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VIEWPOINT

The 'scent' and 'flavour' of hypertension

F.P. Cappuccio*

[a] University of Warwick, WHO Collaborating Centre for Nutrition, Warwick Medical School, Division of Health Sciences (MHWB), Gibbet Hill Road, Coventry, CV4 7AL, UK
[b] University Hospitals Coventry & Warwickshire NHS Trust, