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Evidence that somatostatin sst_2 receptors mediate striatal dopamine release

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1 Somatostatin (SRIF) is a cyclic tetradecapeptide present in medium-sized aspiny interneurones in the rat striatum. We have previously shown that exogenous SRIF potently stimulates striatal dopamine (DA) release *via* a glutamate-dependent mechanism. We now report the ability of the selective sst_2 receptor agonist, BIM-23027, to mimic this effect of SRIF.

2 *In vivo* microdialysis studies were performed in anaesthetized male Wistar rats. In most experiments, compounds were administered by retrodialysis into the striatum for 15 min periods, 90 min and 225 min after sampling commenced, with levels of neurotransmitters being measured by HPLC with electrochemical and fluorescence detection.

3 BIM-23027 (50 and 100 nM) stimulated DA release with extracellular levels increasing by up to 18 fold.

4 Prior retrodialysis of BIM-23027 (50 nM) abolished the effects of subsequent administration of SRIF (100 nM).

5 The agonist effects of both BIM-23027 and SRIF were abolished by the selective sst_2 receptor antagonist, L-Tyr^8-CYN-154806 (100 nM).

6 The AMPA/kainate receptor antagonist, DNQX (100 μM), abolished the agonist effects of BIM-23027 as previously shown for SRIF.

7 This study provides evidence that the sst_2 receptor mediates the potent dopamine-releasing actions observed with SRIF in the rat striatum. Dopamine release evoked by both peptides appears to be mediated indirectly *via* a glutamatergic pathway. Other subtype-specific somatostatin receptor ligands were unable to elicit any effects and therefore we conclude that no other somatostatin receptor types are involved in mediating the dopamine-releasing actions of SRIF in the striatum.

Keywords: Rat; striatum; somatostatin; dopamine; glutamate; GABA; microdialysis

Abbreviations: ACh, acetylcholine; AMPA, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid; AP5, D,L-2-amino-5-phosphopentanoic acid; Arg, arginine; Asp, aspartate; Cit, citrulline; DA, dopamine; DNQX, 6,7-dinitroquinoxaline-2,3-dione; DOPAC, 3,4-dihydroxyphenylacetic acid; GABA γ-aminobutyric acid; Glu, glutamate; Gly, glycine; 5-HIAA, 5-hydroxyindoleacetic acid; 5-HT, 5-hydroxytryptamine; SRIF, somatostatin; Tau, taurine

Introduction

The cycle tetradecapeptide, somatostatin (SRIF), was originally isolated from ovine hypothalamus in 1973 by Brazeau *et al*. The neuropeptide and its receptors have a wide distribution in the brain and periphery (Epelbaum *et al*., 1977; Iversen *et al*., 1978; Schindler *et al*., 1996; 1997). Five distinct SRIF receptor genes have been discovered and cloned, and the complementary receptor proteins are termed sst_{1-5}, one of which, the sst_2 receptor, has two transcriptional isoforms termed $sst_{2(a)}$ and $sst_{2(b)}$ in mouse and rat (Vanetti *et al*., 1992; Schindler *et al*., 1999). These receptors are all composed of seven transmembrane-spanning units and are all coupled to G-proteins.

Within the striatum, SRIF is found in a discrete population of medium-sized aspiny interneurones (~12–25 μm in diameter), which account for 1–2% of the total population of interneurones in this region (Kawaguchi *et al*., 1995). These SRIF-containing interneurones also contain neuropeptide Y (Vincent & Johansson, 1983) and neuronal nitric oxide synthase (Kawaguchi *et al*., 1995) and receive direct glutamatergic cortical inputs (Vuillet *et al*., 1989).

We have previously shown that infusions of SRIF by retrodialysis in the rat striatum elevates extracellular levels of dopamine (DA), GABA, aspartate (Asp) and taurine (Tau), in a concentration-dependent manner (Hathway *et al*., 1998). We also have demonstrated that this effect is dependent upon elevation of glutamate and that the actions of SRIF are calcium-dependent and tetrodotoxin-sensitive. At present neither *in situ* hybridization nor immunohistochemical studies have been able to provide evidence of significant concentrations of any SRIF receptor type in the rat striatum, although Dournaud *et al*. (1998) have shown that some $sst_{2(a)}$ receptors are present in caudal caudate putamen with a specific receptor antibody which labelled SRIF-containing cells. Immunohistochemical studies by Schindler *et al*. (1997; 1999) have reported a very sparse distribution of $sst_{2(a)}$ and $sst_{2(b)}$ receptors in the rat striatum, which they speculated were on dopaminergic nigro-striatal terminals. However, from our previous dialysis data we hypothesized that the receptor type(s) that mediates the effects of SRIF in the striatum is located on the terminals of cortico-striatal projection neurones which contain glutamate (Glu; Hathway *et al*., 1998). In this study, we have

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attempted to determine the functional somatostatin receptor type(s) that is responsible for mediating the effects of SRIF by utilising some selective somatostatin receptor ligands and measuring their effects upon changes in the levels of striatal neurotransmitters.

