464P CONSTITUTIVE AND INDUCIBLE KNOCKOUT OF THE THE 5-HT$_{1A}$ RECEPTOR: BEHAVIOURAL CONSEQUENCES

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The 5-HT$_{1A}$ receptor has been implicated in a number of physiological and pathological responses such as anxiety, depression, and sexual activity. To better understand the involvement of the 5-HT$_{1A}$ receptor in these behaviors, we created two strains of 5-HT$_{1A}$ receptor knockout mice. In the first strain, the 5HT$_{1A}$ gene was disrupted by an insertion of the pGK-neo gene into the coding sequence. The other was created by a deletion of the 5-HT$_{1A}$ gene. Both constructs were electroporated into embryonic stem cells, and homologous recombination events were obtained with a low frequency. Chimeric mice transmitted the mutation to their germlines and the resulting heterozygotes were bred to produce homozygotes. A mendelian ratio was obtained, indicating a normal viability of the homozygote mutants. The 5-HT$_{1A}$ knockout mice do not exhibit any obvious developmental defects. The behavior of these mice is currently under investigation.

A major problem in the interpretation of experiments performed with knockout mice is that the mutant phenotype may be due to developmental compensations caused by an absence of the protein during development. To avoid this problem, we have also generated an inducible 5-HT$_{1A}$ knockout mouse utilizing the tetracycline inducible system developed by Gossen and Bujard (P.N.A.S. 89, 1992). We created a cassette containing the tTA gene (tetracycline transactivator), the pGK neo gene flanked with lox P sites, and the tet-o sequence of the E.Coli Tn 10 tetracycline resistance operon. This cassette was inserted into the 5' untranslated end of the 5-H T$_{1A}$ gene such that the tTA gene was expressed under the control of the endogenous 5-HT$_{1A}$ pro m oter. In the presence of doxycycline. an analogue of tetracycline, tTA can no longer bind to the tet-o sequence and activate transcription of the 5-HT1A gene. The behavior of these mice will be compared to that of the constitutive knockouts.

465P DIFFERENTIAL ADAPTIVE REGULATIONS OF PRE- VERSUS POST-SYNAPTIC 5-HT$_{1A}$ RECEPTOR

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5-HT$_{1A}$ receptors were identified in the early 1980s as high affinity sites for 5-HT in binding studies using [^{3}H]8-OH-DPAT as a radioligand (Gozlan *et al.*, 1983). These receptors are present both on the soma and dendrites of 5-HT neurones (somatodendritic autoreceptors) and on postsynaptic neurones in various regions of the limbic system (Verge *et al.*, 1986). Identical pharmacological binding profiles have been found for 5-HT$_{1A}$ receptors expressed on different neurones and in different regions of the brain. However, evidence has also been reported that somatodendritic autoreceptors and postsynaptic 5-HT$_{1A}$ receptors exhibit different physiological characteristics and play opposite roles in serotoninergic neurotransmission. Electrophysiological studies were performed in brain slices in order to further assess the respective properties of these receptors located in the dorsal raphe nucleus (DRN) and the hippocampus (CA1, CA3 area).

Pharmacological investigations demonstrated that the non-selective 5-HT$_{1A}$ agonist, 5-CT (5-carboxyamidotryptamine) was equipotent to hyperpolarize 5-HT$_{1A}$-bearing neurones in the DRN and the hippocampal CA1 area (respective EC50 values: 1.4 and 1.8 nM). Similarly, no differences were found in the potencies of the selective 5-HT$_{1A}$ antagonist WAY 100635 and (-)pindolol to prevent the 5-CT-induced hyperpolarization in the hippocampus (K_b values: 0.23 nM and 115 nM, respectively) and in the DRN (K_b values: 0.25 and 131 nM, respectively). Conversely, marked regional differences were noted with other 5-HT$_{1A}$ receptor ligands, since the selective agonists ipsapirone and lesopitron were more potent to hyperpolarize 5-HT cells in the DRN (respective EC_{50} values: 60 nM and 0.1 µM) than pyramidal cells in the CA1 area of the hippocampus (respective EC_{50} values: 0.2 µM and 10 µM).

