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Temperature Regulation in Depression: Functional 5HT1A Receptor Adaptation Differentiates Antidepressant Response

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Observations in humans and animals have indicated that chronic, but not acute, antidepressant treatment (ADT) can desensitize 5-HT1A receptor-mediated responses, such as hypothermia. We hypothesized that 5-HT1A desensitization would be necessary for an antidepressant response (ADR) to occur. To test this hypothesis, we examined 5HT1A-agonist ipsapirone (IPS)-induced hypothermia in 28 depressed patients being treated with fixed doses of nortriptyline (75 mg) at 3-day and 3-week treatment points. Decreases in 24-item Hamilton scores (>12) were used to dichotomize the response data into ADR groups of 13 responders (ADR+) and 15 nonresponders (ADR−). A two-way repeated measures analysis of variance indicated significant temperature differences in the area under the curve between response groups across time from 3-day to 3-week intervals ($df = 1, 26$, $F = 6.6$, $p < 0.02$). In comparison to 3 days treatment, at 3 weeks, the ADR+ patients showed blunted hypothermic responses to IPS. ADR− did not show this effect, implicating ADR+ patients to be less responsive to 5HT1A-receptor stimulation after 3 weeks treatment. Similar effects were not found for 5HT1A postsynaptically mediated ACTH and cortisol responses. These results indicate that to achieve ADR, serotonergic neurotransmission needs to be altered as reflected by the change in 5-HT1a receptor responsiveness documented herein.
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INTRODUCTION

Evidence suggests that the phenomenon of antidepressant reasponse (ADR) may be linked to serotonin. Drugs specific for 5-HT activity can ameliorate depression (Montgomery *et al*, 1981; Muijen *et al*, 1988). Genetic (Kim *et al*, 2000; Pollock *et al*, 2000; Rausch *et al*, 2002; Smeraldi *et al*, 1998) and kinetic (Rausch *et al*, 2001, 2002, 2003) differences in the 5-HT transporter (Rausch *et al*, 2002) have been linked to response. Also, 5-HT depletion, via administration of the 5-HT depleting agent paracholorophenylalanine (PCPA) (Shopsin *et al*, 1976), or a tryptophan deficient diet (Delgado *et al*, 1990), can reverse an ADR.

Further support corroborates a possible role for the 5-HT1A receptor in antidepressant response. A polymorphism in the 5-HT1A gene resulting in nonrepression of the receptor has been associated with poor response in unipolar (Lemonde *et al*, 2004) and bipolar subjects (Serretti *et al*, 2004). Further evidence of lack of response with increased expression of the 5-HT1A receptor, increased 5-HT1A mRNA has been identified in the brains of suicide victims (Escriba *et al*, 2004). Finally, a neuroimaging study has identified a trend level correlation between decreased midbrain 5HT1A binding and decreased time to remission (Meltzer *et al*, 2004).

As is well known, AD drugs that increase extracellular 5-HT, such as SSRIs, TCAs, or MAOIs, can increase the 5-HT concentration within the first day of treatment, but it takes several weeks for an ADR to occur. Although other systems are also relevant (Banerjee *et al*, 1977; Koch *et al*, 2002; Newton *et al*, 2004; Tiraboschi *et al*, 2004), some evidence suggests that a component of the delay in response to ADT could be attributable to the time dependent desensitization of 5-HT1A receptors. Serotonin 1A-mediated responses in animals (Goodwin *et al*, 1986, 1987c; Green, 1987, 1988; Hensler *et al*, 1991; Le Poul *et al*, 1997; Li *et al*, 1994; Martin *et al*, 1992; Mizuta and Segawa, 1988; Sleight *et al*, 1988), and in humans (Lesch *et al*, 1990; Rausch *et al*, 1990) have been shown to undergo adaptive changes with chronic ADT that are not seen with acute ADT. However, no one has explored whether adaptation in 5-HT1A receptor-mediated responses could account for lack of therapeutic effect to a given antidepressant. We hypothesized that it would.