Methods

Animals

Adult male Wistar rats (250–300 g) were used in all experiments. Animals were anaesthetized intraperitoneally with a 25% urethane solution and mounted in stereotaxic apparatus (Kopf Instruments, U.S.A.) *via* two ear bars and an incisor bar set at 7° above the interaural line. Incisions were made in the scalp, and coordinates for microdialysis probe placement were calculated relative to bregma according to a stereotaxic atlas (Pellegrino *et al*., 1979). Microdialysis probes (CMA/12; CMA Microdialysis, Stockholm, Sweden; 0.5 mm o.d., 3 mm membrane length) were placed in the medial portion of the right striatum at the coordinates 2 mm rostral to bregma, 2.5 mm lateral to the midline and 6 mm down from the surface of the brain. Body temperature was maintained using a homeothermic heated blanket (Harvard Apparatus, U.K.) at 37°C. All animal use procedures were in strict accordance with the U.K. Home Office guidelines and specifically licensed under the Animals (Scientific Procedures) Act 1986.

Microdialysis sampling and HPLC methods

Microdialysis sampling started 90 min after probe implantation. A Krebs-Ringer solution (pH 7.4) was made up with Milli-Q (Waters, Milford, MA, U.S.A.) deionized water (resistivity 18.2 $M\Omega\ cm^{-1}$) containing (in mM): NaCl 138, $CaCl_2$ 1.5, $NaHCO_3$ 11, KCl 5, $MgCl_2$ 1, and NaH_2PO_4 1; Neostigmine sulphate (5 μM; Sigma) was also added to enable measurement of acetylcholine (ACh) levels. This solution was passed through the probes at 1.5 $\mu l\ min^{-1}$ using a syringe pump (CMA-10; CMA Microdialysis). Samples were collected from the outflow tube of the probe into 500 μl Eppendorf tubes containing 2 μl of 10% acetic acid (v v^{-1}) at 15 min intervals using a fraction collector (CMA-142; CMA Microdialysis). A liquid switch (CMA-110; CMA Microdialysis) was placed between the syringe pump and the probe to switch between perfusion solutions without introducing air bubbles into the probe. The dead space between the switch and the end of the outflow tubing at the end of the probe was calculated to be 10.5 μl, and this was taken into account when switching between solutions. Collected samples (25 μl) were frozen (−20°C) immediately upon collection and subsequently used for HPLC analysis.

The amino acids Glu, Asp, GABA, glycine (Gly), citrulline (Cit), arginine (Arg), and Tau were quantified by HPLC using automated precolumn derivatization with o-phthaldialdehyde (Sigma) performed with a Gilson model 231 autosampler and fluorescence detection as previously described (Kendrick *et al*., 1996). The detection sensitivity of the system was 2–5 nM with 8 μl of sample derivatized. Arg and Cit were also separated and simultaneously quantified by this method with a detection limit of 4 nM.

DA and 5-HT and their respective metabolites, 3,4-dihydroxyphenylacetic acid (DOPAC) and 5-hydroxyindoleacetic acid (5-HIAA), were quantified by HPLC with electrochemical detection (LC4B with a Unijet cell and a 6 mm glassy carbon cell at +0.65 V; Bioanalytical Systems, West Lafayette, IN, U.S.A.). The mobile phase was NaCl 10 mM, sodium acetate 85 mM, octane sulphonic acid 150 mg ml^{-1}, EDTA 100 mg L^{-1} and 4% methanol (pH 4.5) and a flow rate of 210 $\mu l\ min^{-1}$ was used (Gynkotek M480). The column was a C18 reversed-phase Spherisorb (S3ODS2; Waters, U.K.; 2 mm i.dx 15 cm length). A CMA-200 refrigerated microinjector (CMA Microdialysis) was used to inject the samples (7–10 μl injection volume). The detection sensitivity was 100–200 pM.

At the end of each experiment, rats were killed by cervical dislocation and the brains rapidly dissected and sectioned to confirm the accuracy of probe placements. Examination of the dissected brains revealed that in all animals the microdialysis probes were localized in the medial portion of the right striatum.

