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To study the anxiolytic effect of different angiotensin receptor blockers on rodent model

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Abstract: **Background**: Hypertension is a major global health problem and is frequently accompanied by anxiety-related disorders and cognitive decline. Angiotensin receptor blockers (ARBs), a widely prescribed antihypertensive class, are also reported to influence central nervous system (CNS) function. **Objectives**: This study compared two commonly used ARBs, losartan and irbesartan, for their influence on anxiety-like behaviour, locomotion and exploration in fructose-induced hypertensive rats. **Methods**: Hypertension was produced in thirty albino rats by providing 10% fructose in their drinking water. The animals were allocated to three groups (n=10 each): control (10% fructose + distilled water), losartan and irbesartan. Treatments were given orally for 60 days. Behaviour was assessed with the open field, head dip and light and dark box tests and the data were analysed by one-way ANOVA with Tukey's post hoc test. **Results**: Losartan raised the number of central square entries and prolonged the stay in the light compartment and it also increased locomotion and exploration, pointing to an anxiolytic action without obvious sedation. Irbesartan markedly lowered peripheral square entries, consistent with anxiolysis, but shortened the time spent in the light compartment, suggesting a prominent sedative component. Both agents altered exploratory behaviour, with irbesartan producing the stronger calming and sedative profile. **Conclusion**: ARBs do not affect CNS behaviour uniformly in hypertensive animals. Losartan may suit hypertensive patients with anxiety in whom sedation is undesirable, whereas irbesartan may be useful where a degree of sedation is acceptable or beneficial. Further work on the neurobehavioural actions of ARBs is warranted, given their possible value in managing hypertension with coexisting anxiety and cognitive problems.

Keywords: Anxiety; Angiotensin receptor blocker; Cage crossing; Hypertension

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INTRODUCTION

Hypertension ranks among the commonest chronic non-communicable conditions globally and continues to be a principal contributor to cardiovascular illness and death (Mills *et al*., 2020). Recent worldwide figures show that its burden is still growing, most notably in low- and middle-income countries, where many patients remain undiagnosed, untreated or poorly controlled (Aggarwal *et al*., 2021). Long-standing high blood pressure predisposes individuals to stroke, ischaemic heart disease, kidney damage and vascular cognitive impairment (Levine *et al*., 2022). Although numerous classes of antihypertensive agents are available, satisfactory blood pressure control is often difficult to achieve owing to non-adherence, drug-related adverse effects and the complex, multifactorial origin of the disease (Carey *et al*., 2022; Hamrahian *et al*., 2022). The two-way link between hypertension and psychiatric conditions, anxiety in particular, has attracted growing interest. Persistent anxiety and psychological stress drive prolonged sympathetic overactivity, disturb the hypothalamic-pituitary-adrenal (HPA) axis, impair endothelial function and stimulate the renin-angiotensin system (RAS); each of these changes can favour the onset and worsening of hypertension (Webb and Werring, 2022). In the opposite direction, poorly controlled blood pressure has been linked with anxiety symptoms, cognitive deficits and a poorer quality of life (Livingston *et al*., 2020). Clinical and laboratory data indicate that anxiety disorders commonly coexist in hypertensive patients, where they can aggravate cardiovascular outcomes and reduce adherence to therapy (O'Donnell *et al*., 2021).

Beyond its cardiovascular functions, the brain RAS also takes part in the regulation of emotion and behaviour. Stimulation of angiotensin type-1 (AT1) receptors by angiotensin II has been connected with the stress response, neuroinflammation, oxidative stress and anxiety-like behaviour (Saavedra, 2021). Blocking AT1 receptors may therefore offer advantages that extend beyond lowering blood pressure. ARBs, routinely used to treat hypertension, have shown neuroprotective, anxiolytic and cognition-modifying actions in a number of experimental studies (Chen *et al*., 2018). Losartan and irbesartan are two of the most frequently prescribed members of this class, owing to their good cardiovascular safety and their ability to reach the central nervous system (CNS). Animal data suggest that losartan can reduce anxiety-like behaviour and reverse stress-related neurobehavioural changes (Ranjbar *et al*., 2018) and that irbesartan exerts neuroprotective and calming effects in rodent models of stress and depression (Ayyub *et al*., 2017).

