Effects of flibanserin on appetitive and consummatory aspects of sexual behavior in ovariectomized female rats primed with estrogen and progesterone

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Background

- **Flibanserin** a 5-HT1A agonist and 5-HT2A antagonist

- **Flibanserin** developed for the treatment of hypoactive sexual desire disorder (HSDD) in women

- Proposed relevant experimental model for further **flibanserin** preclinical studies: measure of **sexual appetitive** behaviors in the **female rat**
Female rat sexual behavior

**APPETITIVE / PROCEPTIVE behaviors**
Related to SEXUAL MOTIVATION
- genital investigation
- ear wiggling
- active solicitation
- hops and darts
- pacing

**CONSUMMATORY / RECEPTIVE behaviors**
Related to COPULATION
- lordosis response:
  - lordosis quotient
  - lordosis intensity

**Homologous to women sexual desire**

**No counterpart to women sexual response**
Objective

Aim:
To assess the effects of repeated flibanserin treatment on female rat sexual behavior.

General procedure:
Measure of proceptive and receptive behaviors in female rats during copulatory tests with sexually active male rats, in bilevel chambers.
Methods

1. 52 sexually naive Long Evans female rats

2. Females are ovariectomized and rendered sexually receptive by hormonal priming: estradiol (10µg) and progesterone (500µg) administered 48h and 4h respectively before the copulatory test.

3. 10 sexual training tests (T1 to T10) (30min) with sexually active males

4. 4 treatment groups (p.o., twice a day, for 29 days):
   - Flibanserin 5 mg/kg
   - Flibanserin 15 mg/kg
   - Flibanserin 45 mg/kg
   - Vehicle (0.5% Natrosol + 1% Polysorbate)

5. 5 treatment tests: (T11: acute treatment test, T12 to T15: once a week)
Flibanserin enhanced active solicitations toward males

Number of solicitations before beginning of treatment (Baseline)

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Mean number</th>
</tr>
</thead>
<tbody>
<tr>
<td>vehicle</td>
<td></td>
</tr>
<tr>
<td>Flib 5 mg/kg</td>
<td></td>
</tr>
<tr>
<td>Flib 15 mg/kg</td>
<td></td>
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<tr>
<td>Flib 45 mg/kg</td>
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</tbody>
</table>

Number of solicitations after 15-days of treatment

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Mean number</th>
</tr>
</thead>
<tbody>
<tr>
<td>vehicle</td>
<td></td>
</tr>
<tr>
<td>Flib 5 mg/kg</td>
<td></td>
</tr>
<tr>
<td>Flib 15 mg/kg</td>
<td></td>
</tr>
<tr>
<td>Flib 45 mg/kg</td>
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</tbody>
</table>
Flibanserin enhanced active solicitations toward males

Number of solicitations after 22-days of treatment

![Graph showing the mean number of solicitations after 22-days of treatment for Flibanserin at different doses: vehicle, Flib 5 mg/kg, Flib 15 mg/kg, and Flib 45 mg/kg. The graph indicates a significant increase in solicitations with the higher doses of Flibanserin, compared to the vehicle group, with the 45 mg/kg dose showing the most significant effect. The data is represented with error bars indicating variability.](image-url)
Flibanserin did not modify other behavioral parameters after 15-days of treatment (same after 22-days)

**Number of hops and darts**

<table>
<thead>
<tr>
<th></th>
<th>Vehicle</th>
<th>Flib 5 mg/kg</th>
<th>Flib 15 mg/kg</th>
<th>Flib 45 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

**Number of level changes**

<table>
<thead>
<tr>
<th></th>
<th>Vehicle</th>
<th>Flib 5 mg/kg</th>
<th>Flib 15 mg/kg</th>
<th>Flib 45 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>100.00</td>
<td>100.00</td>
<td>100.00</td>
<td>100.00</td>
</tr>
</tbody>
</table>

**Lordosis quotient**

<table>
<thead>
<tr>
<th></th>
<th>Vehicle</th>
<th>Flib 5 mg/kg</th>
<th>Flib 15 mg/kg</th>
<th>Flib 45 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>0.95</td>
<td>0.95</td>
<td>0.95</td>
<td>0.95</td>
</tr>
</tbody>
</table>

**Number of ejaculations**

<table>
<thead>
<tr>
<th></th>
<th>Vehicle</th>
<th>Flib 5 mg/kg</th>
<th>Flib 15 mg/kg</th>
<th>Flib 45 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>2.00</td>
<td>2.00</td>
<td>2.00</td>
<td>2.00</td>
</tr>
</tbody>
</table>
Flibanserin did not modify other behavioral parameters after 22-days of treatment.

### Number of hops and darts

- **Vehicle**: 0
- **Flib 5 mg/kg**: 1
- **Flib 15 mg/kg**: 2
- **Flib 45 mg/kg**: 4

### Number of level changes

- **Vehicle**: 0
- **Flib 5 mg/kg**: 2
- **Flib 15 mg/kg**: 120
- **Flib 45 mg/kg**: 130

### Lordosis quotient

- **Vehicle**: 0.90
- **Flib 5 mg/kg**: 0.95
- **Flib 15 mg/kg**: 1.00
- **Flib 45 mg/kg**: 1.00

### Number of ejaculations

- **Vehicle**: 0.5
- **Flib 5 mg/kg**: 1.0
- **Flib 15 mg/kg**: 1.5
- **Flib 45 mg/kg**: 3.0

### Number of hops and darts

- **Vehicle**: 0
- **Flib 5 mg/kg**: 1
- **Flib 15 mg/kg**: 2
- **Flib 45 mg/kg**: 4

### Number of level changes

- **Vehicle**: 0
- **Flib 5 mg/kg**: 2
- **Flib 15 mg/kg**: 120
- **Flib 45 mg/kg**: 130

### Lordosis quotient

- **Vehicle**: 0.90
- **Flib 5 mg/kg**: 0.95
- **Flib 15 mg/kg**: 1.00
- **Flib 45 mg/kg**: 1.00

### Number of ejaculations

- **Vehicle**: 0.5
- **Flib 5 mg/kg**: 1.0
- **Flib 15 mg/kg**: 1.5
- **Flib 45 mg/kg**: 3.0
SUMMARY

• **15-days** of chronic **45 mg/kg flibanserin** treatment results in a significant increase in female solicitations, compared to lower flibanserin doses (5 and 15 mg/kg) or vehicle

• This facilitatory effect of **45 mg/kg flibanserin** on female solicitations is still observed after **22-days** of chronic treatment

• Chronic flibanserin treatment did not modify **other** proceptive or receptive female sexual behaviors
CONCLUSION

These results evidence, for the first time, the prosexual effect of flibanserin in female rats receiving 45 mg/kg, twice daily administered for 15 days.

Since flibanserin has shown efficacy in treating premenopausal women with HSDD, these data combined suggest this animal model may be useful in supporting further pre-clinical drug studies for female sexual dysfunction.