Possible changes in the functional characteristics of 5-HT$_{1A}$ receptors were investigated after long term stimulation by a selective 5-HT$_{1A}$ agonist (BAY X-3702 0.3 mg/kg/day s.c. for 14 days), or by endogenous 5-HT due to the chronic blockade of 5-HT reuptake (fluoxetine, 5 mg/kg/day i.p. for 14 days). We also examined the effects of the stimulation of glucocorticoid receptors, either by delivering exogenous corticosterone *in vitro* in the vicinity of 5-HT$_{1A}$ receptors (in brain slices), or by increasing *in vivo* endogenous corticosterone by different stressors. In all these conditions, only the somatodendritic 5-HT$_{1A}$ autoreceptors in the DRN and not the postsynaptic 5-HT$_{1A}$ receptors in the hippocampus were found to desensitize. Thus, the potency of 5-CT to hyperpolarize 5-HT$_{1A}$ bearing cells was significantly decreased in the DRN (by ~4 fold, $p<0.01$) but not in the hippocampal CA1 area.

These data indicate that the functional properties of 5-HT$_{1A}$ receptors are different in the DRN and the hippocampus. Despite the apparent similarity in their binding profiles, somatodendritic 5-HT$_{1A}$ autoreceptors and postsynaptic 5-HT$_{1A}$ receptors exhibit distinct pharmacological and regulatory mechanisms, which could be of relevance with regard to the effects of psychotropic drugs acting, directly or indirectly, at these receptors.

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The role of oestrogen in the control of mood and mental state is suggested by the sex differences in schizophrenia and depression and the increased incidence of depression during the menopause, puerperium and menstruation, times in the life cycle of women at which plasma oestrogen concentrations drop precipitously to low or undetectable levels. Our experimental studies in the female rat showed that, in its positive feedback mode for stimulating gonadotrophin release, oestrogen increases by 3-fold the amount of serotonin 2A receptor (5-HT2AR) mRNA and by 50% the amount of serotonin transporter (SERT) mRNA in the dorsal raphe nucleus (Sumner & Fink, 1995; Fink & Sumner, 1996; McQueen et al., 1997). This increase in mRNA is associated with a concomitant increase in the density of binding sites for the 5HT2AR in frontal, cingulate and primary olfactory cortex and in the nucleus accumbens, and in the density of SERT sites in basolateral amygdala, ventromedial hypothalamic nucleus, ventral thalamus and lateral septum. The brain regions in which oestrogen increases the density of binding sites for the 5HT2AR and SERT sites are involved in behaviour in the rat and the control of mood and mental state in the human. The effect of oestrogen on the 5HT2AR may be relevant to the sex differences in schizophrenia since this receptor is a target of the potent atypical antipsychotics (clozapine and risperidone) and also for hallucinogens such as LSD. The action of oestrogen on the SERT may be relevant to depression since the SERT is the target of potent antidepressants (serotonin reuptake inhibitors). In the male rat, testosterone, but not 5α-dihydrotestosterone, affects the 5HT2AR in a manner similar to that of oestrogen, suggesting that the action of testosterone is mediated by its conversion by aromatase to oestrogen (Sumner & Fink, 1997). The possible mechanisms of oestrogen action on central serotonergic mechanisms and the significance of these findings for the control of mood and mental state and the development of new psychotropic drugs and formulations will be discussed.

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A novel peptide, Leu-Ser-Ala-Leu (LSAL), was isolated from mammalian brain and named 5HT-moduline (Rousselle *et al..*, 1996). This peptide was shown to interact with the 5HT1B receptor in a non-competitive manner with a very high apparent affinity ($EC_{50} = 10^{-10}$ M). Its effect appears specific for $5HT_{1B}$ receptors as none of the other serotonergic (5HT1A,E,F, 5HT2, 5HT3, 5HT6 and 7) and non serotonergic receptors (α and β adrenergic, dopaminergic, histaminergic, muscarinic, opiates, benzodiazepine) were affected by the peptide (Massot *et al..*, 1996). The effect is clearly related to the chemical structure of LSAL since other peptides, in particular ALLS having the same composition in aminoacid in a different sequence, are ineffective. As expected, the distribution of the binding of [^{3}H]5HT-moduline resembles that of 5HT1B receptors in rat or mouse brain sections. The binding sites totally disappear (as those for ^{125}I-cyanopindolol), in 5HT1B receptor gene knocked out mouse (Cloëz-Tayarani *et al..*, in preparation). Polyclonal antibodies were raised in rabbit against 5HT-moduline-keyhole limpet hæmocyanin complex. The obtained antibodies were shown to recognize LSAL structure in a very specific manner; using immunocytochemistry technique, it was shown that the corresponding immunoreactivity was heterogeneously distributed within rat brain. The observed labelling likely involved neuronal profiles with elongated processes which may correspond to axonal elements. Numerous cellular profiles were located in cortex, hippocampus, pallidus, substantia nigra, strongly suggesting that LSAL is present in various brain areas in particular neuronal cells. The fact that the cellular bodies of a number of these cells are located outside the raphe area indicate that LSAL may be present in non-serotonergic cells (Grimaldi *et al..*, 1997). Recently, a gene coding for a new member of the chromogranin family was cloned (Ischia *et al..*, 1997). LSAL is present in the corresponding protein sequence ; it may be cleaved by specific enzymes from the protein (NESP55) which likely plays the role of precursor of 5HT-moduline.

