Allicin, a SUR2 opener: possible mechanism for the treatment of diabetic hypertension in rats

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Abstract: The garlic (Allium sativum L., Amaryllidaceae) has been popularly used in the treatment of diabetes and cardiac complications. In the present work, we have studied the possible mechanisms, sulfonylurea receptor (SUR) selectivity of allicin in diabetic hypertensive rats. Diabetic hypertension was induced by intraperitoneal injection of streptozotocin (50 mg/kg) followed by daily administration of dexamethasone (10 μg/kg, s.c.). Different parameters, blood pressure and blood glucose levels were studied in the rats weekly up to eight weeks. Allicin (8 mg/kg, p.o.) shows potent antidiabetic (*p<0.001) as well as antihypertensive effect (**p<0.001, *p<0.01). It may act as a vasodilator by hyperpolarizing the membrane of normal vascular smooth muscle cells. The hyperpolarization in vascular smooth muscle occurs due to K+ channel opener activity. Antihypertensive effect of allicin is inhibited by glibenclamide, nonselective SUR blocker while combination of allicin with nateglinide, selective SUR1 blocker exerted synergistic antihypertensive effect. The results indicates that allicin is effective in the treatment of diabetic hypertension; through a mechanism that might involve selective opening of SUR2.

Keywords: Allicin, diabetic hypertension, hyperpolarizing, streptozotocin, sulfonylurea receptor, vasodilator

Introduction

Diabetes mellitus (DM) represents a spectrum of metabolic disorders, becomes a major health challenge worldwide (Moore et al., 2009). Cardiovascular disease is the leading cause of mortality (52% of deaths) in individuals with DM (Aminot Gilchrist & Anderson, 2004). Hypertension is an extremely common co morbid condition in DM, affecting about 20-60% of patients with diabetes (Sydow et al., 2005; Wilhelm et al., 2007; Shin & Chung, 2009).

The ATP sensitive potassium (K_{ATP}) channels are found in pancreatic β-cells, cardiac and smooth muscles. K_{ATP} channel blockers are used to treat DM and openers are used to treat angina and hypertension (Ghasemi et al., 2007; Gribble & Reimann, 2003). Two genes for sulphonylurea receptors (SUR) have been identified, encoding the proteins SUR1/Kir6.2 and SUR2/Kir6.2, which are expressed in different tissues. SUR1/Kir6.2 are predominantly found in pancreatic β-cells and neurons. Alternative splicing of SUR2/ Kir6.2 produces a cardiac muscle isoform (SUR2A/ Kir6.2) and a smooth muscle isoform (SUR2B/Kir6.2) (Gribble & Reimann, 2003; Lebrun et al., 2008). Binding of K_{ATP} channel inhibitors to the SUR1/Kir6.2 causes closure of the K_{ATP} channels in the β-cell induces membrane depolarization and a further influx of Ca^{2+} through the voltage dependent Ca^{2+} channels leading to the release of insulin from pancreatic β-cells by exocytosis. K_{ATP} channels can be nonspecifically blocked in pancreatic as well as nonpancreatic tissues by some sulfonylurea like glibenclamide; it causes hypertension as a side effect due to blocking of SUR2 while nateglinide specifically blocked SUR1/Kir6.2 channels with high affinities but SUR2A/Kir6.2 and SUR2B/Kir6.2 channels only with low affinity. So nateglinide do not produced hypertension as a side effect (Chachin et al., 2003). K_{ATP} channel openers targeting the pancreatic β-cell are used therapeutically to reduce insulin secretion. Agents such as nicorandil, cromakalim, diazoxide, which open SUR2B/ Kir6.2, K_{ATP} channels in vascular smooth muscle, by contrast, are increasingly used in the treatment of angina and hypertension, but it causes hyperglycaemia due to opening of SUR1/Kir6.2, as an adverse effect (Gribble & Reimann, 2003; Szewczyk, 1997; Seino, 2003).

Modulation of K_{ATP} channel activity is an important therapeutic tool for the treatment of type 2 DM and cardiovascular disease. Drugs have been developed which selectively inhibit K_{ATP} channels in pancreatic β-cells, or open those in vascular smooth muscles and...
cardiac muscles. We need a single drug entity to treat diabetic hypertension that can lower blood glucose along with blood pressure.