Experimental protocol for concentration-dependent effects of somatostatin receptor ligands

Five different receptor ligands were investigated in this study, BIM-23027 (sst_2 receptor agonist; Bell & Reisine, 1993), CYN-154806 (sst_2 receptor antagonist; Bass *et al*., 1996), NNC 26-9100 (sst_4 receptor agonist; Ankersen *et al*., 1998), L-362,855 ($sst_{2,5}$ receptor agonist; Williams *et al*., 1997) and BIM-23056 (sst_5 receptor antagonist; Wilkinson *et al*., 1997); these were all applied *via* the microdialysis probes (retrodialysis). Dialysate samples were collected initially for 90 min to establish baseline values. All of the compounds were dissolved in Krebs-Ringer (containing neostigmine) and retrodialysed for a 15 min period 90 min after the commencement of sampling and once again 135 min later. Between challenges the perfusing solution was changed back to Krebs-Ringer. In experiments using NNC 26-9100, L-362,855 and BIM-23056, three concentrations of each compound were tested (1, 50 and 1000 nM).

In experiments using BIM-23027, three concentrations of the compound were tested 10, 50 and 100 nM. Studies were also performed with BIM-23027 (50 nM) and L-Tyr^8-CYN-154806 (100 nM) applied together in the first administration and BIM-23027 (50 nM) alone in the second. The actions of BIM-23027 were also investigated in the presence of the ionotropic glutamate receptor antagonists, D,L-2-amino-5-phosphonopentanoic acid (AP5; an NMDA receptor antagonist) and 6,7-dinitroquinoxaline-2,3-dione (DNQX; an α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA)/kainate receptor antagonist). Both DNQX (100 μM) and AP5 (100 μM) were retrodialysed singly and together for 90 min before administration of 50 nM BIM-23027; perfusing solutions were then changed to Krebs-Ringer for 135 min before a second administration of BIM-23027 (50 nM).

A double agonist study was also performed in which BIM-23027 (50 nM) was administered to the striatum 90 min after the commencement of sampling; 100 nM SRIF was then administered 30 min later. In separate experiments to investigate whether CYN-154806 (100 nM) had any agonist actions itself, it was retrodialysed for 15 min, 90 min after the commencement of sampling.

Statistics

In each experiment it was confirmed that the mean concentrations of substances measured in the four control samples taken before a drug challenge did not differ significantly from one another using a repeated-measures ANOVA. To assess the effects of drugs under the different

conditions in each animal, the sample taken immediately before the drug administration was defined as 100%, and the change from this during the 15-min sample with the drug and that immediately after it were expressed as a percentage. In each case a repeated-measures ANOVA was carried out, and, where significant ($P<0.05$), *post hoc* comparisons made with Tukey's test to compare the effects of the drugs. For comparisons across concentrations and across treatment groups, an ANOVA was carried out and where significant ($P<0.05$) *post hoc* comparisons were made with a *t*-test. Effects of DNQX and AP5 on basal concentrations of substances were analysed by calculating a mean concentration in two samples before treatment and expressing this as 100%. An overall mean for substance concentrations during drug administrations was calculated and expressed as a percentage of this. A Wilcoxon test was then used to make statistical comparisons.

Drugs

BIM-23027, BIM-23056, NNC 26-9100, L-362,855 and CYN-154,806 were synthesized by Dr J. Murray's team (Glaxo Wellcome Chemistry Unit, University of Cambridge, U.K.). DNQX and AP5 were provided by Tocris Cookson Ltd, Bristol, U.K.

Results

Effects of BIM-23027 on striatal neurotransmitter levels

Administration of BIM-23027 into the rat striatum increased levels of DA at the two highest concentrations (Figure 1). The lowest concentration of BIM-23027 tested, 10 nM, did not significantly increase levels of DA (1.24±0.3 fold) or any of

