

# The novel monoamine reuptake inhibitor and potential antidepressant, S33005, induces *Arc* gene expression in cerebral cortex

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## Abstract

Recent data show that corticolimbic expression of the effector immediate early gene *Arc* is up-regulated by standard antidepressant drugs. Here, we tested the effect upon *Arc* expression of a novel antidepressant and selective 5-hydroxytryptamine/noradrenaline reuptake inhibitor (SNRI), (–)-1-(1-dimethylaminomethyl) 5-methoxybenzocyclobutan-1-yl cyclohexanol (S33005). *Arc* mRNA abundance in frontal, cingulate, orbital and parietal cortices, hippocampus (CA1 pyramidal layer) and striatum was elevated in rats treated daily for 14 but not 7 days with 10 mg/kg i.p. S33005 compared to saline. Fourteen but not 7 days treatment with 10 mg/kg i.p. venlafaxine, the prototypical SNRI, also elevated *Arc* mRNA, but its effects were not as pronounced and detected in fewer regions, compared to S33005. Neither S33005 nor venlafaxine altered *Arc* mRNA after acute injection nor altered brain derived neurotrophic factor mRNA after repeated administration. These data demonstrate that sustained treatment with SNRIs increases *Arc* expression in corticolimbic regions, and underpin previous neurochemical and behavioural evidence that S33005 is efficacious in models predictive of antidepressant action.

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**Keywords:** Antidepressant; *Arc* (activity-regulated cytoskeletal associated protein); 5-hydroxytryptamine; SNRI (selective 5-HT/noradrenaline reuptake inhibitor); Neuroplasticity

## 1. Introduction

Adaptive mechanisms involving changes in neural plasticity have been implicated in the delayed onset of therapeutic action of antidepressants (Grahame-Smith, 1997; Manji et al., 2001; Reid and Stewart, 2001). In this respect, the activity-regulated cytoskeletal associated protein, *Arc* (also known as Arg.1) (Link et al., 1995; Lyford et al., 1995), is of particular interest since this effector immediate early gene is thought to play a fundamental role in activity-dependent neural plasticity in corticolimbic brain regions (Steward and Worley, 2001a,b). Following synaptic stimulation, *Arc* mRNA is rapidly induced, distributed to dendritic processes and translated to facilitate synapse-specific modifications (Wallace et al., 1998; Steward et al., 1998; Ying et al.,

2002). *Arc* has been implicated in the modulation of a range of functions known to be profoundly perturbed in depressive states, including cognition, arousal and sleep (Kodama et al., 1998; Guzowski et al., 1999; Cirelli and Tononi, 2000; Montag-Sallaz and Montag, 2003; Nishimura et al., 2003). For example, disruption of *Arc* expression using antisense oligonucleotides causes deficits both in long-term potentiation (LTP) and in behavioural learning paradigms (Guzowski et al., 2000, 2001; Guzowski, 2002).

In recent work, we found that antidepressant drug administration induces *Arc* gene expression (Pei et al., 2003). Thus, a 2-week course of treatment with paroxetine (a selective 5-HT reuptake inhibitor), desipramine (a tricyclic antidepressant and noradrenaline reuptake inhibitor), venlafaxine (a selective 5-HT and noradrenaline reuptake inhibitor, SNRI) or tranylcypromine (a monoamine oxidase inhibitor) increased *Arc* mRNA in several rat brain regions that have been implicated in mood control. In comparison, acute treatment with these antidepressant drugs, or repeated treatment with the antipsy-

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chotic, chlorpromazine, did not alter *Arc* expression. These findings suggest that antidepressant drugs, which increase extracellular levels of 5-HT and/or noradrenaline, evoke activity-dependent changes in synaptic plasticity in cortical and other brain areas via the induction of *Arc* (Pei et al., 2003).