Some herbal medicines like garlic are used both in diabetes as well as hypertension, acts as vasodilators by hyperpolarizing the membrane of normal vascular smooth muscle cells. The hyperpolarization in vascular smooth muscle occurs due to K⁺ channel opener’s activity (Siegel et al., 1998). Vasodilator activity of garlic is inhibited by glibenclamide, K⁺ channel blocker (Ashraf et al., 2004). So these data support that garlic may act as a K⁺ channel opener. Garlic also acts as an antidiabetic agent by enhancing glucose utilization, inhibition of intestinal absorption of glucose, and increasing the pancreatic secretion of insulin from existing β-cells or release from bound insulin (Eidi et al., 2006). Therefore an attempt was made to evaluate the antihypertensive as well as antidiabetic activity of allicin and confirm the SUR selectivity of allicin.

Material and Methods

Streptozotocin was purchased from Himedia Laboratory Ltd. (Mumbai). Dexamethasone, nateglinide and glibenclamide were procured from Zydus Cadila Healthcare Ltd. (Bangalore), Glenmark Pharmaceuticals Ltd. (Solan, Himachal Pradesh) and Cipla Pvt. Ltd. (Mumbai), respectively. All the other chemicals used for experimental purpose were of analytical reagent grades.

Animals

The albino rats (Wistar strain) of either sex weighing 150-200 g, bred in the animal house of Institute of Pharmaceutical Education and Research (Reg. No.535/02/a/CPCSEA/Jan2002), Wardha were used. All the animals were housed in polypropylene cages under controlled conditions of temperature (22±2 °C), relative humidity (50±5%) under controlled environment and illumination (12 h light-dark cycle), with free access to food (Lab diet) and water ad libitum. The animals were treated in accordance with the CPCSEA guidelines. The experimental protocol was approved by the Institute’s Animal Ethics Committee with the approval number of 10/2009-10.

Induction of hypertensive diabetes

In the experimental rats, first diabetes was induced followed by induction of hypertension. Diabetes was induced in overnight fasted rats by freshly prepared 0.2 mL solution of streptozotocin (50 mg/kg, i.p.) in 0.1 mM sodium citrate buffer (Gupta & Gupta, 2009). Hypertension was induced by subcutaneous injection of dexamethasone (10 μg/kg/day, s.c.) in the evening (Ong et al., 2007; Zhang et al., 2004).

Preparation of garlic aqueous extract

The garlic (Allium sativum L., Amaryllidaceae) was obtained from Wardha region, identified and authenticated by Dr. Alka Chaturvedi, Department of Botany, Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur with a voucher specimen of number 9803. Allicin containing garlic extract was prepared from 10 g of garlic cloves. The cloves were crushed with an electric vegetable crusher and the juice was poured into a sterile centrifuge tube and centrifuged at 5000 x g for 10 min in order to separate the majority of the pulp from the supernatant liquid. The supernatant garlic extract (allicin containing) was either used immediately for activity or stored at 4 °C (Curtis et al., 2004), was relatively stable during the weeks of experiment protocol. Accordingly animals were administered with 8 mg/kg body weight of allicin (Elkayam et al., 2001).

Determination of allicin in fresh garlic extract

Allicin in the garlic extract (10, 20, 30 and 40 μL) was reacted with cysteine via the thiol-disulphide exchange reaction and the remaining cysteine was subsequently determined by reaction with Ellman’s reagent 5,5'-dithiobis-(2-nitrobenzoic acid) (DTNB) to produce the 2-nitro-5-thiobenzoate anion, absorbance was taken at wavelength 412 nm. One mol of thiosulphinate reacts with 2 mol cysteine and since allicin makes up 60-80% of the thiosulphinates produced in garlic, multiplying the total thiosulphinate content by a factor of 0.7 gives the approximate allicin content (Curtis et al., 2004).

Experimental design

The experimental animals were randomized into five groups (six rats in each group). The experiment was conducted for a period of eight weeks. The drugs were administered by oral route in the form of 1% Acacia gum suspension. The allicin (8 mg/kg/day) (Elkayam et al., 2001), nateglinide (50 mg/kg, twice in a day) (Kitahara et al., 2002) and glibenclamide (1 mg/kg/day) (Dewanjee et al., 2008) were administered in the animals of different groups as described below.