In the present study, we sought to examine whether the attenuation of such a hypothermic response would occur in antidepressant responders (ADR+) and not in

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nonresponders (ADR−). If so, it could identify whether the phenomenon of desensitization of 5-HT1A receptors is associated with the phenomenon of ADR. Insofar as the hypothermic response may be mediated through decreased serotonin raphe firing from autoinhibitory receptor agonism (Goodwin *et al*, 1987b; Gudelsky *et al*, 1987; Hutson *et al*, 1987; Wozniak *et al*, 1988) (see Discussion), our hypothesis was that responders would show an attenuation of the hypothermic response to ipsapirone (IPS), indicative of desensitization of such receptors and net facilitation of serotonergic neurotransmission.

If 5-HT1A desensitization were necessary for antidepressant response, it would not be limited to SSRI treatment. Although ADR achieved with potent norepinephrine (NE) reuptake inhibitors has been observed to not be reversed by serotonin depletion (Booij *et al*, 2005; Delgado *et al*, 1999; Page *et al*, 1999), antidepressant effects have been identified that rely on functional interactions between norepinephrinergic and serotonergic neurons. The two systems have reciprocal connections, and it is thought that NE has tonic activation on serotonin neuron firing, regulated through 5-HT1A autoreceptors (Haddjeri *et al*, 2004).

Both norepinephrinergic and serotonergic antidepressants may have similar effects on 5-HT1A binding (Lund *et al*, 1992; Pandey *et al*, 1991; Srinivas *et al*, 2001), 5-HT1A-mediated responses to stress (Lopez *et al*, 1998), and 5-HT1A-mediated hypothermia in rats (Booij *et al*, 2005; Goodwin *et al*, 1987a; Goodwin, 1989; Page *et al*, 1999). For this study, we used nortriptyline (a tricyclic considered to be more norepinephrinergic than serotonergic) as the study's antidepressant treatment (ADT) of study.

METHODS

The study was conducted at the Medical College of Georgia, Augusta VA and the University of California at San Diego, San Diego Veterans Administration Medical Center, after approval was secured through the respective local Institutional Review Boards. To be included in the study, patients had to have a current episode of major depression satisfying criteria for major depressive disorder. After informed consent was obtained, diagnoses of major depression were established by SCID interview, with medical history, physical examination, urinalysis, EKG, urine drug screen, clinical chemistries, CBC, urinalysis, and pregnancy test for fecund females to rule out other clinically significant medical conditions. All patients had to be free of psychotropic medication during the previous 4 weeks prior to entry into the study, 8 weeks for fluoxetine. Subjects were required to have a depression score of 18 or greater on the 24 item Hamilton Depression Rating Scale; age 18–65, with willingness and ability to give informed consent.

Subjects were excluded for cardiovascular disease including myocardial infarcts within the past 3 months, heart block, slowed cardiac conduction, heart failure, or other evidence of compromised cardiac function, hypertension with systolic blood pressure >160, or diastolic >95, thyroid disease, significant liver disease, adrenocortical disease, or exogenous steroid administration, anemia or hemophilia, evidence of clinically significant gastrointestinal, hepatic, renal, endocrine, ophthalmologic, neurologic, endocrine, or hematologic disease, schizophrenia or organic brain syndromes on the SCID, bipolar affective disorder, or any other primary Axis I major psychiatric disorder other than major depression, including substance abuse or dependence syndrome including alcoholism during the last year. Patients were likewise excluded for a present or past history of psychosis. Women not using an effective method of birth control (barrier method and/or IUD) were excluded, as were women using oral contraceptives. Also excluded were pregnant or lactating women, those with menometrorrhagia, or hysterectomy without ovariectomy if premenopausal, and those with a history of allergy or intolerable side effects to the protocol medications.

Patients were initiated on nortriptyline 25 mg tid and kept at constant dose at 75 mg through 3 weeks treatment. Depressed patients were evaluated before and after nortriptyline AD response was established at 3 weeks. After treatment was initiated, response was assessed at 3 weeks to allow for an approximate 50% response rate. Our previous studies with nortriptyline had shown this dose and duration of treatment to be an approximate ED_{50} for treatment response (Rausch *et al*, 2003). In this way, our response hypothesis could be tested in approximately equal size groups (for those patients not responding to 75-mg nortriptyline at 3 weeks, dosage was subsequently titrated upward).