S33005 ((-)(1-Dimethylaminomethyl) 5-methoxybenzocyclobutan-1-yl) cyclohexanol (S33005) is a novel and potent SNRI which displays robust antidepressant properties in a diversity of preclinical behavioural and neurochemical models (Millan et al., 2001a,b). Both in vitro and in vivo studies indicate that S33005 exerts its actions more potently and, in certain procedures, more efficaciously than the prototypical SNRI, venlafaxine (Millan et al., 2001a,b). In the present study, we tested the influence of acute and long-term administration of S33005 upon on *Arc* expression in rat brain and compared its actions to those of venlafaxine.

## 2. Materials and methods

### 2.1. Animals

Male Sprague–Dawley rats (220–250 g, Harlan Olac, Bicester, UK) were used for all experiments. Rats were housed at constant temperature ( $21 \pm 1$  °C) and humidity under a 24-h light–dark cycle (lights on 07:00 h). All experiments were carried out in accordance with the UK Scientific Procedures Act (1984) and Home Office guidelines.

### 2.2. Experimental design

Groups of five to six rats were administered 10 mg/kg i.p. S33005, 10 mg/kg i.p. venlafaxine or saline either once (acute treatment) or once daily for 7 or 14 days (repeated treatment). Sixteen hours after the last injection, brains were removed and snap frozen in isopentane ( $-40$  °C) prior to sectioning. To minimize stress immediately prior to tissue removal, all animals were maintained in their home cages and holding room throughout the treatment period, and then dispatched immediately following a short transfer to the procedure room. All treated animals were dispatched within a short period on the same day. Brains were sectioned and processed in a random fashion to control for any possibility of uneven tissue preservation/storage.

### 2.3. In situ hybridisation

Abundance of mRNA encoding for *Arc* and brain-derived neurotrophic factor (BDNF) were measured by in situ hybridisation as described previously (Zetterström et al., 1999; Pei et al., 2000). In brief, cryostat-cut sections (12 µm) were thaw-mounted onto gelatine-subbed slides and pretreated using standard methods. An oligonucleotide complementary to either *Arc* mRNA (5'-CTTGTTGCCCATCCTCACCTGGCACCCAAGACTGGTATTGCTGA-3') or BDNF mRNA (5'-GGTCTCGTAGAAATATTGGTTTCAGTTGGCCTTTTGATACCGGGAC-3') was labelled with [<sup>35</sup>S]dATP and applied to each section in hybridization buffer ( $1 \times 10^6$  cpm/section). After overnight incubation