Various experiments were carried out to examine the functional effect of 5HT-moduline on the activity of the $5HT_{1B}$ receptor. It was shown that :

1) 5HT-moduline antagonizes the inhibitory effect of a $5HT_{1B}$ specific agonist (CGS 12066B or CP93129) on the cyclic adenosine monophosphate (cAMP) production in synaptosomal membrane preparations obtained from rat substantia nigra.
2) 5HT-moduline antagonizes the inhibitory effect of a $5HT_{1B}$ agonist on the K^+ evoked release of [^{3}H]5HT from cortical synaptosomal preparations in rat.
3) 5HT-moduline reverses the effect of a selective $5HT_{1B}$ agonist on mouse behavior in the model of social interaction test.

These results indicate that the interaction of 5HT-moduline observed with the binding of 5HT on the $5HT_{1B}$ receptor corresponds to an antagonistic effect under the experimental conditions used in our assays.
Finally, we have shown that 5HT-moduline is released from synaptosomal preparations via a K^+-Ca^{++} dependant mechanism. Moreover, the peptide administered via a single intracerebroventricular injection (100 µg to 500 µg) desensitizes the $5HT_{1B}$ receptors as shown by the decrease of the efficacy of $5HT_{1B}$ specific agonists to inhibit the adenylate cyclase activity previously stimulated by forskolin (Seguin *et al..*, 1997). After an acute stress of immobilization in a glass cylinder for 15 to 40 minutes, the efficacy of $5HT_{1B}$ receptors was tested by the ability of a $5HT_{1B}$ specific agonist to interact with the cAMP production in substantia nigra membranal preparations. It was shown that $5HT_{1B}$ receptors were significantly desensitized. These results tend to suggest that *in vivo*, 5HT-moduline may be released under stress situations and desensitizes $5HT_{1B}$ receptors.

In conclusion, 5HT-moduline is the first endogenous peptide shown to interact directly with a G.protein coupled receptor. It may be a prototypic allosteric modulator for this class of receptors and suggests the existence of analogous regulatory peptides for other G.protein related receptors. The activity of 5HT-moduline on 5HT1B receptors results in a desensitization of the receptor leading to an increase of the amount of 5HT released in the synaptic deft. This mechanism may correspond to a physiological role particularly in the control of the homeostasis of the CNS and may be involved in various psychiatric disorders involving the serotonergic system i.e. anxiety and depression.

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468P AUTORECEPTOR AND HETEROCEPTOR CONTROL OF 5-HT, DOPAMINE (DA) AND NORADRENALINE (NAD) RELEASE IN FRONTAL CORTEX: STRATEGIES FOR IMPROVED ANTIDEPRESSANT AGENTS

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Depression is a debilitating and generally chronic illness which increasingly afflicts younger individuals and which currently presents a life-time incidence of ca. 15 %. The social cost of depression, largely due to frequent hospitalisation and lost productivity, is very high (estimated at ca. 45 billion dollars in the USA in 1993). Improved antidepressant (AD) agents are, thus, urgently required both to reduce the social burden of depression and to alleviate the intense, personal suffering associated with this disease.

Depression is characterised by both emotional symptoms, such as anhedonia (inability to experience pleasure), melancholia, hopelessness and worthlessness and marked cognitive-attentional deficits, including a compromised mnesic function and poor concentration. Motor symptoms involving psychomotor retardation and/or agitation, as well as somatic symptoms, such as a loss of appetite, libido and energy and a disturbance of sleep patterns, (typically, early-morning waking) are also prominent.