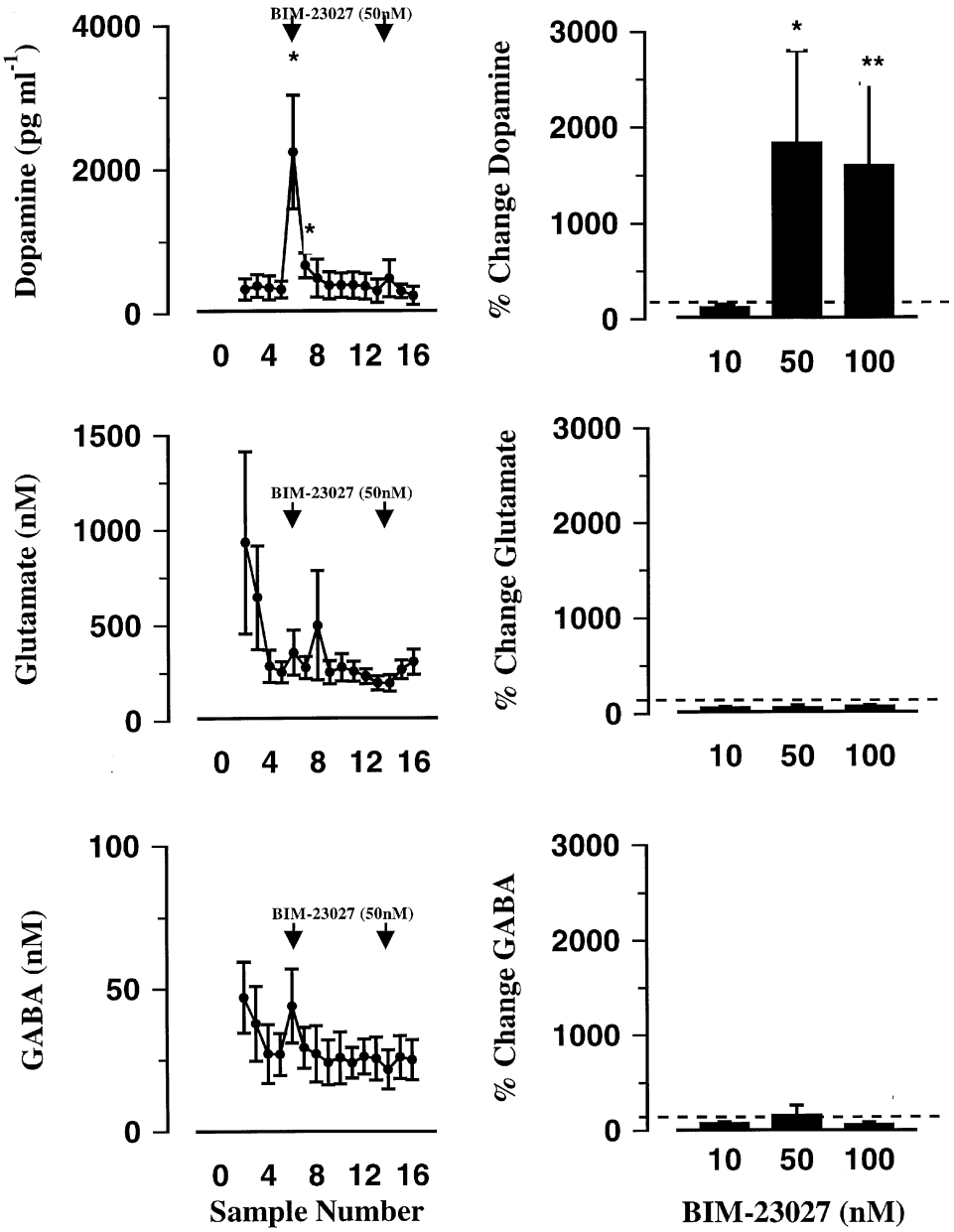

Figure 1 The neurochemical effects of BIM-23027 upon striatal neurotransmitter levels. The graphs in the left column show the changes in concentration of the neurotransmitters in response to 50 nM BIM-23027 with time. The histograms in the right column show the percentage increases in the levels of DA, Glu and GABA upon application of three concentrations of BIM-23027 (10, 50 and 100 nM). Dotted line indicates baseline levels (100%). All values are the mean of determinations from six animals, bars indicate s.e.mean with statistical significance shown at $*P<0.05$ and $**P<0.01$.

the other transmitters tested. BIM-23027 (50 nM) applied 90 min after the commencement of sampling significantly and potently increased levels of DA by 18.4±9.6 fold (compared with mean baseline value, $P<0.05$). The higher concentration of 100 nM, BIM-23027 also increased the levels of DA (10±8.5 fold; $P<0.01$). Unlike the reported effects of SRIF, BIM-23027 had no significant effects upon any of the other transmitters measured at any concentration ($P>0.05$). The increases in DA levels evoked by BIM-23027 were always confined to the sample taken during the 15 min administration period, except for the 50 nM concentration of BIM-23027 where DA levels were also elevated in the subsequent sample (3.5±1.25 fold; $P<0.05$). In all cases when the same concentration of BIM-23027 was repeated 135 min after the first, it did not increase significantly the concentrations of any of the transmitters.

