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Regulation of rat cortical 5-hydroxytryptamine$_{2A}$ receptor-mediated electrophysiological responses by repeated daily treatment with electroconvulsive shock or imipramine

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Abstract

Down-regulation of 5-hydroxytryptamine$_{2A}$ (5-HT$_{2A}$) receptors has been a consistent effect induced by most antidepressant drugs. In contrast, electroconvulsive shock (ECS) up-regulates the number of 5-HT$_{2A}$ receptor binding sites. However, the effects of antidepressants on 5-HT$_{2A}$ receptor-mediated responses on identified cells of the cerebral cortex have not been examined. The purpose of the present study was to compare the effects of the tricyclic antidepressant imipramine and ECS on 5-HT$_{2A}$ receptor-mediated electrophysiological responses involving glutamatergic and GABAergic neurotransmission in the rat medial prefrontal cortex (mPFC) and piriform cortex, respectively. The electrophysiological effects of activating 5-HT$_{2A}$ receptors were consistent with 5-HT$_{2A}$ receptor binding regulation for imipramine and ECS except for the mPFC where chronic ECS decreased the potency of 5-HT at a 5-HT$_{2A}$ receptor-mediated response. These findings are consistent with the general hypothesis that chronic antidepressant treatments shift the balance of serotonergic neurotransmission towards inhibitory effects in the cortex.

1. Introduction

Blockade of the serotonin transporter (SERT) by the tricyclic antidepressants (TCA) clomipramine and imipramine, selective serotonin reuptake inhibitors (SSRIs), or serotonin/norepinephrine reuptake inhibitors (SNRIs) appears related to the therapeutic effects of these drugs in treating depressive and anxiety disorders (Delgado et al., 1990; Delgado et al., 1999; Little et al., 1999; Richelson, 2001). SERT inhibition results in wide-spread elevations of 5-hydroxytryptamine (5-HT) throughout the brain, with subsequent activation of all fifteen 5-HT receptor subtypes both acutely and after the return of serotonergic neuron firing rates during chronic antidepressant drug administration (Chaput et al., 1986; Rueter et al., 1998). The actual 5-HT receptors involved in mediating the antidepressant effects of most antidepressant drugs has not been clarified, although

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postsynaptic 5-HT_{1A} receptors have been suggested to be a principal target (Haddjeri et al., 1998). Given the complexity of the serotonin receptor families, it would seem surprising that optimal antidepressant action would occur by 5-HT acting on all 5-HT receptors with the corresponding corollary that blockade of one or more 5-HT receptors would enhance the therapeutic action of SSRIs and other antidepressants.

Activation of 5-HT_{2A} receptors may be counterproductive to the optimal efficacy of SSRIs and SNRIs. Activation of 5-HT_{2A} receptors in rodents appears to increase certain forms of impulsivity and interfere with arousal and attention (Carli et al., 2004; Koskinen et al., 2000; Winstanley et al., 2003; Winstanley et al., 2004). Activation of 5-HT_{2A} receptors in humans also appears to result in a disturbance of attentional processes (Umbricht et al., 2003; Vollenweider et al., 1998). Blockade of 5-HT_{2A} receptors was found to enhance the antidepressant-like action of the SSRI fluoxetine in a rodent behavioral screen for antidepressant drugs involving suppression of "inappropriate" or impulsive responding (Marek et al., 2005). At a clinical level, addition of drugs which block 5-HT_{2A} receptors (mirtazapine, mianserin, olanzapine, quetiapine) to ongoing treatment with SSRIs appears to result in enhanced antidepressant efficacy (Calabrese et al., 2005; Marek et al., 2003; Tohen et al., 2003). An increased density of 5-HT_{2A} receptors has been associated in many, but not all, studies of suicide victims with either depression or schizophrenia or alcoholism (Laruelle et al., 1993; Pandey et al., 2002; Stanley and Mann, 1983; Stockmeier et al., 1997; Underwood et al., 2004). A polymorphism of 5-HT_{2A} receptor has been associated with poor medication tolerability in elderly depressed patients treated with a high dose of paroxetine (40 mg qd) but not the 5-$HT_{2A/2C}$ antagonist mirtazapine (Murphy et al., 2003). Furthermore, a different polymorphism of the 5-HT_{2A} receptor has also been associated with a good treatment response to an SSRI in the STAR-D depression trial (McMahon et al., 2006). Finally, most antidepressant drugs either acutely block 5-HT_{2A} receptors (mirtazapine, mianserin, trazodone, nefazodone, amitriptyline, nortriptyline, imipramine) or decrease the density of 5-HT_{2A} receptors following chronic drug administration (TCAs; monoamine oxidase inhibitors, MAOIs; atypical antidepressants such as trazodone, mianserin and mirtazapine) (Blackshear and Sanders-Bush, 1982; Conn and Sanders-Bush, 1986; Peroutka and Snyder, 1980; Riblet and Taylor, 1981; Richelson, 2001; Sanders-Bush et al., 1989). Human PET imaging studies have found that chronic treatment with the TCA desipramine decreases 5-HT_{2A} receptor binding (Yatham et al., 1999). Thus, a wide range of studies at both the preclinical and clinical level lend support to the notion that modulation of 5-HT_{2A} receptors may be related to depression, suicide and therapeutic responses to antidepressant drugs.

