Escitalopram: a unique mechanism of action

The 5-HT (5-hydroxytryptamine, serotonin) transporter (SERT) mediates the reuptake of 5-HT from the synaptic cleft into the neuron, and inhibition of this uptake is the target of selective serotonin reuptake inhibitors (SSRIs). Escitalopram (S-citalopram) is the most selective SSRI available, whereas the other enantiomer, R-citalopram, is approximately 30–40 times less potent than the S-enantiomer. Both biochemical experiments (measurement of extracellular 5-HT in the frontal cortex of rats) and behavioural studies (using the chronic mild stress and conditioned fear stress models) demonstrate that R-citalopram appears to counteract the effect of escitalopram, and that it is a dose-dependent action. When escitalopram is administered at a specific dose, it produces a greater effect than when the same dose of the S-enantiomer is administered in combination with the R-enantiomer, i.e. when citalopram is administered. While mainly the S-enantiomer is bound to the primary binding site on the SERT, both enantiomers bind to the allosteric binding site. However, the R-enantiomer stabilises the binding of the S-enantiomer at the primary site less than the S-enantiomer. Furthermore, R-citalopram has an inhibitory effect on the association of escitalopram with the transporter, thereby possibly reducing escitalopram’s effect. In summary, escitalopram appears to possess a unique mechanism of action at the 5-HT transporter protein. Furthermore, escitalopram (S-citalopram) is different from citalopram because R-citalopram counteracts the activity of the S-enantiomer.

Keywords
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ESCITALOPRAM: PHARMACOLOGICAL STUDIES

An early, pre-clinical report of Montgomery and colleagues (using a rat chronic mild stress model of depression) indicated that the onset of effect of escitalopram occurred earlier compared with citalopram. Thus, Sánchez et al demonstrated that escitalopram (3.9 and 7.8 mg/kg per day) had a rapid and potent effect compared with vehicle (Figure 1). In this model, difference from vehicle controls occurred at week 1 of treatment (P < 0.01) and continued to week 5 (P < 0.01–0.001). An equivalent dose of S-enantiomer contained in citalopram (i.e. 8.0 mg/kg of racemate) separated from vehicle controls at week 2. A more recent study using the same model further supports the notion that the R-enantiomer counteracts the activity of the S-enantiomer.

Microdialysis studies were also performed to measure the effects of escitalopram, R-citalopram, racemic citalopram (equal amounts of S- and R-enantiomer) and different ratios of escitalopram and R-citalopram on extracellular 5-HT (5-hydroxytryptamine, serotonin) levels in the frontal cortex of freely moving rats. Escitalopram (2 mg/kg) resulted in a more pronounced increase in extracellular 5-HT levels than an equivalent dose of S-enantiomer contained in a racemic citalopram (4 mg/kg) (Figure 2). Furthermore, when escitalopram was administered with 2- or 4-times greater amounts of R-citalopram, a dose-dependent inhibition of the escitalopram-induced increase in 5-HT was seen (Figure 2). These results supported previous findings, that R-citalopram counteracts the effect of escitalopram.

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THE SEROTONIN TRANSPORTER: BIOCHEMICAL STUDIES

The 5-HT transporter (SERT) is responsible for the reuptake of 5-HT from the synaptic cleft into the neuron. In terms of 5-HT reuptake inhibition, escitalopram (S-citalopram) is the most selective among the serotonin reuptake inhibitors (SSRIs) available in clinical practice. The R-enantiomer, R-citalopram, is approximately 30–40 times less potent than escitalopram.4

Biochemical studies have demonstrated that there are at least two distinct binding sites on the 5-HT transporter: a high-affinity, primary binding site that mediates the inhibition of 5-HT reuptake, and a low affinity site that allosterically modulates the affinity of ligands at the primary site.5 Escitalopram binds to the primary site, while R-citalopram has low affinity for this site. However, both S-citalopram and R-citalopram bind to the allosteric site with low stereoselectivity. The nature of the allosteric binding was investigated using a classical radioligand binding method in a membrane preparation from COS-1 cells expressing human SERT (hSERT). Dissociation rates from the escitalopram:hSERT complex were measured in the presence of various concentrations of S-citalopram and R-citalopram.

The dissociation rate of [3H]escitalopram from the [3H]escitalopram transporter complex decreased as the concentration of added unlabelled escitalopram increased (Figure 3).6 These findings indicate a stabilising/self-potentiating effect of escitalopram on the [3H]escitalopram:transporter complex.

The self-potentiating effect of the R-enantiomer on [3H]escitalopram binding was less than for the S-enantiomer. Furthermore, other 5-HT reuptake inhibitors like fluoxetine and venlafaxine are devoid of this effect, while paroxetine and sertraline mainly stabilised the [3H]-paroxetine:hSERT complex.
Thus, it appears that escitalopram possesses a unique mechanism of action at the 5-HT transporter protein. The proposed mechanism of action of escitalopram on the 5-HT transporter is shown schematically in Figure 4. The proposed inhibitory effect of R-citalopram is also shown.

**CONCLUSION**

In conclusion, preclinical evidence from several models demonstrates that escitalopram shows consistently improved efficacy and faster onset of action when compared with citalopram. In fact, R-citalopram counteracts the effects of escitalopram. Biochemical studies further support that escitalopram has a distinct allosteric mode of action compared with citalopram and other 5-HT reuptake inhibitors. Although the molecular mechanism is not fully understood, currently available data points to the 5-HT transporter itself as being the site where R-citalopram interferes with the effects of escitalopram.

**KEY POINTS**

- Escitalopram (S-citalopram) is the most selective SSRI available.
- R-citalopram has an inhibitory effect on the effect of escitalopram.
- Escitalopram appears to possess a unique mechanism of action at the 5-HT transporter protein.

**REFERENCES**


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