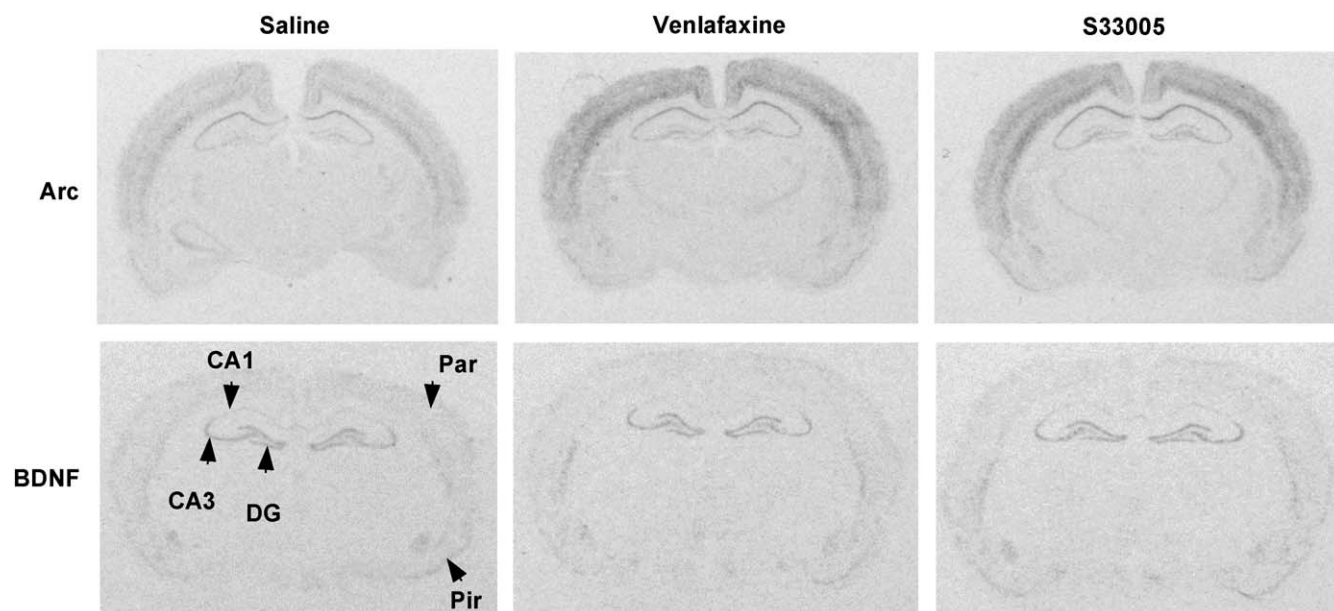


Fig. 1. Representative autoradiograms showing the localisation of *Arc* and BDNF mRNA in rats treated repeatedly with S33005 and venlafaxine (10 mg/kg i.p. for 14 days). Images are coronal sections at the level of the hippocampus. Abbreviations: Par, parietal cortex (superficial layer); Pir, piriform cortex; DG, dentate gyrus; CA1 and CA3 pyramidal cell layers of hippocampus.

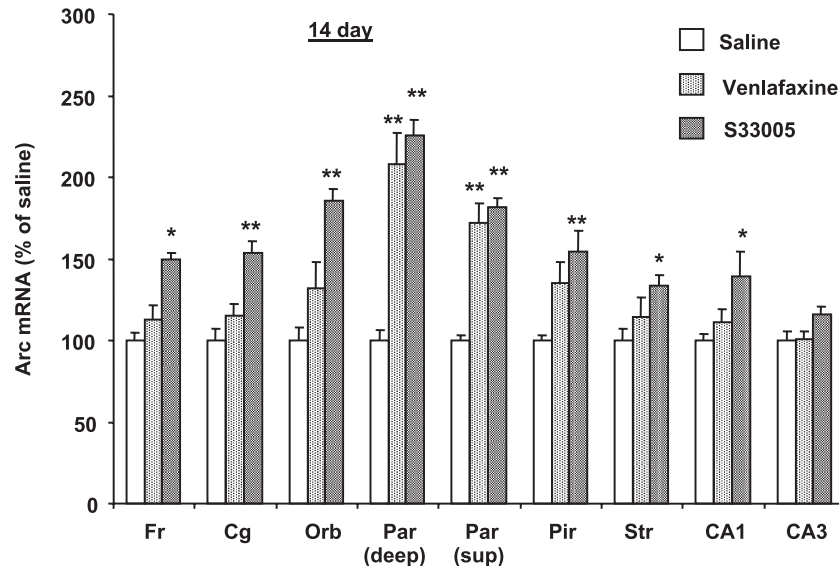


Fig. 2. Effect of 14 days administration of S33005 and venlafaxine (10 mg/kg i.p. daily) on *Arc* mRNA abundance in different rat brain regions. Each column represents a mean  $\pm$  S.E.M. value ( $n=6$ /group). \*\* $p<0.01$  and \* $p<0.05$  versus saline. Abbreviations: Fr, frontal cortex; Cg, cingulate cortex; Orb, orbital cortex; Pir, piriform cortex; Par-deep, parietal cortex deep layer; Par sup, parietal cortex superficial layer; Str, striatum.

at 37 °C in a hybridization oven, slides were washed in  $0.5 \times$  SSC (standard saline citrate) at 55 °C for  $3 \times 20$  min followed by  $2 \times 60$  min at room temperature. Sections were then air-dried and exposed to Biomax film (Amersham, UK) for 5–7 days at room temperature. Previous experiments have established the specificity of the oligonucleotide probes, including the hybridization of sections using oligonucleotides in the sense orientation and displacement with unlabelled probes (Zetterström et al., 1999; Pei et al., 2000).