Group A: Normal control rats (C) were administered 1 mL of 1% Acacia gum suspension for eight weeks.

Group B: Diabetic hypertensive control rats (DH₁) were administrated 1 mL of 1% Acacia gum suspension for eight weeks.

Group C: Diabetic hypertensive rats (DH₂) were administrated allicin (8 mg/kg/day) orally and nateglinide (50 mg/kg, twice in a day) in 1% Acacia gum suspension
for eight weeks.

Group D: Diabetic hypertensive rats (DH₄) were administrated allicin (8 mg/kg/day) orally and glibenclamide (1 mg/kg/day) in 1% Acacia gum suspension for eight weeks.

Group E: Diabetic hypertensive rats (DH₅) were administrated allicin (8 mg/kg/day) orally daily 1% Acacia gum suspension for eight weeks.

**Measurement of blood glucose level**

Fasting serum glucose of each animal was measured every week by using a commercially available kit (One touch ultra, Johnson & Johnson) based on glucose oxidase method (Eidi et al., 2006).

**Estimation of systolic blood pressure (SBP)**

SBP measurements were recorded weekly by the same investigator, between 10 am and 12 noon, using the integrated BIOPAC and NIBP 200A system. The animal is placed in the restrainer (animal holder) leaving the tail outside and adjusted to the position where the animal has limited movements. The restrainer is placed in heating chamber and heated up to 32 °C. BSL PRO software is used for recording of SBP, prior to starting the measurement the basic software setup is done and IR SENSORS are calibrated. IR SENSOR is then connected to the tail of the animal inside the restrainer. After the required setup and calibration of IR SENSORS, SBP was recorded.

**Estimation of body weight, food intake and water intake**

The body weight, food and water intake of the rats of each group were measured weekly up to eight weeks of the drugs treatment.

**Statistical analysis**

Statistical analysis was carried out by one-way analysis of variance (ANOVA) followed by Dunnett's multiple comparison test. All the values were expressed as mean±SEM. The results of all groups of animals were compared with control group results. A p<0.05 was considered to be statistically significant.

**Results**

**Quantification of allicin from fresh garlic aqueous extract**

Garlic extracts contained 12.8 mg allicin/mL of the fresh garlic aqueous extract.

**Effect of K⁺ channel modulators on blood glucose level in diabetic hypertensive rats**

As shown in Table 1, there was significant increase in the blood glucose level in DH₀ (hypertensive diabetic) group when compared with C (normal control) group (*p<0.001). Blood glucose level was significantly (*p<0.001) decreased in DH₁ (allicin+nateglinide), DH₂ (allicin+glibenclamide) and DH₃ (allicin treated) groups as compared to DH₀ group.

**Effect of K⁺ channel modulators on SBP in diabetic hypertensive rats**

Table 2, shows that SBP significantly (**p<0.001) increased in DH₀ (Diabetic hypertensive control) when compared with normal control group. SBP of DH₁ (allicin nateglinide treated) and DH₂ (allicin treated) groups were found to be significantly (***p<0.001) decreased when compared with DH₀ group and SBP of DH₃ (allicin+glibenclamide treated) group was less significantly decreased (*p<0.01) in SBP when compared with DH₀ group.

