IS DESENSITIZATION OF INHIBITORY AUTORECEPTORS ESSENTIAL FORTHE LONG TERM EFFECTIVENESS OF ANTIDEPRESSANTS ?

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Antidepressant drug effectiveness is known to take place after a delay of a couple of weeks to more than one month. Electrophysiological and neurochemical evidence has been provided that prolonged exposure to antidepressants induces desensitization of autoreceptors inhibiting neurotransmitter synthesis and release. On this basis it has been hypothesized that the delay for antidepressant drug action would depend on the delay for inactivation of inhibitory autoreceptors. Therefore, pharmacological blockade of inhibitory autoreceptors has been proposed as a means to anticipate the action of antidepressants. Experimental evidence for autoreceptor desensitization consists in potentiation of the presynaptic effects of antidepressants (as estimated by microdialysis and by recording of monoaminergic firing activity) and in reduction of the presynaptic inhibitory effects of alpha2 and 5HT1A receptor agonists. However, the evidence provided thus far has been obtained after interruption of chronic antidepressant exposure, a condition not corresponded to the clinical situation. We therefore set to reexamine this issue by testing the effect of challenge with autoreceptor agonists and antagonists and with antidepressants themselves in rats chronically exposed to antidepressants and not withdrawn from them. Male Sprague Dawley rats were administered with desipramine (10 mg/kg, i.p. every 24 hours for 14 days) or escitalopram (5 mg/kg/day by Alzet minipumps) or saline (0.9% 3 ml/kg, same conditions). On the 14th day, microdialysis probes were implanted vertically in the prefrontal cortex (PfCX) and on the 15th day, microdialysis experiments were carried out and rats were challenged with the alpha2 agonist clonidine or the 5HT1A agonist 8-OHDPAT, the alpha2 antagonist idazoxan or the 5HT1A antagonist. The data showed that: 1) chronic DMI and chronic escitalopram increase extracellular NA and respectively 5HT in PfCX to levels superimposable to those reached after acute administration of the same dose to naive rats. 2) acute challenge of rats chronically exposed to DMI and to escitalopram with the same antidepressant failed to further increase NA and 5HT respectively. 3) Alpha2 and 5HT1A receptor stimulation and blockade were similarly effective in affecting monoamine levels in rats chronically exposed to antidepressants and in rats acutely challenged with them. These observations challenge the hypothesis that desensitization of presynaptic inhibitory autoreceptors occurs during chronic antidepressant treatment and suggest that alternative hypotheses should be utilized to explain the mechanism of the delay in antidepressant drug action.