INTERACTION BETWEEN FLUOXETINE AND OLANZAPINE IN THE MODULATION OF TROPHIC FACTOR FGF-2 WITHIN THE RAT BRAIN

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The therapeutic action of antidepressant drugs now available is of proved effectiveness, but neurobiological mechanisms underlying this effect are still unclear. It is known that, although biochemical effects induced by antidepressant drugs (reuptake inhibition of noradrenaline and serotonin) are evident within hours from administration, therapeutic effects become evident only after prolonged treatment (2-3 weeks), suggesting that adaptative processes may come into play to produce the long term action of antidepressants. It is known that a great number of patients treated for an episode of major depression (unipolar or bipolar) is resistant to pharmacological treatment; it is observed that most depressive patients do not reach complete remission from the disease. The patients with TRD (treatment resistant depression), do not respond to classic drugs, such tricyclic antidepressants and reuptake of serotonin inhibitors (SSRI). Drug combination has been proven more effective in TRD therapy than single drugs. Recently, neurotrophic factors have been suggested as possible targets of antidepressant action (Nibuya et al., 1995). Neurotrophic factors are a heterogenous group of proteins essential for cell survival, both during development and adult life. They have been shown to prevent neuronal degeneration, to promote synaptic plasticity and to modulate neurogenesis in the adult animal. Recent studies have demonstrated that combination of fluoxetine, an antidepressant SSRI, and olanzapine, an atypical antipsychotic, has synergistic effects on dopaminergic and noradrenergic transmission in prefrontal cortex (Zhang et al., 2000). Since recent studies performed in our laboratory have demonstrated that these two systems increase the FGF-2 expression (Riva M.A. et al., 1996; Roceri et al., 2001) in specific cerebral structures, we have hypothesized that such combination could regulate the trophic factor expression. Fluoxetine and olanzapine were administered either alone or in combination. Three different treatments have been carried out: acute (one single intraperitoneal injection killing the animals 2 hours later); subchronic (seven days of administration killing the animals 2 hours after last injection), and chronic (fourteen days of administration killing the animals 2 hours after last injection). BDNF and FGF-2 expression was evaluated in this experimental paradigm as possible marker of synaptic plasticity. Although it has been published that chronic fluoxetine treatment increases BDNF expression in hippocampus, we did not observe significant alterations of mRNA levels for BDNF in hippocampus or prefrontal cortex, both with molecules alone as well and with combination. Acutely we observed that FGF-2 expression is increased only following drug combination, in prefrontal and frontal cortex, with no effect in hippocampus. Chronically, fluoxetine and olanzapine alone did not alter FGF-2 mRNA levels, while coadministration produces synergistic effect on FGF-2 levels in prefrontal, frontal cortex and hippocampus. With respect to frontal and prefrontal cortex, these data are in agreement with the possibility that the concomitant administration of fluoxetine and olanzapine has a synergistic effect on dopamine release. In effect previous results obtained in our laboratory have demonstrated that the expression of FGF-2 is markedly induced by dopaminergic agents (Roceri M. et al., 2001), and by events known to increase dopamin release, like stress (Molteni et al., 2001). Recently combination of fluoxetine and olanzapine has been used in the treatment of patients with TRD, with an improvement in the symptomatology of depressive syndrome (Shelton et al., 2001). Ours data demonstrate that such combination can modulate FGF-2 expression in specific cerebral areas: it is possible therefore to assume that the modulation of FGF-2 can contribute to mechanisms of synaptic remodelling that occur in therapeutic effect of antidepressant drugs and to synaptic changes important for therapeutic effect of antidepressant and antipsychotic drugs.

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