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While the blood pressure-lowering efficacy of ARBs is well documented, little is known about how individual agents compare in their effects on anxiety-like behaviour and locomotion in the hypertensive state. Earlier work has concentrated mainly on cardiovascular end points and the behavioural consequences of hypertension, as well as their modification by ARBs, have received comparatively little attention. In particular, head-to-head comparisons of losartan and irbesartan in fructose-induced hypertensive animals using validated behavioural paradigms are lacking. This gap is clinically relevant, since psychological comorbidity is common among hypertensive patients and can strongly shape their response to treatment and their quality of life. Accordingly, this study was undertaken to compare the anxiolytic and wider neurobehavioural effects of losartan and irbesartan in rats made hypertensive with fructose, using standard behavioural tests and to establish whether these two ARBs differ in their influence on anxiety-related behaviour.

MATERIALS AND METHODS

Selection and administration of drug

Two ARBs, losartan and irbesartan, were selected for this work. Both drugs were obtained from the pharmacy of a JCIA-accredited hospital. Fresh suspensions were prepared in distilled water each day and the calculated volume was given by mouth, while control rats received distilled water alone.

Choice of animals

The study was designed to examine the CNS effects of different ARBs. Thirty albino rats were procured from the Animal House of Dow University of Health Sciences and acclimatised for one week in the Animal House of the Department of Pharmacology, Faculty of Pharmacy and Pharmaceutical Sciences, before being divided into three groups of ten. The protocol was approved by the Institutional Board of Advanced Studies and Research and all procedures complied with the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals (Abebe *et al*., 2024). CNS screening covered anxiety, memory and exploratory behaviour. Throughout the study, the animals were kept in the animal house of the Department of Pharmacology, Faculty of Pharmacy and Pharmaceutical Sciences, University of Karachi, under controlled lighting (10 h light/14 h dark), humidity (50% and 10%) and temperature (2 to 3 °C). They received freshly prepared standard feed and were housed ten per cage in clean polypropylene cages with standard bedding. Before hypertension was induced, the rats spent one week in the laboratory for training. Their body weight ranged from 120 to 160 g.

Induction of hypertension

Hypertension was produced by giving 10% fructose in the drinking water for 14 days (Xu and Yu, 2022) and fructose intake was maintained for the remainder of the study. The groups were as follows:

Group I = 10% fructose + Distilled water
Group II = 10% fructose + Losartan
Group III = 10% fructose + Irbesartan

Dosing protocol

Doses were adjusted to each animal's body weight and the required dilutions were made freshly in distilled water every day, as described below:

Losartan

The usual adult oral dose of losartan is 50 mg/60 kg once daily (Kumari *et al*., 2022). The animal dose was derived from this on a weight basis using the unitary method.

Irbesartan

The usual adult oral dose of irbesartan is 150 mg/60 kg once daily and the animal dose was likewise derived on a weight basis using the unitary method.

Open field test

The open field test is widely applied to assess locomotion, exploration and anxiety-like behaviour. The apparatus was a square arena (76 × 76 cm) with 42 cm high walls and no roof. Its transparent floor was divided into 25 equal squares of 15 cm each and a 15 × 15 cm central square was marked by hand. Each rat was released in the centre of the arena and the number of peripheral and central squares it entered over the following 10 min was recorded. The arena was wiped with an alcohol swab between animals (Munawwar *et al*., 2024).