IPS-induced hypothermic responses were determined after a 3-day period of nortriptyline treatment 75 mg per day and after a 3 week period of nortriptyline treatment 75 mg per day. After 3 days of nortriptyline, the treatment drug was discontinued for the day of the IPS challenge, and then restarted the next day. After 3 weeks treatment, nortriptyline was again stopped for the 3-week IPS challenge. No nortriptyline was given on the day of the challenge studies to reduce the possibility of masking receptor adaptations by biochemical actions attributable to a pharmacodynamic presence of treatment drug. As our intent was to study differences in response to drug, rather than differences in drug effects *per se* before *vs* after treatment, comparisons with the 3-week treatment time point were anchored against the 3-day treatment time point. This was performed rather than anchor against the pretreatment baseline so as to control for the presence of drug in all cases while differentiating response at the 3-week time point. In this way, we could observe the initial conditions of drug presence at three days, too soon for an ADR to occur, compared with the subsequent conditions of response *vs* nonresponse at 3 weeks, with all observations controlled for drug presence independent of response.

Subjects were instructed to report at 0800, having fasted overnight, and have an intravenous catheter inserted. The participants had an intravenous line with 5% dextrose/0.45% sodium chloride placed into an antecubital vein at 0800. ACTH and cortisol levels were also examined to test period for a potential 5-HT1A mediated hormone response that could account for ADR differences. Blood samples for the measurement of plasma ACTH and cortisol levels were drawn from the intravenous line into EDTA-containing vacutainer tubes (total sample volume of 5 ml) and placed immediately on ice. Oral temperature was recorded simultaneously using a Diatek digital thermometer after 3 min. No drinking or eating was allowed for 15 min prior,

and no talking for 5 min prior, to each temperature measurement. Baseline blood samples and temperature measurements were taken at −30 min (0830) and 0 min (0900) relative to the administration of IPS capsules. The capsules were administered directly after the second set of measurements and blood samples likewise obtained after IPS challenge at +30, +60, +90, +120, +150, and +180 min.

Statistical Methods

The data were analyzed by two way repeated measures analysis of variance (ANOVA). Data were examined for differences between response groups analyzing area under the curve for the respective days, using the trapezoidal method. The data were also analyzed by repeated measures analysis of covariance (ANCOVA) and partial correlation for potential confounds, using individual time point measures of temperature.

RESULTS

Thirty patients had complete data available for the study. The data was first examined to assign subjects into ADR+ *vs* ADR− groups. Changes in 24-item Hamilton scores between the acute (3-day) *vs* chronic (3-week) treatment between these intervals were used to categorize patients into dichotomous response groups.

Consistent with our supposition that the 3-day time point would be too soon for an ADR to occur, the pretreatment Hamilton scores (30.5 + 1.0) were not different from the 3-day treatment scores (30.0 + 1.0). The Hamilton score changes between 3-day and 3-week treatment points ranged from an increase of 3 points to a decrease of 27 points. The criterion used to divide the cohort into upper- and lower-response groups was determined blind to the endocrine or hypothermia results. The closest and most conservative point that could approximate equally sized response groups was the criterion of decreases in Hamilton scores of 12 or greater, yielding 13 responders and 17 nonresponders between the 3-day and 3-week treatment time point. In this way, the Hamilton score change could be coupled with the temperature response change between the acute and chronic time points. Two patients had missing temperature data from the 3-day treatment time point, both of whom were nonresponders by our criteria, leaving 13 responders and 15 nonresponders available for temperature analysis.

