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Influence of serotonin on anxiety-like behaviour in rat

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin,
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av

Robert Pettersson

Fakultetsopponent:
Göran Engberg, professor
Karolinska Institutet

Avhandlingen baseras på följande delarbeten

I. **Pettersson R**, Näslund J, Nilsson S, Eriksson E, Hagsäter SM. Acute escitalopram but not contextual conditioning exerts a stronger "anxiogenic" effect in rats with high baseline "anxiety" in the acoustic startle paradigm. Psychopharmacology (Berl), 2015, 232:8.

II. **Pettersson R**, Hagsäter SM, Eriksson E. Serotonin depletion eliminates sex differences with respect to context-conditioned immobility in rat. Psychopharmacology (Berl), 2016, 233:8.

III. **Pettersson R**, Hagsäter SM, Näslund J, Holmäng A, Pettersson C, Eriksson E. Antagonism of the 5-HT2A receptor unmasks an anxiolytic effect of acute SSRI treatment in the contextual fear paradigm. *Preliminary manuscript*

IV. Hagsäter SM, **Pettersson R**, Carlsson B, Karlsson L, Eriksson E. Chronic escitalopram administration reduces contextual conditioned fear. *Preliminary manuscript*

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Influence of serotonin on anxiety-like behaviour in rat

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Abstract

It is well-established that serotonin is involved in the regulation of mood and behaviour, partly implied by the therapeutic effect of prolonged treatment with selective serotonin reuptake inhibitors (SSRI) on mood and anxiety disorders. However, the mechanisms behind the paradoxical exacerbation of anxiety described during initial treatment, as well as behind the therapeutic effects of prolonged treatment with SSRIs, remain poorly understood.

In the research described in this thesis, the effects of different manipulations of the serotonin system on anxiety-related behaviour was studied in rat models of contextual fear.

In Paper I, we investigated whether rats could be classified as more or less 'anxious' based on two behaviours, namely startle and freezing, and to what extent this baseline 'anxiousness' predicted subsequent startle and freezing behaviour in the response to acute administration of an SSRI, escitalopram, with or without further aggravation of fear by so-called contextual fear conditioning. Startle and freezing correlated and showed good inter-test stability before contextual conditioning and were both enhanced by escitalopram, where the enhancement of startle was more pronounced in animals with high startle and freezing before contextual conditioning. This resembles the clinical picture, in the sense that anxiety-prone patients can experience worsening of their anxiety symptoms during early medication with SSRIs.

The work of Paper II evaluated whether startle and freezing in the model of Paper I were dependent on serotonin and whether sex was an important factor. Startle and freezing responses were assessed in male and female rats after treatment with a serotonin-depleting agent, para-chlorophenylalanine (PCPA), with or without prior contextual conditioning. The main finding, i.e. that PCPA reduced contextual conditioned freezing solely in male rats, thereby abolishing a sex difference in this parameter, indicates that both sex and serotonin can influence anxiety-like behaviour.

In Paper III, the possible involvement of specific serotonin receptor subtypes for the effect of acute SSRI administration on contextual conditioned freezing was examined. Without exerting any effect on their own, the combination of a 5-HT2A receptor antagonist and escitalopram resulted in a pronounced reduction in freezing behaviour. A remarkable freezing reduction was also observed after administration of any of two agents normally causing a more robust increase in extracellular serotonin than do the SSRIs, i.e. 5-hydroxytryotophan (5-HTP) (a serotonin precursor) or fenfluramine (a serotonin releaser). It is suggested that the effect of 5-HT2A antagonism may be mediated by inhibition of negative feedback leading to higher extracellular serotonin, but it is also possible that it unmasks an anti-freezing effect of escitalopram by blocking freezing-promoting postsynaptic receptors normally activated by the SSRI. The possibility that the anti-freezing effect of escitalopram plus the 5-HT2A antagonist is mediated by postsynaptic 5-HT1A receptors was explored; however, this appeared not to be the case.

The experiments described by Paper IV showed that long-term treatment with escitalopram reduced contextual conditioned freezing whereas acute escitalopram administered at a dose causing similar serum levels of the compound did not influence the behaviour. These results mirror the clinical situations and suggest this model as useful for studying mechanisms underlying the effect of short- versus long-term SSRI treatment. It remains unsolved whether the reduction in freezing by long-term SSRI treatment is caused by a negative or positive influence on extracellular serotonin level; since a powerful reduction of freezing may be obtained both by serotonin-reducing and serotonin-enhancing agents, neither of these options can be ruled out. The finding that the freezing-reduction caused by long-term SSRI could not be reversed by serotonin-enhancing treatment however favours the latter possibility.

In conclusion, the experiments indicate (1) that there are notable similarities between the studied behaviours and human anxiety (2) that intact serotonergic transmission seems important for freezing behaviour and (3) that the 5-HT2A receptor seems to play an important role in the underlying mechanisms.

Keywords: Anxiety, Serotonin, SSRI

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