Oestrogen and its effect on hypertension

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Abstract

Non-menopausal women have a lower incidence of hypertension and cardiovascular complications compared to age-matched men. This cardiovascular advantage is thought to be the result of oestrogen's antihypertensive effects. However, results of current studies contradict each other and therefore our knowledge on the topic is limited.

Oestrogen has been shown to decrease the production of oxidative stress in the vasculature. Oxidative stress has been linked to high blood pressure (BP) and therefore its decrease is thought to aid in prevention of high BP. Excessive vasoconstriction is opposed by nitrogen oxide. However, nitrogen oxide production decreases with age and therefore poses a hypertension risk.

Studies in mice have shown that low doses of oestrogen given to non-ovariectomised mice have the effect of increasing oxidative stress. Additionally, high doses of oestrogen in ovariectomised mice have shown the same effect, however, low doses were shown to decrease oxidative stress.

Surprisingly, it is shown that the oestrogen in oral contraceptive pills (OCPs) given to premenopausal women causes an increase in BP. The effects of hormone-replacement therapy on BP have been shown to depend on the administration route.

Hypertension

Long-term hypertension is associated with a range of cardiovascular diseases such as coronary heart disease and stroke.[1] In New Zealand, hypertension affects 31% of the population.[1] The American Heart Association reports that on average, more men than women have high BP, this difference disappears at around 55–64 years of age.[2] The prevalence of hypertension, regardless of sex, increases with age.[2]

Sex is a large determinant in the likelihood of developing hypertension.[3] It has been found that non-menopausal women are at lower risk of developing hypertension than men; however, this difference disappears after menopause.[3] The complexity of hypertension combined with the high prevalence of the condition has led to numerous attempts to elucidate the pathophysiology of hypertension and its possible treatments. One of the suggested connections is the link between the hormone oestrogen, the renin-angiotensin-aldosterone system (RAAS), and oxidative stress.

Oestrogen

Oestrogen is a sex hormone mainly produced by the ovaries.[4] Its general functions include promoting the growth of secondary female sex characteristics and triggering ovulation.[4] As hypertension prevalence increases post-menopause, it is suggested that oestrogen, more specifically the form 17β-oestradiol (E2), provides an antihypertensive effect on BP that is otherwise lost post-menopause.[4]

It has been shown that 17β-oestradiol activates antihypertensive mechanisms such as stimulation of nitrogen oxide (NO) release and a decrease in oxidative stress,[5] both of which result in relaxation of vascular smooth muscle, thereby conferring protection from excessive vasoconstriction.[5]

The renin-angiotensin-aldosterone system

The RAAS is a mechanism regulating BP and blood volume.[6] It is activated by a reduction in glomerular filtration rate and one of its final effectors is angiotensin II (Ang II). Ang II causes vasoconstriction, production of vasopressin, and the release of aldosterone. All these actions eventually lead to an increase in water reabsorption, leading to an increase in BP.[6]

The angiotensin II receptor 1 and oxidative stress

One of the effector receptors of Ang II is the angiotensin receptor type 1 (AT1).[7] AT1 is expressed in many parts of the body, but particularly in vascular smooth muscle cells (VSMC). One of the effects of the VSMC AT1 receptor is production of reactive oxygen species (ROS).[8]

ROS are produced in the Ang II pathway as an intracellular signalling molecule. Usually, ROS are in balance with antioxidants to prevent oxidative damage, however, an excess in ROS production results in an imbalance, termed oxidative stress.[9] Vessel wall oxidative stress has been found to be involved in the development of hypertension. AT1 is mainly linked to production of the ROS superoxide anion (O_2^-) by the nicotinamide adenine dinucleotide phosphate (NADPH) oxi-

dase in the VSMC. NADPH is a part of the electron transport chain involved in the aerobic production of ATP.[9] ATP is necessary for contraction and therefore vasoconstriction. When the vasoconstrictor Ang II binds to AT1, production of ATP, and therefore activation of the electron transport chain, will occur. Normally, O_2, which is created as a by-product, would be reduced to water.[9] However, when it is produced in excessive amounts it can escape the reduction and gain an electron to become O_2^-.[9]

Experimental studies in rodents have shown that Ang II causes an increase in NADPH activity, leading to an excess production of O_2^-.[8] It has also been shown that O_2^- alone can cause vasoconstriction, which contributes to the development of hypertension.[10] O_2^- production can also affect the activity of Ca^{2+} and K^+ ion channels through the activity of CaMKII, which alters contraction of muscles, adding further to vasoconstriction[11]

Nitrogen oxide

Additional evidence suggests O_2^- interacts with nitrogen oxide (NO). NO is produced by the endothelium of blood vessels and causes vasodilation, contributing to the lowering of BP.[5] NO generates peroxynitrite ($ONOO^-$) by reaction with O_2^-.[5] By this action, the amount of NO is reduced, causing a reduction in its vasodilative effects.[5] But, as mentioned, $ONOO^-$ is created, which can form peroxynirous acid, a very reactive oxygen species of similar effects as O_2^-.[5] The absence of NO, and therefore impaired vascular relaxation, is one of the suggested mechanisms for the development of hypertension.

Oestrogen and oxidative stress

Deficiencies in antioxidants have been found in patients suffering from hypertension.[12] This suggests that not only are ROS increased in hypertension, but also the concentrations of antioxidants are decreased. It has been shown that oxidative stress levels tend to be higher in males than in females and that when induced by a dose of Ang II, a larger amount of O_2^- is produced in male arteries than female arteries.[13,14] This suggests that there is a difference between either the oxidative stress levels or in the amount of ROS the body can produce between males and females.