#### 2.4. Image analysis

The relative abundance of *Arc* and BDNF mRNA in selected areas was determined by densitometric quantification of autoradiograms (MCID, St. Catherine, Canada) by an observer blind to treatment. Optical density values were calibrated to [ $^{35}$ S] tissue equivalents using  $^{14}$ C microscscales (Amersham). Densitometric values were measured from three sections of each animal and averaged. Data are expressed as nCi/g tissue and presented as mean  $\pm$  S.E.M.

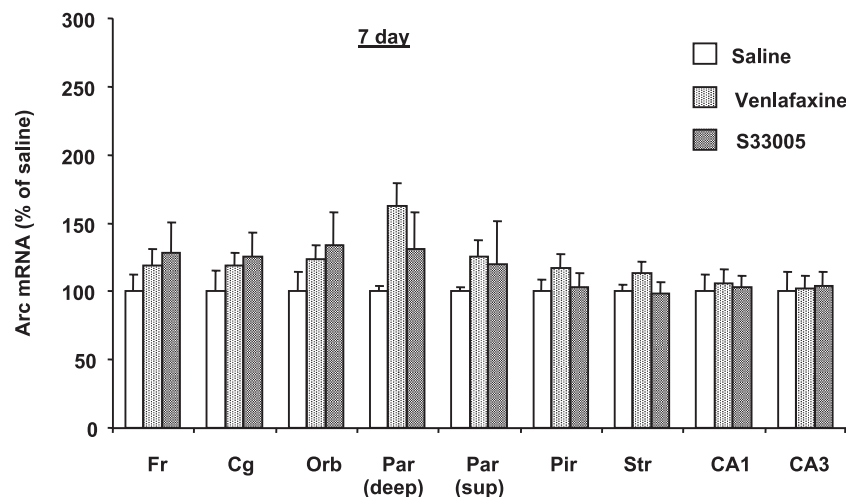


Fig. 3. Effect of 7 days administration of S33005 and venlafaxine (10 mg/kg i.p. daily) on *Arc* mRNA abundance in different rat brain regions. Each column represents a mean  $\pm$  S.E.M. value ( $n=6$ /group). Abbreviations as in legend to Fig. 2.

Table 1

Effect of acute administration of S33005 and venlafaxine (both at 10 mg/kg i.p.) on *Arc* mRNA abundance in different rat brain regions

Region	Par-deep	Par-sup	Pir	Str	CA1
Saline	173.9 ± 32.1	162.2 ± 31.1	185.0 ± 32.9	178.4 ± 38.5	180.2 ± 40.4
Venlafaxine	227.1 ± 36.9	187.3 ± 25.5	193.7 ± 33.4	174.9 ± 26.1	203.1 ± 31.6
S33005	193.5 ± 23.9	169.4 ± 21.5	195.1 ± 25.6	173.9 ± 25.9	200.8 ± 27.1

Each column represents mean ± S.E.M. ( $n=5$ /group) amounts of *Arc* mRNA (nCi/g tissue). Abbreviations as in legend to Fig. 2. No differences were statistically significant.

values. Statistical differences between groups was tested by one-way analysis of variance followed by Dunnett's *t*-test.

### 2.5. Drugs

Both S33005 and venlafaxine were synthesised at Servier. These drugs were dissolved in warm 0.9% saline and injected i.p. at 1 ml/kg.

## 3. Results

### 3.1. Effect of 14 days administration of S33005 or venlafaxine on *Arc* mRNA

The distribution of *Arc* mRNA expression was similar to that described in recent studies with levels being most abundant in cortical regions and pyramidal cells layers (CA1, CA3) of the hippocampus (Fig. 1).