There was a significant difference between responders and nonresponders in the way their temperature responses changed between 3 days and 3 weeks treatment. A two-way analysis of variance indicated significant temperature differences in the area under the curve between response groups across time from 3-day to 3 weeks ($F = 6.6$, $p < 0.02$) (Figures 1 and 2). Similar group × time interactions were not found for ACTH ($F = 0.04$, NS), or for cortisol ($F = 0.83$, NS). There was a potential trend ($p = 0.17$) toward higher cortisol levels in the nonresponders on the acute treatment day.

All patients had Hamilton Depression ratings above 20 at the 3 day time point (see Table 1). However, there were more 3 week responders than nonresponders in the MCG

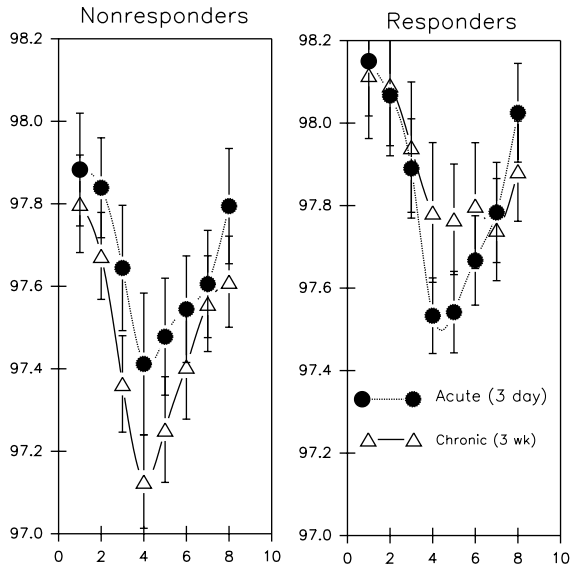

Figure 1 Mean (±SEM) body temperature in response to IPS is shown in the respective nortriptyline ADR groups at 3 days (dark circles) and 3 weeks (open triangles) treatment.

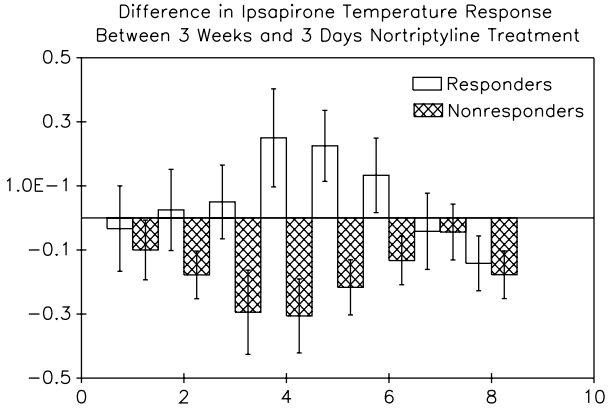

Figure 2 Data from Figure 1 plotted as mean change scores between 3 days and 3 weeks treatment for responders (open bars) and nonresponders (hatched bars).

sample (9 *vs* 8) compared to the UCSD sample (4 *vs* 9), and site was a significant covariate in the change in depression scores between 3 days and 3 weeks ($df = 1, 27$, $F = 8.2$, $p < 0.01$). However, the differences in hypothermic response between ADR groups were still significant after covariance for site ($F = 6.0$, $p = 0.02$). Also, there were no significant site main effects on the temperature data ($F = 0.346$, $p = 0.56$).

IPS levels were measured at 60 and 90 min after the challenge. There was no significant difference in IPS levels between responders and nonresponders, ($F = 0.050$, NS). There also was not any significant time × day × response interaction in IPS levels between groups ($F = 0.65$, NS). Consequently, it appears that different IPS pharmacokinetics would not explain the hypothermic differences between response groups.

There was also no significant difference in nortriptyline levels measured at 3 weeks between responders (79.0 ± 12.2, SEM) and nonresponders (64.5 ± 10.5), ($F = 0.8$, NS).

