantia nigra following stimulation of the neostriatum, is presumed to be from the axon terminals of striatonigral neurons.[9] The present experiments extend this finding by demonstrating that the enhanced release of GABA in the substantia nigra following stimulation of neurons in the neostriatum is due to the propagation of action potentials along the striatonigral pathway as the release was abolished in the presence of TTX. These findings are consistent with previous studies demonstrating an enhanced release of GABA in the substantia nigra following electrical stimulation of striatonigral axons in the internal capsule.[10] The enhanced release of GABA that we observed in the substantia nigra may be the net effect of several factors as activation of neostriatal neurons that project to the globus pallidus (indirect pathway) will inhibit these neurons and thus lead to a reduced release of GABA from the terminals of pallidonigral neurons. Furthermore, activation of the indirect pathways has been proposed to enhance GABA release by an indirect effect on striatonigral terminals.[71]

Most of the previous studies on the effect of NMDA or non-NMDA agonists on striatal GABA release were performed using *in vitro* preparations, measuring preloaded radiolabelled GABA from striatal slices,[34,35] striatal neurons in culture[87,88] or endogenous GABA from striatal neurons in culture.[70] Preloaded radiolabelled GABA was also used in *in vivo* microdialysis studies.[94] Microdialysis studies on endogenous GABA release are consistent with both NMDA[61–63] and non-NMDA[9,17–19] agonists stimulating the release of GABA in a manner that is blocked by their respective selective

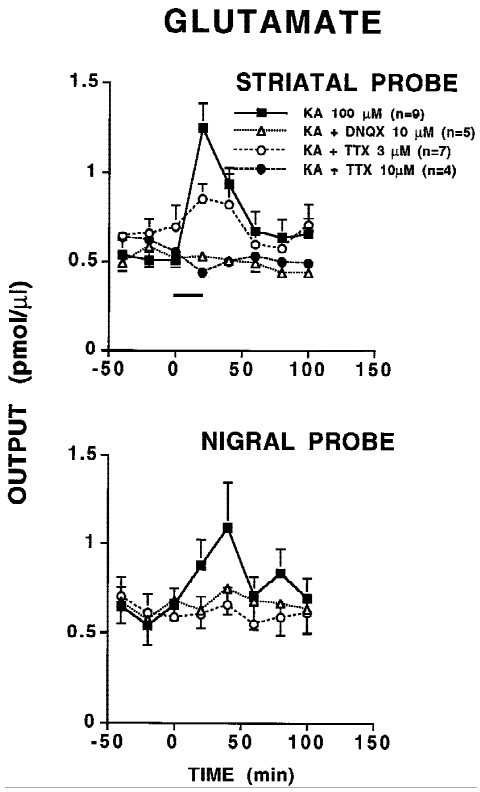

Fig. 3. Time-course of the release of endogenous glutamate from the neostriatum (upper panel) and the substantia nigra (lower panel) in response to intrastriatal administration of KA (100 μM). Data are expressed as pmol of amino acid/μl of perfusate in 20 min fractions and presented as mean ± S.E.M of the number of samples indicated by *n*. The curves show the effect of KA alone, administered at time 0 for 20 min, KA administered in the presence of DNQX (10 μM) or TTX (3 or 10 μM). TTX and DNQX were present throughout the experiment.

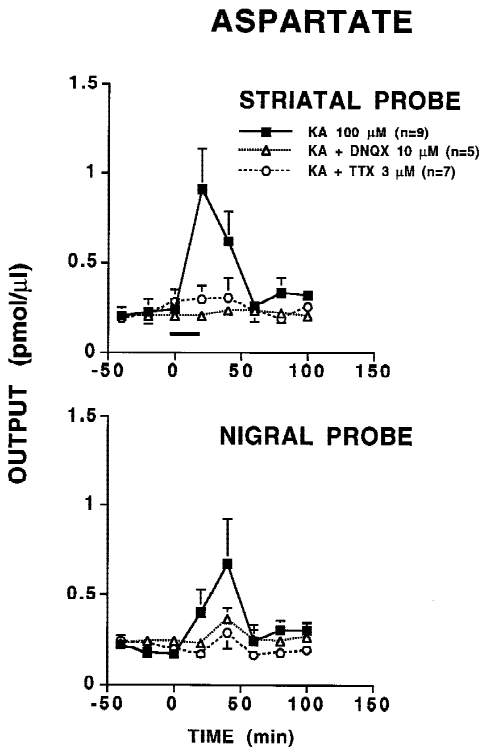

Fig. 4. Time-course of the release of endogenous aspartate from the neostriatum (upper panel) and the substantia nigra (lower panel) in response to intrastriatal administration of KA (100 μM). Data are expressed as pmol of amino acid/μl of perfusate in 20 min fractions and presented as mean ± S.E.M. of the number of samples indicated by *n*. The curves show the effect of KA alone administered at time 0 for 20 min, KA administered in the presence of DNQX (10 μM) or TTX (3 μM). TTX and DNQX were present throughout the experiment.

