INVESTIGATIONS INTO THE MECHANISM OF ACTION OF THE ADHD DRUG ATOMOXETINE

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Dysfunction of catecholaminergic systems, particularly in prefrontal cortex, are clearly involved in Attention/Deficit Hyperactivity Disorder (ADHD). In this regard, we have investigated the mechanism of action of atomoxetine, a drug with efficacy in the pharmacotherapy of ADHD. Atomoxetine is a selective norepinephrine transporter inhibitor and uniquely is *not* a psychostimulant. In vitro binding studies demonstrated that atomoxetine is highly selective for the norepinephrine transporter versus other neurotransmitter transporters or neuronal receptors, and, furthermore, the selectivity is maintained in vivo. Using in vivo microdialysis in rats, we have demonstrated that atomoxetine increased extracellular levels of norepinephrine and dopamine in prefrontal cortex, but did not alter dopamine levels in the dopamine-rich brain regions nucleus accumbens (reward area) or dorsal striatum (motor area) (Bymaster et al., 2002). Uniquely in prefrontal cortex, dopamine is cleared by the norepinephrine transporter, so blockade of the norepinephrine transporter gives parallel increases of norepinephrine and dopamine in that region. The psychostimulant methylphenidate also increased norepinephrine and dopamine in prefrontal cortex, but in contrast, increased dopamine in nucleus accumbens and striatum, brain areas where dopamine is involved in reward and motor functions, respectively. We also found that atomoxetine, through effects on catecholaminergic systems, increased extracellular concentrations of acetylcholine in prefrontal cortex, but not in subcortical brain regions (Tzavara et al., 2005). Since the biogenic amines norepinephrine, dopamine, and acetylcholine in the prefrontal cortex are associated with memory, attention and motivation, processes dysregulated in ADHD, we investigated the effects of atomoxetine in two memory tasks in normal, adult rats. Atomoxetine in the same dose range that enhanced biogenic amine levels facilitated performance in the object recognition test and the radial arm-maze test (Tzavara et al., 2005), and, additionally, was active in a behavioural model of ADHD (Moran-Gates et al., 2005). These data indicate that atomoxetine (1) increases prefrontal cortical levels of norepinephrine, dopamine, and acetylcholine (2) and the subsequent increase in biogenic amine neurotransmission facilitates prefrontal cognitive processes which are deficient in ADHD. (3) Due to its lack of effect on dopamine neurotransmission in brain regions associated with reward and motor processes, atomoxetine does not have drug abuse or motor liabilities.