In animals treated once daily for 14 days with 10 mg/kg i.p. S33005, there was a marked increase on the abundance of *Arc* mRNA compared to saline-injected controls (Figs. 1 and 2). This effect was observed in the majority of cortical areas examined (frontal, cingulate, orbital, parietal and piriform) as well as striatum and the CA1 pyramidal layer of hippocampus (Fig. 2). The greatest increase in *Arc* expression was in the parietal cortex

where the effect was localised to the deep and superficial layers (Figs. 1 and 2).

Administration of 10 mg/kg i.p. venlafaxine once daily for 14 days also increased *Arc* expression compared to saline-treated controls (Figs. 1 and 2). This increase in *Arc* was the generally smaller in magnitude than S33005 and statistically significant in fewer regions (Fig. 2). As with S33005, the greatest effect of venlafaxine was present in the deep and superficial layers of the parietal cortex.

### 3.2. Effect of 7 days administration of S33005 or venlafaxine on *Arc* mRNA

In rats treated once daily for 7 days with 10 mg/kg i.p. S33005, there was a tendency for *Arc* mRNA to be increased but this did not reach statistical significance (Fig. 3). Similarly, *Arc* expression did not show a statistically significant increase in rats treated once daily for 7 days with 10 mg/kg i.p. venlafaxine (Fig. 3).

### 3.3. Effect of acute administration of S33005 or venlafaxine on *Arc* mRNA

The effect of a single injection of S33005 and venlafaxine was tested in selected regions to confirm previous findings that monoamine reuptake inhibitors do not increase *Arc* expression following acute administration (Pei et al.,

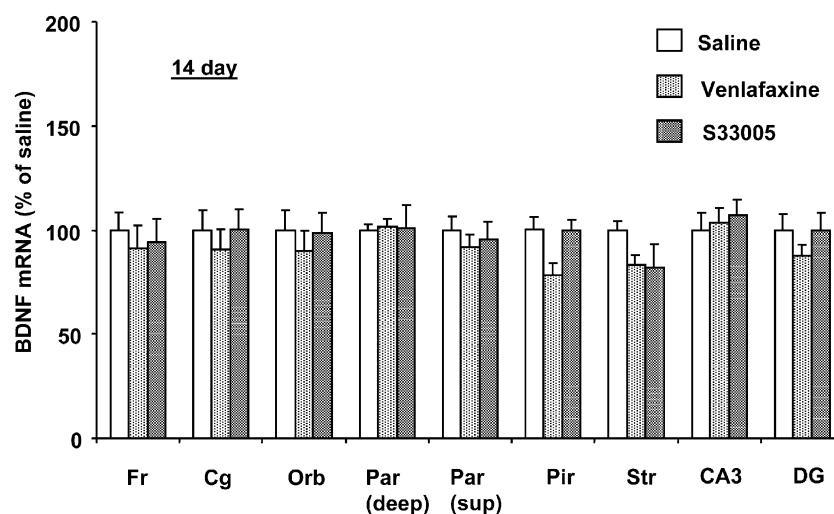


Fig. 4. Effect of 14 days administration of S33005 and venlafaxine (10 mg/kg i.p. daily) on BDNF mRNA abundance in different rat brain regions. Each column represents a mean ± S.E.M. value ( $n=5-6$ /group). Abbreviations as in legend to Fig. 2.



2003). Neither 10 mg/kg i.p. S33005 nor 10 mg/kg i.p. venlafaxine increased *Arc* expression in any region examined (Table 1).

#### 3.4. Effect of 14 days administration of S33005 or venlafaxine on BDNF mRNA

The distribution of BDNF mRNA expression was similar to that described in recent studies with levels being most abundant in granule cell layer of dentate gyrus and the pyramidal layer of CA3 in the hippocampus (Fig. 1).

In animals treated once daily for 14 days with 10 mg/kg i.p. S33005, there was no change in the levels of BDNF mRNA compared to saline-injected controls in any of the regions examined (Fig. 4). Administration of 10 mg/kg i.p. venlafaxine once daily for 14 days was similarly ineffective (Fig. 4).