antagonists, and are in agreement with the present study. The present findings of a dose-dependent attenuation of the KA-evoked striatal GABA release by TTX (total inhibition at 10 μM TTX), supports the dependence of this effect on the stimulation of non-NMDA receptors localised either on the perikarya, or dendrites and spines of the striatonigral neurons,[7] whereas the observation by Morari *et al.*[61] that 10 μM TTX does not affect the NMDA-evoked GABA release, suggests the possibility of a different localization of NMDA receptors on the GABAergic neurons, mainly at the terminals of their local collaterals. Although a selective enrichment of NMDA receptors has been shown on striatonigral neurons,[81] there is, however, no evidence for a selective localization of these receptors on their terminals. Furthermore, the detection of a KA-evoked, TTX-sensitive release of aspartate and glutamate simultaneously to that of GABA, does not support the idea that the KA-stimulated release of GABA is mediated by glutamate/aspartate released from corticostriatal terminals. Consistent with this are previous data where NMDA and non-NMDA agonists were able to evoke the release of GABA from striatal cultured neurons and data on the insensitivity of striatal KA-evoked release of GABA to decortication[17] and to blockade of the release of glutamate.[94] It should be noted however, that others[19] have reported a dependence of the KA-stimulated GABA release on the intact corticostriatal pathway.

One of the objectives of the present study was to determine whether taurine, which has been suggested to be present in striatonigral neurons,[27] behaves in a similar manner to GABA when the neostriatum is stimulated by KA, i.e. is taurine released simultaneously from both neostriatum and ipsilateral substantia nigra following neostriatal stimulation and is the release dependent on receptor stimulation and axon potential propagation? The present results demonstrate that the local application of KA to the neostriatum does indeed induce an increase in the output of endogenous taurine from the neostriatum and, simultaneously, from the distal probe in the ipsilateral substantia nigra. The release in the substantia nigra was sensitive to the application of DNQX or TTX to the neostriatum and, although

smaller in magnitude, followed a pattern similar to that of GABA. These data are thus consistent with the hypothesis that the administration of KA to the neostriatum stimulates medium spiny projection neurons, the propagation of TTX-sensitive axon potentials along the striatonigral pathway which then induces the release of taurine from their axon terminals in substantia nigra. These findings and those relating to GABA release are thus consistent with the observed immunocytochemical localization of subunits of the AMPA/KA receptors on striatal neurons[7,57] and the anatomical and physiological evidence indicating that these neurons receive excitatory inputs (see Introduction).

The present findings provide further support for the hypothesis that taurine may play a neurotransmitter role in the striatonigral system. The physiological significance of the release and the nature of its targets remains to be established. In the substantia nigra, however, taurine has been shown: (i) to behave like GABA, when locally applied, causing contralateral turning in the rat,[46,47,55] an effect that was blocked by the putative[92] taurine antagonist, 6-aminomethyl-3-methyl-4H-1,2,4-benzothiadiazine-1,1-dioxide;[55] (ii) to behave like glycine, another established inhibitory neurotransmitter, both inhibiting the firing rate of nigral dopaminergic neurons by increasing a specific membrane Cl^- conductance;[41] and (iii) to bind to a $GABA_A$ receptor subclass, which is particularly enriched in the substantia nigra.[15] Furthermore, recently Ye *et al.*[93] have shown that taurine inhibits substantia nigra pars reticulata neurons by activation of GABA- and glycine-linked chloride conductance.

Of course it cannot be excluded as yet, whether the release of both GABA and taurine in the neostriatum and substantia nigra are secondary to the release of the excitatory amino acids, glutamate and aspartate (see below). Furthermore, it should be noted that although potassium stimulation of the substantia nigra releases both GABA and taurine, only GABA is released following the electrical stimulation of the internal capsule.[10]

In contrast to the release detected in the substantia nigra, the stimulation of the neostriatum with KA produced an increase in taurine release that was not affected by doses of DNQX or TTX that either blocked or markedly attenuated the stimulated release of GABA. Furthermore, the magnitude of the release was far greater than in the substantia nigra. The lack of effect of both DNQX and TTX suggests the involvement of mechanism(s) different from that responsible for the local release of GABA induced by KA. One possibility is that it is an excitotoxic effect of the locally applied KA although these effects have been reported to be due to activation of their specific receptors.[23,33] Cellular swelling is an early component of the toxicity produced by these agonists, due to Na^+ entry through receptor-operated channels and subsequent entry of Cl^- plus water.[22,72] Since taurine release has been observed following several stimuli inducing osmotic stress in the rat brain,[67,77,84] taurine released by excitatory amino acids may be involved in correcting osmotic imbalances, thus behaving as an osmolite. It is interesting to note that part of the KA-induced release of taurine from rat hippocampus, either in *in vitro*[54] or in *in vivo*[59] conditions has been suggested to be related to excitotoxicity/osmotic stress.