Effects of BIM-23027 upon the actions of SRIF

A 15 min period of administration of BIM-23027 (50 nM) prior to a 15 min infusion of SRIF (100 nM) significantly attenuated the actions of the naturally-occurring peptide. Administration of SRIF to the striatum following the challenge of BIM-23027 did not elicit significant effects upon any striatal neurotransmitter levels (see Figure 2a). The effects of SRIF (100 nM) upon DA levels were abolished by prior administration of BIM-23027, i.e. 1.0±0.6 fold compared with 28.7±1.5 fold without pre-administration (see Hathway *et al*., 1998).

Effects of CYN-154806 upon the actions of BIM-23027 and SRIF

A 15 min period of co-administration of the sst_2 receptor antagonist, CYN-154806 (100 nM), significantly attenuated the actions of BIM-23027 (50 nM). Thus in these experiments, BIM-23027 did not elicit a significant increase in DA (1.5±0.7 fold, $P<0.05$). Nor were there any changes in any of the other neurotransmitters measured (see Figure 3). In analogous experiments, a 15 min concomitant period of administration of CYN-154806 (100 nM) significantly attenuated the actions of SRIF (100 nM; DA 1.0±0.03 fold, $P>0.05$; Figure 3).

Effects of DNQX and AP5 upon the actions of BIM-23027

Retrodialysis of the AMPA/kainate receptor antagonist, DNQX (100 μM), for 90 min prior to a 50 nM application of BIM-23027 abolished the ability of the peptide to elicit increases in DA levels (0.5±0.4 fold compared to 18.4±9.6 fold $P<0.01$; Figure 2b). The NMDA receptor antagonist AP5 also significantly decreased the amount of DA released in response to administration of BIM-23027 (50 nM; 5.2±2.5 fold, $P<0.05$; Figure 2b).

Effects of NNC 26-9100, L-362,855 and BIM-23056 on striatal neurotransmitter levels

Retrodialysis of NNC 26-9100, the sst_4 receptor agonist (1, 50 and 1000 nM), L-362,855, the sst_5 receptor agonist (1, 50 and 1000 nM), and BIM-23056, the sst_5 receptor antagonist (1, 50 and 1000 nM), did not alter levels of any of the compounds measured (data not shown).

Discussion

The experiments described here have provided the first evidence for a striatal effect of the selective sst_2 receptor agonist, BIM-23027, and hence proof of the existence of functional sst_2 receptors in the rat striatum. This agonist, concentration-dependently increased extracellular levels of DA (but not DOPAC) in the striatum although the concentration-response relationship appeared all or none, on the basis of the concentrations studied. No effects upon levels of 5-HT, 5-HIAA, or the amino acid neurotransmitters were seen at any concentration of this compound tested. A second administration of BIM-23027 (50 nM), given 120 min after the first, did not alter significantly the release of DA suggesting that receptor desensitization occurs even at concentrations close to threshold for overt agonist activity. Although BIM-23027 potently increased levels of DA in the striatum, the degree of this effect was less than that observed with SRIF (100 nM) (Hathway *et al*., 1998). However, the most potent dose of BIM-23027 used (50 nM), was 50% of the most potent dose of