#### 4. Discussion

The present data show that administration of the novel SNRI and potential antidepressant, S33005 (Millan et al., 2001a,b), increased the abundance of *Arc* mRNA in a several regions of the rat forebrain. The prototypical SNRI, venlafaxine, also elevated *Arc* mRNA expression but its effects were less pronounced in magnitude and seen in fewer regions. The actions of both S33005 and venlafaxine were present following 14 but not 7 days of administration, and neither drug altered *Arc* expression after a single injection. These data underscore and extend recent evidence that repeated but not acute administration of antidepressant drugs of different pharmacological classes, enhances *Arc* expression (Pei et al., 2003).

Repeated administration of S33005 increased *Arc* mRNA abundance in specific regions of the anterior cortex (orbital, cingulate, frontal, parietal and piriform cortices), in the hippocampus (CA1 but not CA3) and in the striatum. This regional pattern of change is very similar to that which we previously observed following administration of the selective inhibitors of 5-HT and noradrenaline reuptake, paroxetine and desipramine, respectively (Pei et al., 2003). The other SNRI tested, venlafaxine, also increased *Arc* expression although its effects were smaller than those of S33005 and restricted to a few regions. Specifically, venlafaxine caused a statistically significant increase in *Arc* mRNA in layers of the parietal cortex but only a trend for an increase was present in other cortical regions, hippocampus and striatum. This effect of venlafaxine confirms that observed in our recent study (Pei et al., 2003). While more robust increases in *Arc* expression might, in theory, be detected with a higher dose of venlafaxine, the dose employed herein exerts clear-cut actions in neurochemical and behavioural models of antidepressant activity. Although the present study tested S33005 and venlafaxine at single doses, previous evidence indicates that S33005 is more potent and

efficacious than venlafaxine in a range of in vitro and in vivo models predictive of antidepressant properties (Millan et al., 2001a,b).

Several lines of evidence suggest that the mechanisms underlying the elevation of *Arc* expression by S33005 (and venlafaxine) involves an increase in monoamine function. Firstly, chronic administration of other inhibitors of monoamine reuptake or metabolism increase *Arc* expression (Pei et al., 2003). Secondly, *Arc* expression in cortical and other brain regions increases in response to the administration of direct and indirect 5-HT agonists (Pei et al., 2000; Castro et al., 2003; Tordera et al., 2003), and other evidence also suggests an stimulatory influence of noradrenaline and dopamine (Berke et al., 1998; Fosnaugh et al., 1995; Kodama et al., 1998; Cirelli and Tononi, 2000). Finally, S33005 increases extracellular levels of 5-HT in the striatum, cortex and hippocampus, noradrenaline in the cortex and hippocampus, and dopamine in the striatum (Millan et al., 2001a,b).

It should be pointed out, however, that there is no simple relationship between the elevation in *Arc* expression and increases in extracellular levels of monoamines evoked by S33005 and other agents. Thus, S33005, venlafaxine and other antidepressants increase extracellular monoamine levels upon both chronic and acute administration (Millan et al., 2001a), whereas the increase in *Arc* expression requires their repeated administration. Indeed, this observation underpins the argument that alterations in *Arc* are downstream of adaptive changes in other plastic mechanisms (adaptive changes in receptor and intracellular signals) initiated by long-term exposure to antidepressant agents. Further, the effects of acute administration of S33005 on monoamine transmission may be offset by an autoreceptor-mediated decrease in the firing of 5-HT and noradrenaline neurones (Millan et al., 2001b). Thus, the net effect of long-term antidepressant treatment upon monoamine transmission is probably enhanced through autoreceptor (5-HT<sub>1A</sub> receptor and  $\alpha_2$ -adrenoceptor) desensitisation (Millan et al., 2000). Similar mechanisms have been proposed to explain the delay in onset of the *Arc* expression by other antidepressant drugs (Pei et al., 2003). In line with this contention, acute administration of SSRIs increases *Arc* expression when co-administered with a 5-HT<sub>1A</sub> autoreceptor antagonist (Castro et al., 2003; Tordera et al., 2003).