**Effect of K⁺ channel modulators on body weight**

There were significant (***p<0.001) decrease

<table>
<thead>
<tr>
<th>Group(s)</th>
<th>0 week</th>
<th>1st week</th>
<th>2nd week</th>
<th>3rd week</th>
<th>4th week</th>
<th>5th week</th>
<th>6th week</th>
<th>7th week</th>
<th>8th week</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>88.67±3.91</td>
<td>91.17±1.79</td>
<td>94.83±1.64</td>
<td>96±2.6</td>
<td>100±3.39</td>
<td>101±2.06</td>
<td>97±1.62</td>
<td>96±2.6</td>
<td>96±2.17</td>
</tr>
<tr>
<td>DH₀</td>
<td>321.5±33.7*</td>
<td>367.2±28.3*</td>
<td>406.5±29.4*</td>
<td>441.5±26.7*</td>
<td>497.5±25.3*</td>
<td>530.6±23.27*</td>
<td>546.3±20.8*</td>
<td>568.6±16.3*</td>
<td>588.1±8.96*</td>
</tr>
<tr>
<td>DH₁</td>
<td>310.8±31.93*</td>
<td>169.3±9.32*</td>
<td>147.0±6.80*</td>
<td>130.1±5.87*</td>
<td>115.8±4.20*</td>
<td>104.5±3.45*</td>
<td>97.3±1.89*</td>
<td>92.8±1.49*</td>
<td>94.3±1.22*</td>
</tr>
<tr>
<td>DH₂</td>
<td>142.8±5.03*</td>
<td>125.6±3.12*</td>
<td>118.7±2.76*</td>
<td>103.6±2.04*</td>
<td>93.6±1.23*</td>
<td>87.1±1.81*</td>
<td>85.8±1.70*</td>
<td>83.8±1.86*</td>
<td>81.0±1.86*</td>
</tr>
<tr>
<td>DH₃</td>
<td>326.8±26.39*</td>
<td>183.2±7.61*</td>
<td>163.6±6.43*</td>
<td>146.6±5.03*</td>
<td>130.3±4.06*</td>
<td>122.1±2.50*</td>
<td>116.0±2.64*</td>
<td>112.8±2.18*</td>
<td>111.0±1.86*</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SEM. (n = 6). One way ANOVA followed by Dunnett's multiple comparison test (*p<0.001). For statistical analysis, results of all the groups were compared with normal control group. C-Normal control, DH₀-Hypertensive diabetic control, DH₁-(allicin+nateglinide) treated, DH₂-(allicin+glibenclamide) treated, DH₃-allicin treated.
Table 2. Effect of K⁺ channel modulators on systolic blood pressure (SBP) in diabetic hypertensive rats.

<table>
<thead>
<tr>
<th>Group(s)</th>
<th>0 week</th>
<th>1st week</th>
<th>2nd week</th>
<th>3rd week</th>
<th>4th week</th>
<th>5th week</th>
<th>6th week</th>
<th>7th week</th>
<th>8th week</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>109.5±2.52</td>
<td>108.66±1.56</td>
<td>105.00±2.09</td>
<td>103.00±1.21</td>
<td>103.83±1.56</td>
<td>103.16±2.68</td>
<td>103.83±3.17</td>
<td>104.16±2.90</td>
<td></td>
</tr>
<tr>
<td>DH₀</td>
<td>113.5±2.3**</td>
<td>121.16±2.08**</td>
<td>125.83±2.02**</td>
<td>130.33±2.15**</td>
<td>133.16±2.34**</td>
<td>141.00±1.57**</td>
<td>142.50±1.43**</td>
<td>144.16±1.94**</td>
<td></td>
</tr>
<tr>
<td>DH₁</td>
<td>107.3±2.13**</td>
<td>111.83±2.15**</td>
<td>110.83±2.15**</td>
<td>106.83±2.08**</td>
<td>104.33±1.87**</td>
<td>107.16±2.08**</td>
<td>107.51±2.10**</td>
<td>100.66±0.84**</td>
<td></td>
</tr>
<tr>
<td>DH₂</td>
<td>111.6±2.5</td>
<td>113.33±2.88</td>
<td>110.33±2.76</td>
<td>120.33±1.89*</td>
<td>123.33±2.54*</td>
<td>124.16±2.21*</td>
<td>127.83±1.74*</td>
<td>130.83±1.01*</td>
<td></td>
</tr>
<tr>
<td>DH₃</td>
<td>109.5±1.76</td>
<td>115.16±2.67**</td>
<td>119.66±0.89**</td>
<td>119.33±2.32**</td>
<td>117.51±2.10**</td>
<td>117.5±0.98**</td>
<td>116.3±1.89**</td>
<td>116.5±0.76**</td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Effect of K⁺ channel modulators on body weight, water intake and food intake in diabetic hypertensive rats.