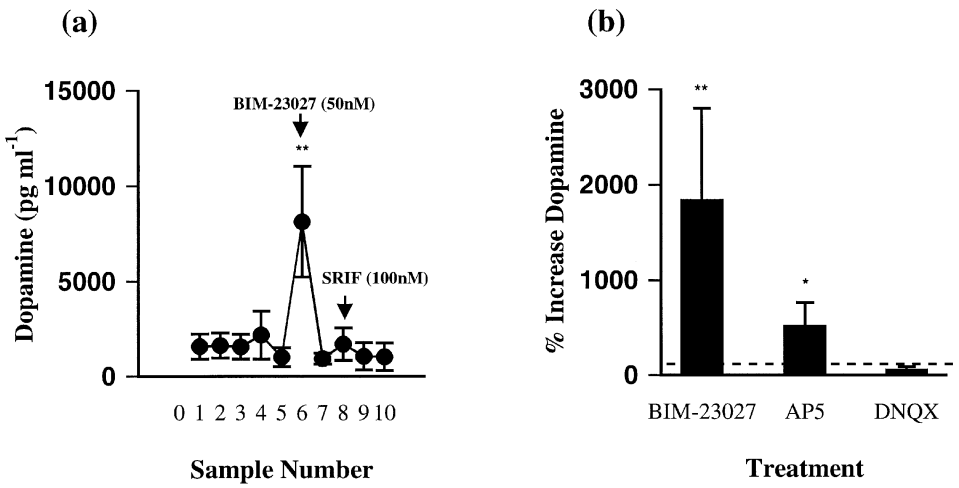

Figure 2 Figures showing that in (a) BIM-23027 (50 nM) abolished the effects of a subsequent concentration of SRIF (100 nM) and in (b) the antagonism by AP5 (100 μM) and DNQX (100 μM) on the ability of BIM-23027 (50 nM) to increase DA levels is shown. All values are the mean of determinations from six animals in each treatment (BIM-23027 control; BIM-23027 in AP5-treated animals; BIM-23027 in DNQX treated animals). Dotted line indicates baseline levels (100%), bars indicate s.e.mean with statistical significance shown at $*P<0.05$ and $**P<0.01$.

