What role do adrenoreceptor polymorphisms play in modifying cardiovascular responses in obstructive sleep apnoea?

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ABSTRACT
OSA (obstructive sleep apnoea) is a common condition that is strongly associated with cardiovascular disease. It is remains unclear what role OSA plays in determining cardiovascular risk. The immediate physiological changes that occur during upper airway obstruction are potential contributors to cardiovascular risk in OSA. These changes include increased sympathetic activity, which is responsive to treatment of OSA with CPAP (continuous positive airway pressure). In this issue of Clinical Science, the possible role of a common polymorphism in the β₁-adrenoreceptor [R389G (Arg389Gly)] has been investigated by Börgel and co-workers. Measurements of heart rate and blood pressure in untreated OSA patients were not related to the R389G polymorphism. There were changes in heart rate and diastolic blood pressure with CPAP treatment that were related to this polymorphism. Reduction in heart rate with CPAP treatment was associated with the R389R genotype. By contrast, a reduction in diastolic blood pressure was associated with the Gly389 carriers. These findings are intriguing, but difficult to fully explain. Further study is needed to determine if there is an important role of the R389G polymorphism in modifying cardiovascular responses among OSA patients.

Key words: β₁-adrenoreceptor, continuous positive airway pressure, obstructive sleep apnoea, sympathetic nervous system, R389G (Arg389Gly) polymorphism.
Abbreviations: BP, blood pressure; CPAP, continuous positive airway pressure; Gₛ-protein, stimulatory G-protein; HR, heart rate; OSA, obstructive sleep apnoea.
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particularly in regards to finding ways to reduce this risk.

Understanding the underlying mechanisms of increased cardiovascular risk associated with OSA is important if appropriate ways of dealing with this risk are to be found. The immediate physiological changes associated with upper airway obstruction are thought to predispose to vascular disease; particularly important being hypoxia, BP (blood pressure) surges, central nervous system arousal and sympathetic activation. Measures of sympathetic activation are increased in those with OSA [8] and CPAP reduces levels of sympathetic activity [9]. Sympathetic activation appears to predispose to cardiovascular disease, in part, by direct effects on HR (heart rate), cardiac contractility, vasomotor tone and BP.

Sympathetic nervous activity operates through a number of adrenoreceptors. When an endogenous agonist [e.g. adrenaline (epinephrine) or noradrenaline (norepinephrine)] binds to the β1-adrenoreceptor it results in coupling to G-proteins (stimulatory G-proteins) and activation of adenylate cyclase and other pathways. The receptor is expressed in a number of tissues, including the myocardium, where it has inotropic and chronotropic effects. A single-switch nucleotide polymorphism of glycine to arginine at intracellular amino acid 389 of this receptor has been shown to have functional consequences. The arginine variant has 'gain-of-function' effects due to enhanced G, coupling and increased cellular adenylate cyclase activity. This arginine variant may be important in the development of hypertension, since case-control data show that this variant occurs at increased frequency in hypertensive patients [10].

In this issue of Clinical Science, Börgel and co-workers [11] have investigated the role of the R389G (Arg389Gly) polymorphism in the β1-adrenoreceptor gene in modifying HR and BP among patients with moderate-to-severe OSA. The authors [11] assessed 309 consecutive untreated OSA patients who were referred to a sleep clinic and characterized them into three β1-adrenoreceptor genotypes (i.e. G389G, R389G and R389R). The three adrenoreceptor genotypes were similar in important baseline characteristics, such as age, gender, body mass index, apnoea/hypopnoea index and overnight oxygen desaturation measurements, as well as cardiovascular history. The adrenoreceptor groups were also similar in the outcome measures of HR and BP. Furthermore, the genotype groups were not significant in a linear regression model with HR and BP as the dependent variables. The effect of 6 months of CPAP on HR and BP was also assessed in a subgroup of 148 patients who ‘tolerated’ CPAP and in whom antihypertensive medication was unchanged during follow-up. The number of G389G patients in the CPAP follow-up was small and so this group was combined with the R389G group in these analyses. The R389R genotype was associated with a greater reduction in HR than with the other two variants. By contrast, diastolic BP was significantly reduced only in the Gly389 carriers. There were no significant effects of CPAP on systolic BP.

These results are somewhat confusing. It might have been anticipated that those with the R389R variant would have an increased sympathetic response to upper airway obstruction which would, in turn, manifest in increased HR and BP. There are a number of possible explanations for the lack of association of this variant with increased HR and BP. The role of the polymorphism among OSA patients may be small and it may be drowned out by other factors influencing HR and BP in which case a larger sample size may be required. The authors [11] may have used inadequate methods to characterize phenotypic variants, for example 24 h ambulatory BP monitoring may have been better than measurements at three time points. This is particularly relevant to nocturnal BP dipping, since there were no nocturnal measurements made in this study.

The authors [11] take their investigation one step further by assessing changes in their outcome measures (HR and BP) with CPAP; a powerful strategy to assess the functional significance of these adrenoreceptor polymorphisms. The reduction in HR with CPAP seen in the R389R patient group suggests that the polymorphism has a functional role, at least in determining treatment response. However, counterintuitively, only the Gly389 variants show a reduction in diastolic BP with CPAP. This latter result is difficult to reconcile with the findings on HR.

Overall, Börgel and co-workers [11] were unable to find a convincing role for the R389G polymorphism in modifying HR and BP in their OSA patients. However, this intriguing study suggests that further investigation of the R389G polymorphism is warranted. In particular, studies of larger community samples with 24 h ambulatory BP monitoring may be revealing. It seems worth investigating the role of this polymorphism in failure of nocturnal BP dipping found in some patients with OSA. One study suggests that β-blocker medication is the most efficacious antihypertensive medication to use in OSA patients [12]. Further study of the R389G polymorphism may help better tailor the use of β-blocker medication in hypertensive OSA patients.

REFERENCES


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