Head dip test

Exploratory behaviour was evaluated with the head dip test. The apparatus was a wooden box (35 × 45 × 45 cm) with a glass panel in the centre of its roof and three holes, each 2.5 cm in diameter, on every side (Sarfaraz *et al*., 2014). Each rat was positioned centrally in the apparatus and head dips were counted over the next 10 min. Cage crossing in a familiar setting was recorded with a transparent Perspex cage (26 × 26 × 26 cm) whose floor was fully covered with sawdust. The rats were first allowed to become familiar with the cage, which was kept in a quiet, well-lit room; each animal was then placed inside and the number of cage crossings in 10 min was counted.

Light and dark box test

Anxiolytic activity was measured with the light and dark box test, using a two-chamber apparatus (46 × 27 × 30 cm) made up of one illuminated and one dark compartment. Each rat was first placed in the light chamber and the percentage of time it spent in each chamber, along with the total number of crossings between the chambers, was recorded (Munawwar *et al*., 2023).

Table 1: Effect of drugs on central square crossings in open field test.

Groups	Day 15 Mean ± S.D	Day 30 Mean ± S.D	Day 45 Mean ± S.D	Day 60 Mean ± S.D
10% Fructose + distilled water (Control)	2 ± 1.41	2 ± 0.66	2 ± 1.15	2 ± 1.19
10% Fructose + losartan	$4 \pm 1.41^{**, ++}$	2 ± 1.15	$2 \pm 1.19^{++}$	$4 \pm 1.41^{**, +++}$
10% Fructose + irbesartan	2 ± 1.15	2 ± 1.19	$1 \pm 0.66^{**}$,	$1 \pm 0.66^{**}$

Values are mean ± S.D. (n=10), analysed by one-way ANOVA followed by Tukey's post hoc test. *versus control; + versus irbesartan. */+ P<0.05 significant; **/++ P<0.01 very significant; ***/+++ P<0.001 highly significant.

Table 2: Effect of drugs on open field test (peripheral squares crossed).

Groups	Day 15 Mean ± S.D	Day 30 Mean ± S.D	Day 45 Mean ± S.D	Day 60 Mean ± S.D
10% Fructose + distilled water (Control)	77 ± 2.00	68 ± 2.40	68 ± 2.40	64 ± 2.10
10% Fructose + losartan	$60 \pm 2.74^{***, +++}$	$69 \pm 3.10^{+++}$	$63 \pm 1.78^{+++}$	$65 \pm 2.05^{+++}$
10% Fructose + irbesartan	$33 \pm 1.15^{***}$	$34 \pm 1.69^{***}$	$30 \pm 2.40^{***}$	$29 \pm 2.82^{***}$

Values are mean ± S.D. (n=10); one-way ANOVA followed by Tukey's post hoc test.

Table 3: Effect of drugs on head dip test.

Groups	Day 15 Mean ± S.D	Day 30 Mean ± S.D	Day 45 Mean ± S.D	Day 60 Mean ± S.D
10% Fructose + distilled water (Control)	10 ± 1.82	7 ± 1.05	9 ± 1.24	9 ± 1.24
10% Fructose + losartan	$9 \pm 1.24^{+++}$	$11 \pm 1.63^{**, +++}$	$9 \pm 1.24^{+++}$	$10 \pm 1.82^{+++}$
10% Fructose + irbesartan	$16 \pm 1.88^{***}$	$14 \pm 2.00^{***}$	$14 \pm 2.00^{***}$	$16 \pm 1.88^{***}$

Statistical analysis

Results are presented as mean ± S.D. The groups were compared on days 15, 30, 45 and 60 using one-way ANOVA with Tukey's post hoc test in SPSS version 22. Significance was set at P<0.05, with P<0.01 and P<0.001 regarded as very significant and highly significant, respectively.

RESULTS

Effect of drugs on open field test (central squares crossed)

The influence of losartan and irbesartan on the number of central squares crossed in the open field test is presented in table 1.