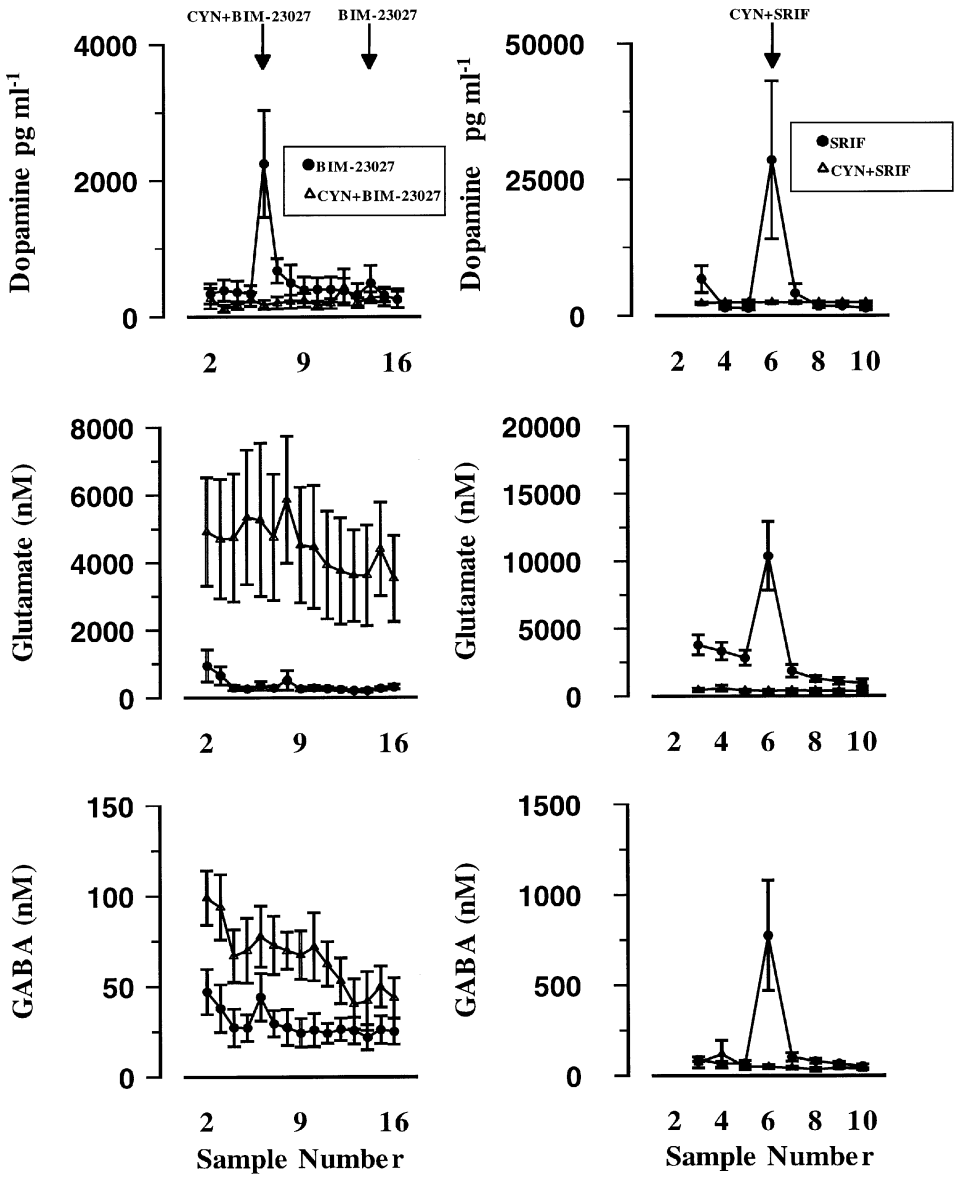

Figure 3 L-Tyr^8-CYN-154806 (100 nM) abolished the effects of either BIM-23027 (50 nM; left hand column) or SRIF (100 nM; right hand column). The agonists were co-applied with the antagonist, 90 min after the commencement of sampling. The graphs on the left show both the effects of BIM-23027 in control conditions and in the presence of CYN-154806. The graphs on the right show the effects of SRIF in the presence and absence of CYN-154806. All values are the means of determinations from six animals.

SRIF used (100 nM) and the increases observed with these compounds at these doses were not significantly different. As with SRIF, the concentration-response relationship with BIM-23027 is bell-shaped and it may be that BIM-23027 at equivalent doses is able to release DA more potently than SRIF. However, the observation that a second application of this compound is ineffective, implying that receptor desensitization occurs, precludes this comparison. It should be noted that neostigmine (5 μM) was included in our perfusing Krebs-Ringer solution to enable measurement of ACh levels from our dialysates. Removal of this compound from the Krebs-Ringer had no influence upon the effects of the compounds used in this study or upon the levels of neurotransmitters measured, except ACh (data not shown).

The results also show that other somatostatin receptor type-selective ligands, L-Tyr^8-CYN-154806, NNC 26-9100, L-362,855, and BIM-23056, had no effect upon levels of any neurotransmitters measured in this study at any concentration tested (Tallent *et al.*, 1996; Wilkinson *et al.*, 1997; Williams *et al.*, 1997; Ankersen *et al.*, 1998). The lack of effect of the agonists, NNC 26-9100 and L-362,855, rules out a possible involvement of sst_4 or sst_5 receptors respectively. The apparent inactivity of L-362,855 may be surprising in view of known agonist activity at sst_2 receptors (see Chessell *et al.*, 1996; Hicks *et al.*, 1998). However, it can behave as a partial agonist at somatostatin receptors and may differentially activate receptor-effector coupling mechanisms compared to SRIF (Williams *et al.*, 1997; Smalley *et al.*, 1998; Sellers *et al.*, 1999). Alternatively an action of L-362,855 at sst_5 receptors could cause an opposing effect. BIM-23056, which has been reported to be an antagonist at sst_5 receptors also had no effect (Wilkinson *et al.*, 1996; 1997). To examine further whether more than one type of somatostatin receptor might mediate the actions of SRIF, the sst_2 receptor population in the striatum was desensitized by administering BIM-23027 (50 nM) 30 min before SRIF (100 nM). Since SRIF had no subsequent effect on any of the transmitters measured in this paradigm, there is no evidence for the involvement of non-sst_2 receptors.

The results also show that BIM-23027-evoked release of DA can be blocked by the presence of the selective sst_2 receptor antagonist, L-Tyr^8-CYN-154806, as well as by DNQX suggesting that the effect of the synthetic hexapeptide on DA release is caused by activation of sst_2 receptors which mediate the release of Glu from the terminals of glutamatergic corticostriatal projection neurones. An indirect glutamatergic link has also been postulated for SRIF's DA-releasing action in rat striatum (see Hathway *et al*., 1998).

The apparent lack of involvement of any other SRIF receptors in mediating striatal neurochemical changes might be thought surprising in view of the widespread distribution of all five SRIF receptors. However, *in situ* hybridization techniques have been unable to specifically identify the particular receptors present in the striatum (Senaris *et al*., 1994; Schindler *et al*., 1997).