Table 1 Hamilton Differences in ADR Groups

	Baseline HAM-D	3-Day HAM-D	3-Week HAM-D
Responders ($N=13$)	31.4 ± 1.9[a]	30.8 ± 5.4[a]	11.8 ± 4.7*
Nonresponders ($N=17$)	29.8 ± 1.1	29.7 ± 5.7	25.5 ± 6.5
	Baseline ACTH	**3-Day ACTH**	**3-Week ACTH**
Responders ($N=13$)	57.5 ± 11.9	40.0 ± 6.5	42.3 ± 10.8
Nonresponders ($N=17$)	43.5 ± 10.4	35.2 ± 6.1	49.5 ± 9.5
	Baseline cortisol	**3-Day cortisol**	**3-Week cortisol**
Responders ($N=13$)	16.5 ± 1.9	15.6 ± 1.5	14.8 ± 1.4
Nonresponders ($N=17$)	14.1 ± 1.7	14.7 ± 1.4	13.4 ± 1.2

[a]NS.
*$p<0.0001$.
Antidepressant response groups (ADR groups) were dichotomized with responder group membership requiring decreases in 24-item Hamilton Depression Rating scores of $\geqslant 12$ between the 3-day and 3-week time points. ACTH and cortisol are given as area under the curve.

However, there was a statistical trend ($F=4.1$, $p=0.06$) for nortriptyline levels to be higher at 3 days in responders (57.4 ± 9.5) than nonresponders (31.7 ± 8.4). This, combined with the observation that the average 3-week nortriptyline levels were below 'therapeutic window', raised the question whether the individual differences in hypothermic responses between groups could be due to individual differences in nortriptyline levels. Consequently, a repeated measures ANCOVA was used to determine whether the groups had different hypothermic responses after controlling for nortriptyline levels, as covariates. The repeated measures ANCOVA indicated that there were still significant hypothermic response differences between groups ($F=4.4$, $p<0.001$), after controlling for nortriptyline levels. The correlation between the 3-day and 3-week change in hypothermia and the 3-day–3-week change in Hamilton scores was $r=0.54$, $p=0.01$, after controlling for both individual differences in nortriptyline and IPS levels between subjects.

The temperature sample consisted of 19 men and nine women, seven males were responders, and six females were responders. Women responded better than men in this trial, with a mean decrease of 20.3 (±1.6 SEM) Hamilton points compared to a mean decrease of 7.1 (±2.5 SEM) points in males. A repeated measures ANCOVA indicated that there were still significant hypothermic differences between response groups however ($F=7$, $p=0.001$), after controlling for gender. In sum neither site, gender or drug levels could account for the hypothermic differences seen with different ADR.

DISCUSSION

Consistent with our hypothesis that desensitization of 5-HT1A autoreceptors would be necessary for ADR, nortriptyline responders showed diminished IPS hypothermia while nonresponders did not. Several groups have shown that chronic ADT (with fluoxetine (Lerer *et al*, 1999), paroxetine or nefazodone (Sargent *et al*, 1997) in normals, or amitriptyline (Lesch *et al*, 1990) in patients) can desensitize 5-HT1A agonist-stimulated hypothermia. However, we could not find studies indicating that the IPS hypothermia differs in nonresponders to ADT. This work suggests that downregulation is a necessary if not sufficient adaptation for ADR occur.