<table>
<thead>
<tr>
<th>Group(s)</th>
<th>Body weight (g)</th>
<th>Food intake (g/day)</th>
<th>Water intake (mL/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>174.5±6.32</td>
<td>12.56±1.6</td>
<td>21.40±1.13</td>
</tr>
<tr>
<td>DH₀</td>
<td>135.3±9.21***</td>
<td>21.6±2.45**</td>
<td>32.53±3.46**</td>
</tr>
<tr>
<td>DH₁</td>
<td>161.8±5.84</td>
<td>15.10±2.1</td>
<td>27.73±2.86*</td>
</tr>
<tr>
<td>DH₂</td>
<td>168.43±3.92</td>
<td>15.89±1.62</td>
<td>29.31±2.25*</td>
</tr>
<tr>
<td>DH₃</td>
<td>159.37±7.36</td>
<td>17.21±2.23</td>
<td>30.68±2.94**</td>
</tr>
</tbody>
</table>

Values are expressed as Mean±SEM. (n = 6), One way ANOVA followed by Dunnett's Multiple Comparison test (*p<0.05; **p<0.01; ***p<0.001). For statistical analysis, results of all the groups were compared with normal control group. Remaining legends are same as that of Table 1.

in the body weight was found in DH₀ when compared to normal control group; and body weight of DH₁ and DH₂ (garlic+glibenclamide treated) groups were not significantly decrease from that of normal control group (Table 3).

Effect of K⁺ channel modulators on water intake

The present study shows, there were significantly (***p<0.01) increased in water intake was found in DH₀ (Diabetic hypertensive control) and DH₂ groups when compared with normal control group and less significant increased water intake in DH₁ and DH₃ groups (**p<0.05) when compared to normal control group (Table 3).

Effect of K channel modulators on food intake

DH₁ group animals shows significant (***p<0.01) increased in food intake, while group shows no significant increased in food intake when compared with normal control group (Table 3).

Discussion

This study presents evidence that K⁺ channel modulators can reduce the severity of diabetes induced hypertension because it acts as antidiabetic as well as antihypertensive agent i.e. K<sub>ATP</sub> channel opener acts as vasodilator and blocker acts as an antidiabetic agent. Modulation of K<sub>ATP</sub> channel activity is an important therapeutic tool for the treatment of diabetic hypertension to avoid the adverse effects. Drugs have been developed which selectively inhibit K<sub>ATP</sub> channels in pancreatic β-cells or open those in vascular smooth muscles. This tissue selectivity is due to the expression of different types of sulphonylurea receptor (SUR1 or SUR2). So the drug used in the treatment of diabetic hypertension must have antidiabetic as well as antihypertensive activity.

Allicin shows potent antidiabetic activity as shown in Table 1. It has been reported that the garlic may affect the insulin secretion from β-cells, release of bound insulin or increase of insulin sensitivity (El-Demerdash et al., 2005). Allicin is the active component of garlic, responsible for enhancing serum insulin activity due to free SH-group. On the other hand, antioxidative property of garlic might be another reason of its beneficial effect on diabetes (Shariatzadeh et al., 2008). Furthermore, it is also suggested that garlic might enhance glucose utilization because it significantly decreases the blood glucose level. It may be due to restoration of delayed insulin response or due to inhibition of intestinal absorption of glucose. This could be due to potentiating of the insulin by release from bound insulin (Eidi et al., 2006; Thomson et al., 2007).

The experimental rats of diabetic hypertensive groups i.e. DH₂ (allicin+nateglinide treated) and DH₃ (allicin+glibenclamide treated) showed potent antidiabetic activity, while rats of DH₁ (allicin) treated group shows less significant antidiabetic activity when compared with DH₁ and DH₂ groups (Table 1). It may be because when
Allicin is given in combination with antidiabetic drugs, it shows the additive antidiabetic effect. Although earlier studies shown that garlic has a relaxant effect on vascular smooth muscle, which appears to be mediated through endothelium by increasing NO production (Ashraf et al., 2005; Oztiirk et al., 1994) some studies suggested that garlic extract might have value as ACE inhibitor to prevent hypertension (Hosseini et al., 2007; Sharifi et al., 2003). Antioxidant as well as antidiabetic effect of garlic (El-Demerdash et al., 2005; Shariatzadeh et al., 2008; Drobiowa et al., 2009) might be responsible for antihypertensive effect because oxidative stress is major cause of hypertension in diabetic patient (De Champlain et al., 2004; Cieriello, 2008; Drobiowa et al., 2009).