Treatment of ovariectomised rats with E2 has been shown to reduce the expression of some NADPH regulatory subunits, suggesting that the production of O_2^- by NADPH can be regulated by E2.[15] Upon exposure to Ang II, the expression of other NADPH regulatory subunits increases and this can then be normalised by treatment with E2.[16]

It has also been found that ovariectomised rats, which cannot produce their own E2, have an increase in AT1 receptor abundance and that this effect can be prevented by E2 replacement.[17] This E2-induced AT1 reduction occurs through a decrease of AT1 translation and a reduction in its binding capacity with Ang II.[17] This suggests that E2 controls the abundance of AT1 receptors and thereby regulates Ang II induced production of O_2^-. By decreasing O_2^- production, E2 protects against oxidative stress. As stated above, an increase in oxidative stress has been linked to hypertension, but the presence of oxidative stress does not necessarily lead to hypertension. Unfortunately, this study did not assess the BP of the rats.

Oestrogen dose and blood pressure

A study by Subramanian et al has explored chronic exposure of non-ovariectomised rats to low levels of E2 and its connection to hypertension.[18] Rats exposed to 20 ng/day of E2 (low dose) had an increase in mean arterial pressure compared to controls. In addition, the E2-treated rats had significantly elevated O_2^- levels.

On the other hand, a study by Meng et al (19) has shown that ovariectomised mice do not have a change in BP in response to 20 ng/day of E2 (low dose).[19] This study also showed that the ovary reduction itself causes an increase in oxidative stress and that this is reversed by a low dose of E2. Ovariectomised mice receiving a high dose of E2, 4.2 µg/day, had an increase in oxidative stress in their vasculature and no significant increase in BP. This is a surprising finding since it conflicts with those of many other studies (see above) that demonstrate how oestrogen leads to a decrease in oxidative stress. The findings of these authors also suggest a dose-dependent association.

Oestrogen and oral contraceptive pills

Oestrogen is the main ingredient in most oral contraceptive pills (OCPs).[20] OCPs are taken mainly by non-menopausal women, so it is supplemental to normal levels and would be comparable to oestrogen given to non-ovariectomised mice. A review by Woods et al has shown that the majority of subjects prescribed OCPs either had an increase or no change in BP.[21] This is again a surprising finding as it is conflicts with results of other studies on the anti-oxidative stress effect of oestrogen.

It is important to consider that OCPs also contains progesterone, which may confound the effects that are being attributed to oestrogen only. The Woods et al article quotes sources supporting the notion that progesterone has an effect on BP.[22] However, other evidence suggests that the effect is negligible.[23] Further consistent research on this topic is required to confirm our understanding of progesterone and its effect on BP.

Oestrogen and hormone replacement therapy

During menopause, the ovarian production of oestrogen decreases and the likelihood of hypertension increases.[3] The onset of menopause is accompanied by many symptoms such as insomnia and migraines. Hormone replacement therapy (HRT) is a hormonal supplement aimed at easing the transition from high to low levels of oestrogen production and to relieve menopausal symptoms.[24] It is also speculated to have an effect on cardiovascular complications such as hypertension.

A study by Ichikawa et al explored the effects of transdermal and oral delivery of low doses of HRT.[24] They found that transdermal delivery of HRT resulted in a decrease in mean BP, but no change in Ang II plasma levels. Additionally, oral delivery of HRT did not change BP, but did increase the Ang II plasma levels. The levels of bradykinin, a vasodilator, decreased in the transdermal HRT group and increased in the oral HRT group. The suggested mechanism includes transdermal oestrogen activation of NO-mediated relaxation of vasculature. This leads to downregulation of sympathetic activity, leading to a decrease in AT1 messenger ribonucleic acid concentration, leading to decreased vasoconstriction and oxidative stress.[25]

However, oral HRT resulted in an increase in Ang II and bradykinin levels, but had no effect on BP. It has been suggested that BP did not change due to the increase in bradykinin alongside Ang II, as their actions are opposite. Therefore, HRT has varying effects on BP depending on its administration.

It is important to consider that while post-menopausal women do not produce as much oestrogen as non-menopausal women, they still produce a small amount.[3] Therefore, post-menopausal women are not strictly comparable to ovariectomised rodents. This is a limitation in study design that appears to be repeated in most previous research. A new rodent model, which is comparable to post-menopausal women, is necessary for future research.

Conclusion: the role of oestrogen

In conclusion, the role of oestrogen in hypertension is complex and not well understood. Studies reviewed in this article have demonstrated that the addition of oestrogen above its normally produced levels (i.e. non-ovariectomised rats receiving oestrogen) is linked to an increase in BP and an increase in oxidative stress. Additionally, it is noted that giving low doses of oestrogen to ovariectomised rats decreases oxidative stress, but that giving high doses increases oxidative stress. These findings demonstrate that the complexity of oestrogenic action is beyond a simple reduction of oxidative stress effect.

Finally, it is important to recognise that the most valuable studies are those that include results from humans, as it is ultimately the oestrogen received by women in the forms of OCPs and HRT that is of interest. Further research on the effect of varying doses of oestrogen in OCPs and HRT is required.

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Conflicts of Interest

Michaela is a student reviewer for the NZMSJ. This article has gone through a double-blinded peer review process applied to all articles submitted to the NZMSJ, and has been accepted after achieving the standards required for publication. The author has no other conflict of interest.

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