The concept that a perturbation of monoaminergic transmission plays a role in the pathogenesis of depression is based upon observations of alterations in the cerebral levels of 5-HT, NAD, DA and their metabolites in depressed patients and experimental models of depression. In addition, drugs depleting central pools of monoamines provoke depressive-like states in animals and man. Correspondingly, drugs known to potentiate monoaminergic transmission are clinically effective in alleviating depressive disorders. In this regard, there are several potential mechanisms via which monoaminergic transmission might be enhanced. 1) An inhibition of monoamine metabolism by blockade of monoamine oxidases (MAOs); 2) A reduction of monoamine reuptake by interference with the terminal transporter; 3) An increase in monoamine release by antagonism of inhibitory autoreceptors on monoaminergic neurones; 4) Mimicking the actions of monoamines by agonist activity at specific receptor types postsynaptic to monoaminergic neurones; 5) An increase in monoamine release by an action at heteroceptors localized on monoaminergic neurones. First-generation ADs, such as amitryptiline, exploit mechanism 2 in inhibiting both 5-HT and NAD reuptake, but they have only a limited therapeutic index due to their cardiotoxicity. In addition, they elicit pronounced side-effects by blockade of histaminic, muscarinic and/or α_1-adrenergic receptors. Irreversible inhibitors of MAO, such as phenelzine, on the other hand, use mechanism 1 but may also present major problems inasmuch as they interact with tyramine in cheese and other food-stuffs to provoke severe hypertensive crises. Recently-introduced reversible MAO inhibitors, such as moclobemide, possess a more benign side-effect profile, but the most successful class of second generation ADs is comprised by selective inhibitors of 5-HT reuptake (SSRIs), such as fluoxetine, which have a superior therapeutic index to tricyclic agents. Nevertheless, SSRIs may also engender side-effects such as sexual dysfunction, insomnia, anxiety and appetite suppression. Further, these and other first and second generation ADs, such as the monoaminergic antagonists, mianserin, nefazodone and mirtazapine, share a delay of 2-3 weeks to their onset of action and are ineffective in a subpopulation of resistant patients. A recently-introduced drug, venlafaxine, by jointly inhibiting both 5-HT and NAD reuptake - in the absence of tricyclic side-effects - seeks to enhance efficacy and reduce the delay to onset of activity. However, this potential advantage awaits clinical demonstration, and the inhibition of NAD uptake may also be associated with hypertension.

A further improvement in the profile of action of ADs might be permitted by the exploitation of those mechanisms for modulating monoaminergic transmission outlined above. In this respect, actions of ADs in several corticolimbic structures, such as the hippocampus and septum, may be of significance, but the frontal cortex (FCX) (and associated anterior cingulate cortex) is of special interest for several reasons. *First*, via interactions with the thalamus, limbic system, basal ganglia and other cortical structures, this region plays a key role in the modulation of mood, cognition and motor behaviour. *Second*, it receives a pronounced monoaminergic input, which may be compromised in depressive states. *Third*, there is evidence from clinical, imaging studies of cerebral metabolism and blood flow that a decreased activity ("hypofrontality") of the FCX is associated with diverse depressive states. It is, thus, reasonable to hypothesise that a deficiency in the activity of frontocortical monoaminergic pathways may be implicated in depressive disorders. Thus, the question arises as to the nature of interactions between various monoaminergic pathways in the FCX and as to how these might be harnessed in order to obtain improved AD agents.

To address these issues, we have developed a novel and remarkably sensitive concentric dialysis system coupled to HPLC and coulometric detection which permits simultaneous detection of extracellular 5-HT, NAD and DA levels in single samples of the FCX of freely-moving rats[1,2,3]. The use of this system, together with electrophysiological recordings from the cell bodies of monoaminergic neurones, has shown that, 1) Inhibitory 5-HT_{1A} and 5-HT_{1B} autoreceptors localised on the dendrites and terminals, respectively, of raphe-cortical serotoninergic pathways decrease 5-HT release in the FCX; 2) Inhibitory dopamine D_3 and D_2 autoreceptors on mesocortical dopaminergic pathways reduce DA release; 3) Inhibitory α_{2A}-adrenergic autoreceptors on coerulocortical adrenergic pathways suppress NAD release and 4) α_{2A}-adrenergic heteroceptors on dopaminergic and serotoninergic terminals diminish the release of DA and 5-HT release, respectively. In addition, 5-HT_{2C} receptors, probably acting via GABAergic interneurones, inhibit FCX release of DA and NAD by actions at the level of their cell bodies in the ventrotegmental area and locus coeruleus, respectively. Finally, an - as yet unidentified - 5-HT heteroceptor in the FCX facilitates DA release. Irrespective of receptor type, control of the activity of dopaminergic and adrenergic neurones is expressed *tonically* and that of serotoninergic neurones, only *phasically*.