The effects of both SRIF and BIM-23027 are antagonized by L-Tyr^8-CYN-154806

Further functional evidence for the neurochemical effects of SRIF being mediated solely by the sst_2 receptor was also provided in this study using L-Tyr^8-CYN-154806, a stereoisomer of the sst_2 receptor antagonist, CYN-154806, reported by Bass *et al*. (1996). They reported that CYN-154806 binds to sst_2 receptors expressed in Chinese hamster ovary cells with an affinity of 0.3 nM and an ED_{50} of 15 nM for antagonism of sst_2 receptor-mediated inhibition of forskolin-stimulated cyclic AMP accumulation in GH4C1 cells (Bass *et al*., 1996). The L-isomer has similar potencies and has been used in electrophysiological studies (Hicks *et al*., 1998) and to antagonize endogenous sst_2 receptors in isolated tissues (Feniuk *et al*., 1998). Thus it fully reversed the stimulant effects of BIM-23027 upon outwardly rectifying K^+ currents in anterior cingulate cortical neurones which express the sst_2 receptor and had a similar effect upon submaximal concentrations of either SRIF (100 nM) or L-362,855 (100 nM). In the study described here L-Tyr^8-CYN-154806 (100 nM) was retrodialysed for the 15 min period during which BIM-23027 was also administered and was found to abolish the DA-releasing actions of BIM-23027. We also showed that application of L-Tyr^8-CYN-154806 prevented the action of a subsequent administration of BIM-23027, 120 min later. This seems somewhat surprising but may result from accumulation or lack of 'wash out' of the antagonist or alternatively BIM-23027 may have caused desensitization of the receptors even in the absence of overt agonist activity. Nevertheless, the ability of L-Tyr^8-CYN-154806 to abolish the effects of both SRIF and BIM-23027 further supports the conclusion that the sst_2 receptor predominantly or exclusively mediates the neurochemical actions of SRIF in the striatum.

The ability of BIM-23027 to increase DA levels is mediated by a Glu-dependent mechanism

Despite much evidence for the involvement of the sst_2 receptor mediating DA release in the striatum, an apparent paradox exists. The full profile of neurotransmitter release seen with SRIF (Hathway *et al*., 1998) was not reproduced with BIM-23027 in this study. The first BIM-23027 (50 nM) administration by retrodialysis increased concentrations of DA by 18 fold, which was not significantly different to that observed with SRIF in the previous study (Hathway *et al*., 1998). However, in that study, the increases in DA levels evoked by SRIF were accompanied by increases in Glu, Asp, GABA and Tau levels which were not observed with BIM-23027 in this study. It was concluded previously that SRIF mediates its effects upon striatal neurotransmitter levels *via* a glutamatergic mechanism with levels of Glu increasing 6 fold on administration of 100 nM SRIF (Hathway *et al*., 1998). The ability of SRIF to increase DA levels was shown to be abolished by the AMPA/kainate receptor antagonist, DNQX (Hathway *et al*., 1998) and in this study, pretreatment of the striatum with DNQX also abolished the effects of BIM-23027. Previously it has been reported that the NMDA receptor antagonist, AP5 (200 μM), abolishes the ability of SRIF (100 nM) to increase amino acid neurotransmitter levels and also significantly decreases the ability of SRIF to release DA (Hathway *et al*., 1998). We have now shown that AP5 significantly attenuates the ability of BIM-23027 to release DA. It must therefore be concluded that BIM-23027, like SRIF, mediates its effects *via* a glutamatergic mechanism although increases in the levels of Glu were not detectable. One obvious explanation might be that BIM-23027 is a partial agonist at sst_2 receptors such that lower amounts of Glu are released but there is no evidence that this is the case *in vitro* (see Castro *et al*., 1996; Wyatt *et al*., 1996).

Other explanations for the inability to detect changes in Glu levels may be technical or physiological. It may be that BIM-23027 interferes with the derivatization of the primary amino acids by o-phthaldialdehyde (see Hathway *et al*., 1998). Indeed it has been shown that addition of known concentrations of BIM-23027 to a solution containing known quantities of all the amino acids does slightly but significantly decrease the levels of these compounds measured (Glu; 195 ± 12 nM compared with 250 nM in the presence and absence of BIM-23027 respectively $n = 6$; Hathway, 1998). However, the degree of this effect was not sufficient to explain completely our inability to measure changes in Glu levels. A greater efficiency of the uptake mechanisms in both neurones and glia for the primary amino acids or alternatively a greater rate of metabolism may explain this effect.

In conclusion, this study is the first to attribute a particular function to a specific somatostatin receptor in the striatum of the rat brain *in vivo*. Nevertheless, further investigation of the role of SRIF and SRIF receptor ligands within the striatum is required to gain a full understanding of the role of the endogenous peptide in this brain region. It may be that anaesthesia may have influenced our results, although at present, no data concerning the effects of these compounds in the 'freely-moving' animal are available. The fact that both SRIF and BIM-23027 have been shown to potently stimulate an increase in DA release suggests that somatostatinergic tone involving sst_2 receptors may play a physiological role in the control of movement or may be pathophysiologically involved in movement disorders. Hence, the development of drugs which target the sst_2 receptor may be useful in the treatment of neurodegenerative disorders affecting the dopaminergic basal ganglia system such as in Parkinson's Disease.

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