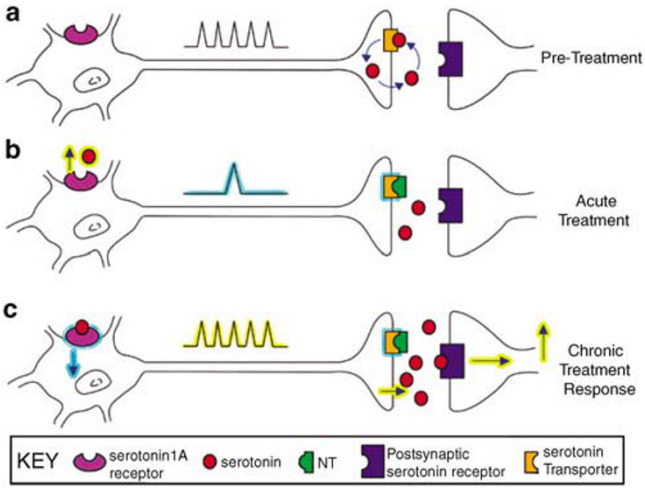

Figure 3 A presynaptic 5HT1A model of inhibitory autoreceptor downregulation in response to ADT. (a) Untreated neuron has normal firing (spikes), transports 5-HT normally (circular arrows), with baseline effects at the post-synaptic receptor. (b) With acute ADT, the 5-HT transporter reuptake is inhibited, increasing extracellular concentrations of 5-HT (circles). The increased extracellular concentrations of 5-HT stimulate 5-HT1A autoreceptors to inhibit 5-HT neuron firing (single spike). (c) Chronic occupancy of the 5-HT1A receptor causes it to desensitize (down arrow), allowing normal firing to return (spikes). Normalized firing in the presence of reuptake blockade facilitates serotonergic transmission (up arrow).

Prior rodent studies support the notion that acute ADT would increase extracellular serotonin concentrations (Bel and Artigas, 1993; Kreiss and Lucki, 1995), and decrease serotonin neuron firing (de Montigny *et al*, 1990) through stimulation of a normally sensitive 5-HT1A receptor (Blier *et al*, 1990), Figure 3. In those who respond to ADT, there is evidence from this work that a desensitization of 5-HT1A receptors occurs. This would be consistent with the

desensitization of presynaptic autoreceptors seen with chronic ADT in rodents (Blier *et al*, 1990; de Montigny *et al*, 1990).

The results suggest that, for the depressed patient, the effect is not simply a phenomenon of ADT, but rather, a component of ADR. Many authors construe the decrease in body temperature to be a function of presynaptic 5-HT1A receptors (Goodwin *et al*, 1987b; Gudelsky *et al*, 1987; Hutson *et al*, 1987; Wozniak *et al*, 1988). Under that scenario, it can be interpreted that 3-week responders apparently adapted less sensitive 5-HT1A inhibitory autoreceptors through the course of treatment, while nonresponders did not.

Several aspects of the design of the study made these observations possible and deserve discussion. To distinguish the pathway underlying the improvement in responders, it was important to differentiate the effects of ADT from the effects of ADR. As this study was aimed at examination of the biological mechanisms of response rather than being aimed at testing the efficacy of the treatment, it required a somewhat different design from that of a typical ADT study.

For an ADR study, a fixed dose design has advantages. The use of fixed dose can control for different doses in different subjects, and also eliminate any confound from increasing dose with inadequate response. Secondly, to compare the patterns of receptor adaptation across time, the design must also differentiate the acute *vs* chronic effects of ADT. Thirdly, unlike study designs aimed at examining the effect of ADT, to study ADR, it was desirable to study approximately equally sized groups of responders *vs* nonresponders. This required dividing the response groups into the upper- and lower-response groups, rather than use the 50% response criterion used in typical efficacy studies. Supportive of this approach, the *post hoc* analyses that controlled for possible confounds demonstrated that the significance increases, with the correlation between the 3-day and 3-week change in hypothermia and the 3-day–3-week change in Hamilton scores, mitigating concerns about the choice of change in HAM-D to define responders *vs* nonresponders. This study included these design features to make these observations possible, although the strategy of observing response at a dose and duration of treatment approximating the ED_{50} makes it different from the typical efficacy (ADT) study.

Our strategy was to take a 'snapshot' of the biological characteristics of response and nonresponse at a point in treatment where the dose and duration of treatment would yield comparably sized ADR+ *vs* ADR− groups. This 'snapshot' approach would not preclude the possibility that a proportion of nonresponders at that point in time would become responders at later points in treatment. However, it allowed for a description of the biological differences in response groups at a given point in time where some patients are responding and others are not.

