Role of ATP sensitive potassium channel on 7-hydroxy flavone induced antinociception and possible association with changes in glycaemic status

P E Venkataramanan, S Parvathavarthini & S Viswanathan
Institute of Pharmacology, Madras Medical College, Chennai 600 003, India
and
S Ramaswamy*
Department of Pharmacology, Jawaharlal Institute of Postgraduate, Medical Education and Research, Pondicherry 605 006, India

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Opioid type of analgesics open ATP sensitive potassium channel at the cellular level to produce antinociceptive response. These channels have also been shown to modulate insulin secretion by the pancreas. 7-hydroxy flavone, an antinociceptive agent shown to act through opioid pathways was investigated for its effect on glycaemic state and associated algesic state. The involvement of ATP sensitive potassium channel in the action was examined by using glybenclamide. The result reveal that 7-HF per se did not elicit any significant change in the glycaemic state simultaneously eliciting antinociceptive response as tested by acetic acid induced abdominal constriction assay procedure. Glybenclamide treatment attenuated the antinociceptive effect of 7-HF and while maintained its hypoglycaemic response. The present finding suggest that 7-HF induces antinociception like morphine, utilise ATP sensitive potassium channel at the cellular level and do not suggest a cause-effect relationship between the changes in the glycaemic and algesic state. Possibly, insulin which is controlled by ATP sensitive potassium channel at the cellular level might also modulate antinociception exhibiting a cause-effect relationship between them.

The cause-effect relationship between changes in the glycaemic and algesic state remains debatable. While a few reports support such a relationship, most of them oppose this contention. An earlier study suggested that use of chemical diabetic models which causes functional and structural changes in the neuronal system may be the contributing factor for these varied results.

At the cellular level, one of the important mechanisms utilised by opioid like antinociceptive agents is ATP sensitive potassium channels. Earlier studies established that opioid receptors in the central nervous system elicit antinociception by opening ATP sensitive potassium channel. ATP sensitive potassium channel opener pinacidil has been shown to potentiate morphine analgesia. It is noteworthy that α2-adrenergic receptors mediated antinociception which is considered independent of opioid mechanism also utilised these ATP sensitive potassium channel at the cellular level to elicit antinociception. Additionally agents like prolactin which has been shown to elicited opioid mediated antinociception also utilise such mechanism.

Interestingly ATP sensitive potassium channel has been documented to modulate insulin release from the β-islets of pancreas. Considering these available literature, there appears to be a link between antinociception, changes in the glycaemic state and ATP sensitive potassium channel. The present study investigated the cause-effect relationship between changes in glycaemic state and algesic state using physiological manoeuvres instead of chemical models as suggested earlier. 7-hydroxy flavone (7-HF) was used to elicit antinociception since it is almost non-toxic, utilized opioid pathways sans adverse effects. The possible role of ATP sensitive potassium channels was also examined.

Healthy male Swiss albino mice (25-30 g) were housed in polypropylene cages with free access to food and water.

The antinociception was assayed using acetic acid induced abdominal constriction assay procedure. The number of abdominal constrictions for 15 min following intraperitoneal injection of 0.6% acetic acid (10 ml/kg) was recorded. A significant reduction in the number of abdominal constrictions when compared with vehicle treated animals was considered as antinociceptive response.

*Correspondent author
The blood glucose was measured from a drop of blood collected by cutting the tip of the tail of the mouse using AMES glucometer with appropriate glucostick. This was measured prior to any drug exposure and just before acetic acid challenge throughout the study. The results were expressed as percentage considering the initial blood glucose level of that animal as 100%.

**Drug treatment** —7-HF was used in the dose of 100 mg/kg; s.c. (as 1% suspension in carboxy methyl cellulose) 60 min prior to acetic acid challenge. Glibenclamide, an ATP sensitive potassium channel blocker, was administered 10 min prior to acetic acid challenge in vehicle treated animal or 50 min after 7-HF administration.

**Drugs used** —7-HF (synthesized and gifted by Research Organics, Chennai), glibenclamide (gift from Dr. Reddy’s Laboratory, Hyderabad) acetic acid (IDPL), carboxy methyl cellulose sodium salt (Glaxo Laboratory, Bombay) and tween 80 (BDH, Mumbai). 7-HF was prepared as a suspension of 1% carboxymethyl cellulose and glibenclamide in 0.05% tween 80. Appropriate vehicles were used as control.

7-HF, in the dose employed, (selected based on earlier studies) elicited a significant reduction in the number of acetic acid induced abdominal constriction without significantly modifying the blood glucose level. In contrast, glibenclamide *per se* induced significant hypoglycaemia without modifying the number of abdominal constriction. Glibenclamide treatment in 7-HF pretreated animals still elicited hypoglycaemia, however, the degree was significantly less. In contrast, it almost attenuated the 7-HF induced inhibition of acetic acid induced abdominal constriction (Table 1).

The present findings confirm the earlier reported antinociceptive effect of 7-HF which has been shown to act through opioid pathways. However, it was without any effect on the glycaemic state. This observation indicates that 7-HF induced antinociception and alterations in glycaemic state are not cause effective. Glibenclamide treatment attenuated 7-HF induced antinociceptive response similar to that of morphine thus confirming that 7-HF also utilizes ATP sensitive potassium channels at the cellular level like morphine. The dissociated relationship suggested earlier between 7-HF induced antinociception and glycaemic state is supported by the observation that though glibenclamide attenuated 7-HF antinociception it was still able to elicit significant hypoglycaemia. These observations tempt to suggest that the cellular mechanism involving ATP sensitive potassium channels in the elicitation of antinociception does not reflect in the metabolic parameter, i.e. the blood glucose changes. Recently, Takashita and Yamaguchi reported an inherent antinociceptive response for insulin independent of its hypoglycaemic response. Taking into consideration the findings of this report, a new hypothesis relating insulin, antinociception and ATP sensitive potassium channel function could be proposed. A possible cause-effect relationship between algesic and insulinaemic state rather than glycaemic state deserves investigation. This is because at the cellular level ATP sensitive potassium channels have been shown to modulate antinociceptive response and insulin release from β-cells of pancreas. The present study also prove that like morphine, 7-HF utilises ATP sensitive potassium channel.

### Table 1 —Effect of glibenclamide on the blood glucose and acetic acid induced abdominal constrictions in mice (n=7)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Blood glucose (%) change</th>
<th>No. of abdominal constrictions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>104.3 ± 0.5</td>
<td>25.0 ± 1.4</td>
</tr>
<tr>
<td>Glibenclamide, 10</td>
<td>55.1 ± 5.6**</td>
<td>30.1 ± 2.7</td>
</tr>
<tr>
<td>7-HF, 100</td>
<td>110.8 ± 8.3</td>
<td>15.7 ± 1.4**</td>
</tr>
<tr>
<td>7-HF 100 + Glibenclamide, 10</td>
<td>73.7 ± 2.2***</td>
<td>21.7 ±0.9***</td>
</tr>
</tbody>
</table>

*Blood glucose was expressed as the percentage considering the initial value as 100%.

**Glibenclamide was injected i.p. 10 min prior to acetic acid challenge

**7-HF was administered s.c. 60 min prior to acetic acid challenge

**P < 0.01 when compared with vehicle treatment

**P < 0.05 when compared with their respective 7-HF value.

References