Intriguingly, consistent with this complex pattern of reciprocal interactions, SSRIs such as fluoxetine do *not* selectively increase levels of 5-HT, but also, to an equivalent degree, those of NAD and DA in FCX, while selective NAD uptake inhibitors such as desipramine increase levels of both DA and NAD - but not 5-HT - equally. In line with the above-summarised pattern of autoreceptor and heteroceptor control, blockade of 5-HT_{1A} and 5-HT_{1B} receptors synergistically potentiates the increase of 5-HT levels in FCX, but not those of DA and NAD, provoked by fluoxetine. In distinction, blockade of α_{2A}-adrenergic receptors very markedly potentiates the ability of fluoxetine to increase FCX levels of 5-HT, NAD and DA, while blockade of D_2/D_3 receptors enhances the influence of fluoxetine upon DA levels. Blockade of 5-HT_{2C} receptors, does not modify the actions of fluoxetine but may attenuate side-effects of SSRIs such as sexual dysfunction, appetite loss and anxiety.

In conclusion, an improved understanding of functional interrelationships amongst monoaminergic pathways in the FCX and other structures should allow for the more targeted manipulation of their activity and, correspondingly, an enhancement in the efficacy, a reduction in the delay of onset and an optimisation of the therapeutic index of AD agents.

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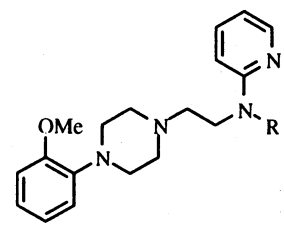
The serotonergic system is strongly implicated in the aetiology of several neuropsychiatric diseases, including depression, anxiety, obsessive compulsive disorder, Alzheimer's disease and schizophrenia. Positron emission tomography (PET) is a powerful imaging technique, capable of delineating neurotransmitter receptors in living human brain and also the interactions of these receptors with high affinity ligands. These types of measurement depend on the availability of ligands which can be labelled with positron-emitters and which prove to be effective *in vivo*. The application of PET to the study of the richly diverse serotonergic system in human brain has been restricted by a lack of effective radioligands. The 5-HT2 receptor has been most studied with radioligands such as [18F]altanserin and [18F]setoperone; more recently the 5-HT2A receptor has been studied selectively with [11C]MDL 100907 (see Pike, 1997).

The 5-HT1A receptor especially merits study because it is well characterised in terms of pharmacology, molecular constitution and physiological function. It is also a target for novel anxiolytics and antidepressants. Initial attempts to develop PET radioligands for 5-HT1A receptors were based on labelling selective agonists with positron-emitters but did not meet with success.

WAY-100635 (I) was the first potent, selective and silent antagonist reported for the 5-HT1A receptor (Fletcher *et al.*, 1994). Initial investigations with tritiated WAY-100635 in rats *in* vivo demonstrated the uptake of this radioligand in brain, with highest uptake in receptor-rich regions, such as hippocampus and entorhinal cortex and low uptake in thalamus, striatum and receptor-devoid cerebellum (Hume *et al.*, 1994). The receptor-specific signal was saturable and could be wholly blocked by high doses of WAY-100635 and partially blocked by 5-HT1A agonists (ipsapirone, buspirone). Labelling of WAY-100635 in the O-methexy position with carbon- 11 (*tl/2* = 20.4 min) (Pike *et al.*, 1994) provided a positron-emitting radioligand which, when administered intravenously to human volunteers, gave the first delineation of human brain 5-HT1A receptors *in vivo* (Pike *et al.*, 1995). The ratio of radioactivity in receptor-rich medial temporal cortex to that in receptor-devoid cerebellum was maximally about 3 at 60 min after radioligand administration, substantially lower than in rats. PET experiments with this radioligand in cynomolgus monkey also delineated brain 5-HT1A receptors; receptor-specific signal was blocked markedly by pretreatment with 5-HT1A antagonists (WAY-100635, pindolol) or agonists (8-OH-DPAT, buspirone) (Farde *et al.*, 1997). Autoradiography of post mortem human brain slices incubated with tritiated or 11C-labelled WAY-100635 provided highly selective definition of the distribution of 5-HT1A receptors (Hall *et al.*, 1997). Investigation of the appearance of radioactive metabolites in human plasma demonstrated that [O-methyl-llC] WAY-100635 was rapidly metabolised, primarily by deacylation to give the descyclohexanecarbonyl analogue, *[O-methyl-l 1C]*-WAY-100634 (II), and polar metabolites (Osman *et al.*, 1996).