Tukey's post hoc test revealed that, compared with the control group, losartan produced a very significant (P<0.01) rise in central square crossings on days 15 and 60. Irbesartan, by contrast, caused a very significant (P<0.01) fall in central square crossings relative to control on days 45 and 60.

When the two ARBs were compared directly, central square crossings were very significantly (P<0.01) higher with losartan on day 15, whereas on day 60 irbesartan produced a very significant (P<0.01) reduction.

Effect of drugs on open field test (peripheral squares crossed)

Table 2 summarises the effects of losartan and irbesartan on peripheral square crossings in the open field test. On post hoc analysis, irbesartan reduced peripheral square crossings highly significantly (p<0.001) relative to control at every time point. Losartan also lowered peripheral crossings highly significantly (p<0.001) versus control, but only on day 15.

In the between-drug comparison, irbesartan produced a highly significant (p<0.001) reduction in peripheral crossings across the whole study period, whereas the highly significant (P<0.001) reduction seen with losartan was confined to day 15.

Effect of drugs on head dip test

The effects of losartan and irbesartan in the head dip test are given in table 3.

Tukey's test showed that irbesartan increased the number of head dips highly significantly (p<0.001) at all time points. Losartan produced a highly significant (p<0.001) rise compared with control on day 30 only. Between the two ARBs, head dips were highly significantly (p<0.001) greater with irbesartan on days 15, 45 and 60.

Effect of drugs on light and dark box test (time spent in light area)

Table 4 presents the effects of losartan and irbesartan on the time spent in the light compartment.

Relative to control, irbesartan caused a highly significant (p<0.001) reduction in time spent in the light area throughout the study, as shown by Tukey's post hoc test. Losartan, on the other hand, produced a highly significant (p<0.001) increase in time spent in the light area on day 60.

Table 4: Effect of drugs on light and dark box test (time spent in light area).

Groups	Day 15 Mean ± S.D	Day 30 Mean ± S.D	Day 45 Mean ± S.D	Day 60 Mean ± S.D
10% Fructose + distilled water (Control)	118 ± 2.16	119 ± 2.70	120 ± 2.78	174 ± 2.40
10% Fructose + losartan	100 ± 2.00^{+++}	118 ± 2.16^{+++}	120 ± 2.78^{*+++}	215 ± 3.23^{***+++}
10% Fructose + irbesartan	68 ± 1.63***	61 ± 2.53***	56 ± 1.94***	55 ± 1.41***

Values are mean ± S.D. (n=10); one-way ANOVA followed by Tukey's post hoc test.

Table 5: Effect of drugs on light and dark box test (number of transitions).

Groups	Day 15 Mean ± S.D	Day 30 Mean ± S.D	Day 45 Mean ± S.D	Day 60 Mean ± S.D
10% Fructose + distilled water (Control)	6 ± 1.88	6 ± 2.88	5 ± 2.05	6 ± 1.88
10% Fructose + losartan	7 ± 1.88^{++}	5 ± 1.82^{+++}	6 ± 1.88^{+++}	6 ± 1.88^{+++}
10% Fructose + irbesartan	4 ± 1.33	1 ± 0.94***	3 ± 1.24**	1 ± 0.94***

n = 10; values are mean ± S.D. Statistical significance was determined by one-way ANOVA with Tukey's post hoc test. * versus control; + versus irbesartan. */+ P<0.05 significant; **/++ P<0.01 very significant; ***/+++ P<0.001 highly significant.

Comparing the two drugs, time spent in the light area after 60 days of treatment was highly significantly (p<0.001) longer with losartan. Effect of drugs on light and dark box test (number of transitions)

The number of transitions between compartments in the light and dark box test is shown in Table 5. Tukey's post hoc test revealed no significant change in transitions with losartan versus control at any time point. Irbesartan likewise had no significant effect after 15 days, but it reduced transitions highly significantly (p<0.001) on days 30 and 60 and very significantly (p<0.01) on day 45 in comparison with control.

