Effect of sustained serotonin reuptake inhibition on the firing activity of dopamine neurons in the ventral tegmental area

University of Ottawa Institute of Mental Health Research

Eliyahu Dremencov*, Mostafa El Mansari and Pierre Blier

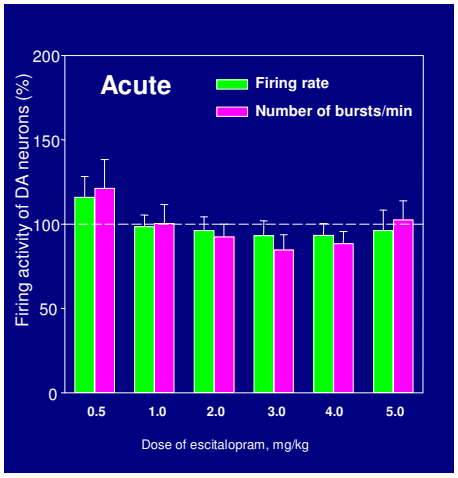
University of Ottawa Institute of Mental Health Research, Ontario, Canada

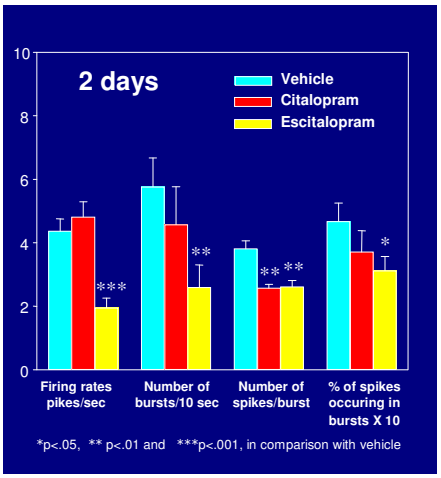
*Current address: Brains On-Line BV, Groningen, Netherlands, email e.dremencov@brainsonline.org

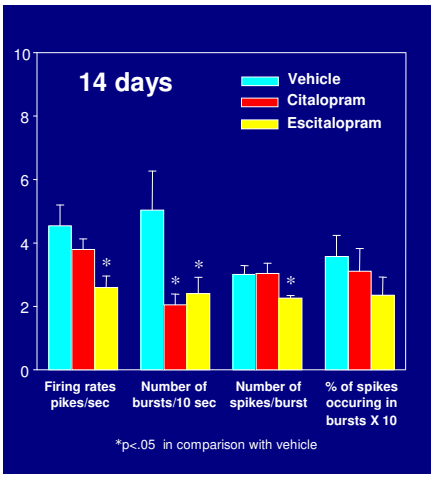
BACKGROUND: Selective serotonin (5-HT) reuptake inhibitors (SSRIs) are efficacious in depression because of their ability to increase 5-HT neurotransmission. However, due to a purported inhibitory effect of 5-HT on dopamine (DA) neuronal activity in the ventral tegmental area (VTA), this increase in 5-HT transmission might result in a suppression of the firing activity of DA neurons. Since the mesolimbic DA system plays an important role in motivation and reward, its suppression may lead, in some patients, to the lack of adequate response to SSRIs.

METHODS: The SSRIs citalopram and escitalopram (20 and 10 mg/kg/day, respectively, for 2 or 14 days each) were administered via osmotic minipumps which were implanted subcutaneously (s.c). Escitalopram was also given acutely (i.v.) at cumulative doses of 0.1-5.0 mg/kg. The selective 5-HT_{2C} receptor antagonist SB 242084 (0.5 or 2.0 mg/kg/day for 2 days) was given (s.c.) alone or in combination with escitalopram. Rats (250-300 g) were anesthetized with chloral hydrate (400 mg/kg, i.p.) and glass electrodes (4-6 mΩ) were lowered into the VTA. DA neurons were identified by their location and firing pattern.

RESULTS: Effects of citalopram and escitalopram on the firing activity of DA neurons in the VTA





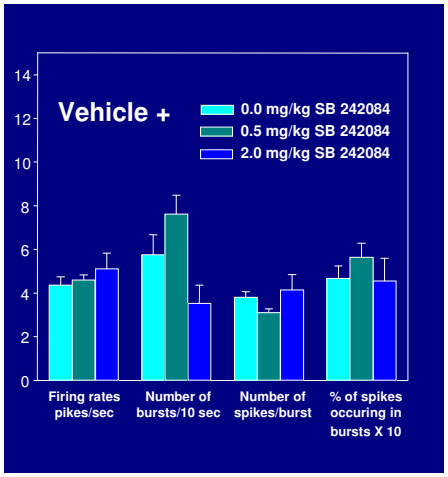


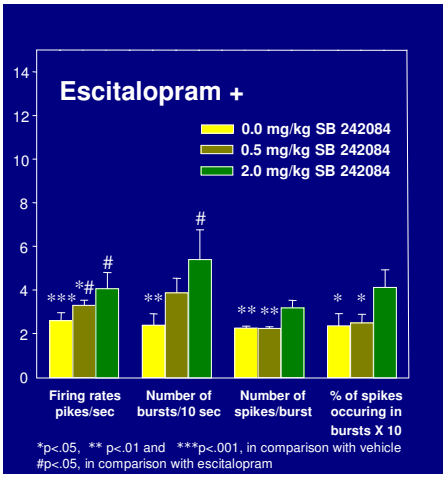
❖**Acute administration of escitalopram** did not alter the firing rate neither the burst activity of DA neurons in the VTA

❖**Sustained administration of escitalopram** (for both 2 and 14 days) decreased both the firing rate and burst activity of DA neurons in the VTA

❖**Sustained administration of citalopram** (for both 2 and 14 days) decreased certain characteristics of burst activity, but did not alter the firing rate of DA neurons in the VTA

Role of 5-HT_{2C} receptors in the SSRI-induced inhibition of firing activity of DA neurons





❖**The selective 5-HT_{2C} receptor antagonist (SB242084), given alone,** did not alter the firing activity of DA neurons in the VTA (0.5 or 2.0 mg/kg/day for 2 days)

❖**The selective 5-HT_{2C} receptor antagonist (SB242084), co-administered with escitalopram,** dose-dependently reversed the escitalopram-induced inhibition of firing activity of DA neurons in the VTA (0.5 or 2.0 mg/kg/day co-administered with 10 mg/kg/day of escitalopram for 2 days)

Conclusions:

❖SSRIs inhibit the firing activity of DA neurons in the VTA after sustained, but not after acute administration

❖The more robust effect of escitalopram on the firing activity of DA neurons can be explained by the greater capacity of escitalopram to increase the extracellular concentration of 5-HT in comparison to citalopram (*Mork et al., Neuropharmacology 45:167, 2003*).

❖The degree of SSRI-induced inhibition of DA neuronal firing activity appears depend on the reuptake potency of the SSRI

❖The SSRIs-induced inhibition of DA neuronal firing activity in the VTA is mediated via 5-HT_{2C} receptors

❖Antagonists of 5-HT_{2C} receptors may thus be effective adjuncts in SSRI-resistant patients

Supported by the Canadian Institutes of Health Research (CIHR) and by Lundbeck A/S