(I) R = cyclohexanecarbonyl, WAY-100635
(II) R = H, WAY-100634

Figure 1. Structures of WAY-100635 and WAY-100634.

WAY-100634 was known to have high affinity for 5-HT$_{1A}$ and α_1-adrenoceptors. Separate labelling of WAY-100634 in its *O*-methyl position with carbon-11 and investigation in rats (Pike *et al.*, 1995) and monkey (Osman *et al.*, 1996) showed that this metabolite could enter brain to interact with 5-HT$_{1A}$ receptors and contribute to the observed level of non-specific binding.

In order to avoid metabolism to [*O-methyl*-^{11}C]WAY-100634, WAY-100635 was labelled with carbon-11 in the carbonyl position (Pike *et al.*, 1997). This radioligand gave greatly enhanced ratios of receptor-specific to nonspecific binding in human brain, with the ratio of radioactivity in receptor-rich medial temporal cortex to that in cerebellum reaching 23 at 60 min (Pike *et al.*, 1997). Presynaptic 5-HT$_{1A}$ receptors were also detected in raphe nuclei. Analysis of plasma revealed that the main radioactive metabolites are all more polar than the parent radioligand. One of these, found in plasma at a low proportion of total radioactivity, was identified as [^{11}C]cyclohexane-carboxylic acid (Osman *et al.*, 1997). This radioactive metabolite was prepared in the laboratory and its brain uptake after intravenous injection studied with PET in cynomolgus monkey. This acid enters brain and to some extent binds nonspecifically.

PET data acquired by administering [*carbonyl*-^{11}C]WAY-100635 at two different specific radioactivities in cynomolgus monkey were subjected to Scatchard analysis and gave values for B_{max} and K_D consistent with data obtained *in vitro* (Farde *et al.*, 1996). Data obtained in human subjects were analysed by a reference tissue compartmental model to give values of binding potential (Lammertsma *et al.*, 1996).

[*carbonyl*-^{11}C]WAY-100635 is currently the preferred radioligand for studies of brain 5-HT$_{1A}$ receptors in human brain. This radioligand is now being applied to clinical research studies, for example in depressed patients treated with selective serotonin reuptake inhibitors (Sargent *et al.*, 1997) and has great potential for the evaluation of 5-HT$_{1A}$ receptor occupancy in human brain by established developmental therapeutics.

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The serotonin transporter (SERT) gene is a candidate gene for susceptibility to depression since it is the target of many antidepressant agents including the highly effective serotonin selective reuptake inhibitors (SSRIs) such as fluoxetine (Prozac). Allelic variation within two polymorphic regions of the SERT gene has been reported to be associated with susceptibility to affective disorder: (1) a variable number tandem repeat (VNTR) polymorphism in the second intron of the gene consisting of 9,10 or 12 copies of a 16/17 bp motif and (2) a polymorphism (5-HTTLPR) 1.2kb upstream of the promoter of the SERT gene which exists in short (484bp) and long (528bp) forms.

We have demonstrated a significant association between the rare 9 repeat form of the intron 2 VNTR and risk of both unipolar (Ogilvie *et al.*, 1996) and bipolar disorder (Battersby *et al.* 1996) in a Scottish population. In this sample, alleles of the 5-HTTLPR were not associated with susceptibility to affective disorder. Haplotype analysis demonstrated strong linkage disequilibrium between the VNTR and 5-HTTLPR polymorphisms. The 9 repeat allele of the VTNR occurs predominantly or exclusively in haplotypes containing the 528bp allele of the 5-HTTLPR.

It remains to be established whether the level of SERT gene transcription may be influenced by the sequences of the repetitive elements in either or both of the polymorphic regions or whether they are in linkage disequilibrium with another more directly relevant gene locus.

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