Relative to losartan, irbesartan produced a highly significant (p<0.001) fall in transitions on days 30, 45 and 60.

DISCUSSION

(Levine, 2022; G Livingston, 2020) Raised blood pressure is an established risk factor for stroke, which can in turn lead to vascular cognitive impairment and vascular dementia (VaD) (Levine *et al*., 2022). Impaired cognition and compromised brain health have long been recognised in people with symptomatic cerebrovascular or cardiovascular disease (Livingston *et al*., 2020). More recent observations indicate that cognitive decline may be present even when cardiovascular risk factors exist without overt cardiovascular disease and several investigators have reported an association between hypertension and anxiety. A systematic review published in 2009 concluded that antihypertensive therapy may lower the incidence and slow the progression of dementia, although the benefit differs between drug classes (Lennon, 2024). Against this background, the present study compared the CNS effects of two commonly prescribed ARBs (Thompson, 2020).

To this end, fructose-induced hypertensive rats were subjected to the open field, head dip and light and dark box tests (Thompson *et al*., 2015), with the aim of identifying which ARB, losartan or irbesartan, might be preferable for hypertensive patients who also suffer from anxiety or cognitive impairment. (Srinivasan, 2003; Ranjbar, 2018) In the open field test, losartan very significantly increased central square entries on days 15 and 60, suggestive of an anxiolytic action, while the reduction in peripheral square entries was highly significant only at the start of treatment (Srinivasan *et al*., 2003). This early fall in peripheral locomotion reflects a calming influence of losartan that is in keeping with its reported anxiolytic activity (Ranjbar *et al*., 2018). The suppression of locomotion was, however, smaller than that seen with irbesartan, being evident only on day 15. In the head dip test, losartan increased head dipping highly significantly, but only on day 30. In the light and dark box, it markedly prolonged the time spent in the light compartment, a change regarded as characteristic of anxiolytic drugs (Kulesskaya and Voikar, 2014). Taken together, these findings indicate that losartan has anxiolytic potential without the sedative element observed with irbesartan. Considerable evidence implicates overactivity of the brain RAS as an important trigger of anxiety (Lanza *et al*., 2021); ARBs and losartan in particular, may therefore relieve anxiety through this pathway, although this mechanism requires confirmation (Ayyub, 2017; Waeber, 2003). With chronic administration, irbesartan lowered central square entries in the open field test and significantly reduced peripheral square entries at all time points. The reduced exploration of the central zone may stem from a calming effect of the drug (Ayyub *et al*., 2017) and the parallel decline in peripheral locomotion points in the same direction, lending further support to an anxiolytic property of irbesartan. Irbesartan also significantly increased head dipping, again suggesting anxiolytic potential (Waeber and Burnier, 2003). In the light and dark

box, it shortened the time spent in the light compartment and reduced the overall number of transitions. These changes are probably explained by diminished locomotion and the calming action of irbesartan, which was also apparent in the open field and cage crossing tests. The shorter stay in the light area may further reflect a sedative effect, since Ajao and Akindele (2013) reported a similar reduction with diazepam and attributed it to sedation. Overall, irbesartan appears to carry greater sedative potential, so the timing of its administration may need attention.

CONCLUSION

Anxiety and stress disorders are associated with increased formation of angiotensin II in the brain and with up-regulated transcription and expression of brain angiotensin receptors, which may explain the anxiolytic activity observed here after ARB treatment. Losartan showed anxiolytic potential without a sedative component, whereas irbesartan displayed more pronounced sedative potential, suggesting that the time of day at which it is given should be considered.

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Author's contributions
Masood Ahmed: Conceptualization, Experimental Research and analysis; Laweaza Sadiq: Manuscript write-up;

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Data availability statement
The data will be provided on request by the corresponding Author.

Ethical approval
All the protocols of the experiments were adhered to the ethical guidelines for the care and use of laboratory animals, approved by the Institutional Board of Advanced Studies and Research.

Conflict of interest
None

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