The small increase in taurine release seen in the substantia nigra (approximately 35% increase) which is presumed to relate to neuronal activity, raises the possibility that in the neostriatum there was also a DNQX- and TTX-dependent release but that this was so small that it was masked by the massive release (approximately 500%) that was not affected by DNQX or TTX. It is possible therefore, that the KA-induced release of taurine observed in neostriatum is partly the result of release from the local collaterals of spiny neurons and partly as a result of excitotoxicity and/or osmotic changes, possibly being derived from glial cells. Astrocytes express excitatory amino acid receptors (for a review see Hösly and Hösly[44]) and in *in vitro* conditions, KA has been shown to stimulate the release of endogenous taurine from type-2 cortical astrocytes in culture.[52] In such experimental conditions, however, none of the KA-evoked release was associated to cell swelling.

An additional aim of the present investigation was to examine the characteristics of the release of aspartate and glutamate, the putative neurotransmitters of excitatory afferents of the neostriatum, in response to the stimulation of excitatory amino acid receptors in the neostriatum. The application of KA to the neostriatum induced an increase in the local output of both aspartate and glutamate which was blocked by DNQX, thus appearing to be mediated by the stimulation of non-NMDA excitatory amino acid receptors. The increased release was also blocked in the presence of TTX. This observation indicates that the release is unlikely to be due to the stimulation of presynaptic receptors on the terminals of corticostriatal, thalamostriatal or other excitatory afferents of the neostriatum, but rather is dependent on the propagation of action potentials. This finding is in agreement with data from electrophysiological studies,[42,86] binding studies[30,39,81,91] and receptor localization studies,[7,21,56,57,79,80] indicating that most ionotropic excitatory amino acid receptors are located at postsynaptic sites rather than on afferent terminals. It should be noted however, that the conclusion of some studies is that at least a proportion of these receptors may be located presynaptically.[12,30] However, it is also possible that postsynaptic non-NMDA receptors present in striatal structures distinct from corticostriatal terminals indirectly modulate the release of glutamate/aspartate through trans-synaptic mechanisms. Additionally, the release of glutamate/aspartate might

also be exerted via a polysynaptic pathway, involving the corticostriatal or thalamostriatal pathways as a final end.

In addition to the local release, the intrastriatal application of kainic acid induced a DNQX- and TTX-sensitive increase in the release of aspartate at the distal site in the substantia nigra. This implies that the enhanced release of aspartate in the substantia nigra following neostriatal stimulation with KA, like the release of GABA, is due to stimulation of neostriatal output neurons and depends on the propagation of action potentials. Although the weight of evidence is in favour of GABA as the principal neurotransmitter of neostriatal output neutrons including those projecting to the substantia nigra, a glutamatergic component of the output neurons of the neostriatum has been proposed on the basis of the retrograde transport of excitatory amino acids.[89] However, the most likely explanation is that the release in the substantia nigra is a polysynaptic effect due to activation of the so-called ''indirect pathway'' of information flow through the basal ganglia mediated by the striato-pallidal-subthalamo-nigral pathway.[1,3,29,36] Thus stimulation of those striatal output neurons that project to the globus pallidus will lead to an inhibition of the tonically active neurons of the globus pallidus. Since virtually all neurons of the globus pallidus use GABA as a transmitter and project to the subthalamic nucleus, their inhibition will lead to a disinhibition of the neurons of the subthalamic nucleus. Increased firing of subthalamic neurons which are glutamatergic will thus lead to the increased release of glutamate and/or aspartate from their terminals in the substantia nigra. This suggestion is consistent with the detection of the release of glutamate and aspartate in the other output nucleus of the basal ganglia, the entopeduncular nucleus, that is regulated by neostriatal dopamine D2 receptors.[11]

The effect of stimulation/destruction of excitatory neurons afferent to the neostriatum, on the release of glutamate and/or aspartate using microdialysis[5,16,17,20,37,60–62,66,74,76,94–96] have provided controversial results. Although most of the available data are on NMDA-evoked release, in agreement with the present findings, in similar *in vivo* experimental conditions, other authors have observed KA-evoked increases in extracellular striatal glutamate and aspartate,[5,96] as well as increases of striatal glutamate following activation of the corticostriatal pathway,[60] or a reduction of K^+-stimulated glutamate and aspartate release following lesion of the sensorimotor cortex. Smolders *et al.*[76] detected a small KA-evoked striatal release of glutamate, but not aspartate.

CONCLUSIONS

The present results suggest that the release of taurine from the substantia nigra has similar characteristics to that of GABA and may be derived from the terminals of striatonigral neurons following the stimulation of their cell bodies in the neostriatum. The release of taurine in the neostriatum however, is likely to be mediated by different mechanisms and the main part of the release is not related to neuronal activity. The release of excitatory amino acids in the neostriatum is likely to involve indirect effects and the release in the substantia nigra is likely to involve polysynaptic pathways, implying that the kainate administration to the neostriatum stimulates striatal neurons giving rise to both the direct and indirect pathways.

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