Electroconvulsive shock is an exception to the pattern of most antidepressant drugs in that an up-regulation of cortical 5-HT_{2A} receptors are found following chronic ECS treatment in rodents (Biegon and Israeli, 1987; Butler et al., 1993; Goodwin et al., 1984; Kellar and Bergstrom, 1983; Kellar et al., 1981; Pandey et al., 1992; Stockmeier and Kellar, 1986; Vetulani et al., 1981). The only robust widely replicated indirect change in 5-HT_{2A} receptor function following repeated daily administration of ECS is an enhancement of head shakes or head twitches induced by 5-HT_{2A} receptor agonists (Godfrey et al., 1988; Goodwin et al., 1984; Lebrecht and Nowak, 1980; Moorman et al., 1996). This head shake response induced by 5-HT_{2A} receptor agonists does appear to involve local 5-HT_{2A} receptors in the mPFC (Granhoff et al., 1992; Willins et al., 1997). However, since head shakes/twitches induced by activation of 5-HT_{2A} receptors are altered by activation or blockade of many other transmitter receptor subtypes (5-HT_{1A} receptors, 5-HT_{2C} receptors, α_1-adrenoceptors, α_2-adrenoceptors, β_2-adrenoceptors [G. Marek, unpublished observations]; dopamine D1 receptors, μ-opioid receptors, mGlu2 receptors, NMDA receptors, AMPA receptors (Zhang and Marek, 2008), adenosine A1 receptors [G. Marek, unpublished observations], melatonin receptors, CB1 receptors and others), it would seem premature to assume that the up-regulation of 5-HT_{2A} receptor binding by ECS is invariably related to an increased functional activation of 5-HT_{2A} receptors (Cheer et al., 1999; Dall'Olio et al., 1999; Eison et al., 1995; Gewirtz and Marek, 2000; Handley and Brown, 1982; Handley and Singh, 1986; Marek, 2003; Schreiber et al., 1995; Vickers et al., 2001). While there is generally a good relationship between 5-HT_{2A} receptor regulation in the primate and rodent, a primate study found that 5-HT_{2A} receptors were not up-regulated following repeated ECS treatments. Since cortical 5-HT_{2A} receptors modulate both glutamatergic (Aghajanian and Marek, 1997; Marek et al., 2001) and GABAergic transmission (Marek and Aghajanian, 1994; Sheldon and Aghajanian, 1990), investigation into the effects of 5-HT_{2A} receptor activation on neurotransmission mediated by both excitatory and inhibitory amino acids is warranted.

Therefore, the purpose of the present experiments was to examine the regulation of 5-HT_{2A} responses on glutamatergic thalamocortical afferents in the mPFC (Lambe and Aghajanian, 2001; Marek et al., 2001; Scruggs et al., 2000) and on GABAergic interneurons in the piriform cortex in the rat (Marek and Aghajanian, 1994; Sheldon and Aghajanian, 1991; Sheldon and Aghajanian, 1990). The tricyclic antidepressant imipramine and ECS were chosen in order to compare the regulation of these electrophysiological responses by these different antidepressant treatments since rodent receptor binding studies suggest that either a down-regulation or an up-regulation occurs for cortical 5-HT_{2A} receptors after chronic treatment with these two different somatic antidepressant treatments, respectively. TCAs and ECS were also chosen as they may both represent two of the most efficacious treatments for major depression as well. The results from the present experiments are consistent with the general hypothesis that a balance of activity away from 5-HT_{2A} receptor activation and toward activation of other 5-HT receptor subtypes in the cerebral cortex might result in optimal antidepressant activity.

2. Experimental procedures

2.1. Animals

Male Sprague–Dawley rats (n=35; Camm, Wayne, NJ) were 120–200 g at the beginning of chronic antidepressant treatment. All subjects were allowed a 7 day adaptation period following arrival from the supplier. They were housed in suspended stainless steel wireless cages (18 × 36 × 20 cm) with two rats occupying each cage.