The expression of *Arc* is positively regulated by several intracellular signals including cAMP (via protein kinase A) and Ca<sup>2+</sup> (via calmodulin kinase II), both of which activate *Arc* by recruitment of mitogen-activated protein (MAP) kinase (Waktereit et al., 2001). Thus, notwithstanding enhanced effects of SSRIs in the presence of 5-HT<sub>1A</sub> autoreceptor blockade (see above), inasmuch as 5-HT<sub>1A</sub> receptors are positively coupled to MAP kinase in vitro (Cussac et al., 2002), direct activation of postsynaptic 5-HT<sub>1A</sub> receptor populations may play a role in the influence of S33005 upon *Arc*. Other candidate 5-HT receptor subtypes include 5-HT<sub>4/6/7</sub> receptors, which are all positively coupled to

cAMP, ionotropic 5-HT<sub>3</sub> receptors, which enhance intracellular concentrations of Ca<sup>2+</sup>, and 5-HT<sub>2A/C</sub> receptors, which activate phospholipase C, calmodulin kinase II and MAP kinase (see references therein).

Recent data indicate that the neurotrophin, BDNF, induces LTP in the hippocampus via the MAP kinase-induced induction of *Arc* (Ying et al., 2002). Moreover, BDNF expression is modulated by 5-HT (Vaidya et al., 1997; Zetterström et al., 1999), and there are several reports that chronic administration of certain antidepressants results in the up-regulation of BDNF mRNA in hippocampus (Coppell et al., 2003). However, the finding of the present study of a lack of effect of S33005 and venlafaxine upon BDNF mRNA levels in hippocampus or other regions indicates that BDNF itself is unlikely to be involved in the induction of *Arc* by these drugs. This latter result coincides with recent work indicating that the relationship between antidepressant exposure and BDNF expression may be more complex than originally conceived (Coppell et al., 2003).

Though a role of noradrenaline in the induction of *Arc* by S33005 (and venlafaxine) cannot be discounted, the potential importance of 5-HT is underlined by the increase in *Arc* expression in the striatum, a structure virtually devoid of noradrenaline and in which S33005 elevates extracellular levels of 5-HT but neither noradrenaline nor dopamine (Millan et al., 2001a). Thus, the mechanism by which S33005 increases striatal *Arc* expression may be different from that underlying the effects of other agents such as amphetamine and cocaine (Fosnaugh et al., 1995; Kodama et al., 1998; Berke et al., 1998). However, a role of dopaminergic mechanisms in the effects of S33005 and venlafaxine should not be excluded inasmuch as their chronic administration is accompanied by a modest elevation in dopamine D<sub>2</sub> receptor expression in this structure (Ainsworth et al., 1998; Sharp and Millan, unpublished observations).

Accumulating evidence suggests that increased *Arc* expression characterizes individual neurones and synapses undergoing activity-dependent modifications in function and structure (see Introduction). While *Arc* mRNA was measured here, our recent work showed that increased *Arc* mRNA was associated with increased protein expression for all the antidepressants tested (Pei et al., 2003). The present finding of increased *Arc* expression following administration of S33005 is evidence that this drug, like other antidepressants, reinforces synaptic strength in mood-related brain regions. This idea is consistent with recent theories that depression at least partially reflects compromised synaptic plasticity and resilience, and that antidepressants can reverse these deficits (Duman et al., 1999; Manji et al., 2001).

In summary, as with other monoamine uptake inhibitors, repeated administration of the novel SNRI, S33005, markedly induced *Arc* expression in several corticolimbic brain regions, supporting a role of this immediate early gene in plastic events underlying the long-term actions of antide-

pressant agents. Moreover, the present findings underpin recent neurochemical and behavioural data (Millan et al., 2001a,b) suggesting that S33005 is an effective antidepressant agent in animal models.

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