In the present study, a significant reduction in SBP, probable reason for this might be allicin hyperpolarized the cell membrane and relaxed the vascular strips concentration-dependently as a K+ channel opener activity (Siegel et al., 1998; Ashraf et al., 2004; Sharifi et al., 2003). DH0 group (allicin+nateglinide treated) shows more potent antihypertensive activity when compared to DH1 (allicin+glibenclamide treated) group (Table 1). It is known that glibenclamide causes hypertension due to blocking of SUR2 (blood vessel) (Seino, 2003). Nateglinide has high affinity to pancreatic SUR1/Kir6.2 channels and very less affinity for blood vessel receptors SUR2A/Kir6.2, so blockade of SUR1/Kir6.2 channels by nateglinide produces antidiabetic effect but not hypertension as a side effect due to free SUR2A/Kir6.2 receptors (Chachin et al., 2003). It means that when combination of nateglinide and allicin is given, allicin is free to bind on SUR2 receptor as opener causing vasodilation while glibenclamide blocks both SUR1 as well as SUR2, causing vasoconstriction.

Results of the present study may suggest that allicin does not act on SUR1 receptor. If allicin had acted on SUR1 receptors as an opener then it should have decreased insulin release and increased blood glucose level, which is not the case. It actually shows in result that there is no rise blood glucose level in DH1 group (Table 1). These data support that allicin may acts as SUR2 opener.

There was decrease in body weight in DH0 (diabetic hypertensive control) group. The reduction in body weight was more prominent in DH0 group (Table 3). Dehydration and loss of body weight have been associated with DM. In diabetic rats, increased food consumption and decreased body weight were observed. This indicates the polyphagic condition and loss of weight due to excessive breakdown of tissue proteins. The decrease in body weight in diabetic rats could be due to dehydration and catabolism of fats and proteins. Increased catabolic reactions leading to muscle wasting might also be the cause for the reduced weight gain by diabetic rats (Rajagopal & Sasikala, 2008). Also hypertension was induced by dexamethasone, it causes decrease in body weight and food intake (Jahng et al., 2008; Carlos & Salaman, 1991). This results in a loss of both fat and lean mass, leading to a significant (**p<0.001) reduction in total body weight in DH0 (diabetic hypertensive control) group.

We also recorded changes in water and food intake. DH0 group showed significant (**p<0.01) increase in food and water intake as compared to normal control group animals. In addition there was significant (*p<0.01) increase in water intake in DH1 group while DH1 and DH2 groups showed less significant (*p<0.05) increase in water intake (Table 3). It is well known that in diabetic condition there is an increase in osmolarity that induces thirst by stimulating thirst center in hypothalamus, causing increased water intake and hyperphagia which is followed by polydipsia. Also it may be due to hypothalamic neuropeptide Y (NPY) because previous study reported that concentrations of hypothalamic NPY in diabetic rats were consistently higher than those found in normal control rats, elevated concentrations of NPY, a very potent central stimulant of eating and drinking, may mediate the hyperphagia and polydipsia characteristic of diabetes (Williams et al., 1988; Sipols et al., 1995). Insulin deficiency in diabetes leads to increased hypothalamic AMPK activity, which contributes to the development of diabetic hyperphagia (Namkoong et al., 2005).

Oral administration of garlic extract and antidiabetic drugs for eight weeks to diabetic rats improved body weight and decreased their food consumption and water intake. This could be due to a better control of the hyperglycemic state in the diabetic hypertensive rats. Decreased Blood glucose could improve body weight in diabetic hypertensive rats.

Conclusion

Diabetes induced hypertension is the most severe complication of present scenario and there is no particular treatment for diabetic hypertension. Considering the literature and the results of our study, allicin may be effective in the treatment of diabetic hypertension. This study may reveal the possible mechanism for antihypertensive activity of allicin by selective opening of SUR2. Furthermore study required to confirm the SUR selectivity of allicin.

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