One caveat in the consideration of this work is that nortriptyline is considered to be a norepinephrine selective TCA based on studies in rat brain and cloned human DNA. However, we have found a significant effect of serotonin transport inhibition in patients treated with nortriptyline and linked the inhibition to antidepressant response (Rausch *et al*, 2003). Nonetheless it is possible that the idea illustrated here may be relevant to norepinephrine systems. Increased norepinephrine levels produced by norepinephrine reuptake blockade may stimulate adrenoreceptors on serotonin cell bodies to alter the firing rate of serotonin neurons (Bortolozzi and Artigas, 2003; Pudovkina *et al*, 2003), and work in concert with the desensitization of 5-HT1A receptors described in this work. As nortriptyline may have relative serotonin reuptake effects (Rausch *et al*, 2003), notwithstanding its potency on the norepinephrine transporter, perhaps the use of a more norepinephrine-specific drug may elucidate whether this 5-HT1A effect can occur independent of drug effects on serotonin reuptake. This study cannot ascertain whether the downregulation of the 5HT1A receptor was mediated through norepinephrine, serotonin, or an interaction of the two.

Another caveat pertains to the debate whether 5-HT1A receptor-mediated hypothermia is pre or postsynaptically mediated. Although there is much evidence to suggest that it is presynaptic, not all studies agree (Blier *et al*, 2002; O'Connell *et al*, 1992). The literature varies with species (Bill *et al*, 1991), and depends on methods. Some evidence favoring a postsynaptic hypothesis is that chronic AD treatment or electroconvulsive shock (ECS) was not found to change serotonin release or firing in response to a 5-HT1A agonist in rats (Blier and Bouchard, 1992; Hjorth and Auerbach, 1994). Also, ECS has been found to decrease hypothalamic 5-HT1A binding in rats (Stockmeier *et al*, 1992). A lack of hypothermic change in normals administered tryptophan depletion has also been interpreted as evidence for postsynaptic mediation (Blier *et al*, 2002), although other subsequent work suggests that such intervention may not be sufficient to alter 5-HT1A binding potential in human brain (Praschak-Rieder *et al*, 2004).

Evidence for a presynaptic mechanism is supported by the observation that 5,7-DHT lesions of the raphe have been shown to attenuate hypothermic responses in mice (Goodwin *et al*, 1985) and sometimes (Goodwin *et al*, 1987b), but not always (Millan *et al*, 1993), in rats. Furthermore, dorsal raphe injection of a 5-HT1A agonist (in the presynaptic area) produces hypothermia (Hillegaart, 1991), although others have suggested that this is due to ventricular leakage to postsynaptic sites (Blier *et al*, 2002), despite care in the methods to avoid penetration of the aqueduct (Hillegaart, 1991). Chronic (Goodwin *et al*, 1985, 1987b), but not acute (Blier *et al*, 2002; Hjorth, 1985; Hutson *et al*, 1987), serotonin depletion from raphe nerve terminals also diminishes the hypothermic response, supportive of the presynaptic hypothesis. Finally, a recent study in humans has shown 5-HT1A receptor binding in the dorsal raphe nucleus (an area of brain where the 5-HT1A receptors would be expected to be presynaptic) tends to correlate with ADR (Meltzer *et al*, 2004). The current study cannot delineate whether the hypothermic effect was pre or postsynaptic. Nonetheless, our results clearly distinguished ADR as a function of 5-HT1A agonist sensitivity.

A possible mechanism for the relationship of 5HT1A desensitization to response may be found in a recently identified polymorphism in the 5HT1A gene. The C(−1019)G polymorphism has been associated with suicide and major depression (Albert and Lemonde, 2004). The receptor gene is repressed in raphe cells from the C allele, but not from the G allele of the polymorphism. (Lemonde

et al, 2003). A study of treatment response found that those with the homozyogous G genotype were twice as likely to be antidepressant nonresponders as those with the C genotype (Lemonde *et al*, 2004), though another study in unipolar depression did not identify this effect (Serretti *et al*, 2004). In bipolar depression, however, subjects with the C/C genotype did show a better ADR (Serretti *et al*, 2004).

This finding of receptor desensitization in response may be important in understanding how an ADR occurs. Receptor desensitization could be conceptualized as a response-dependent drug effect. This study implies that it may be necessary if not sufficient for 5-HT1A receptors to desensitize to manifest a response.

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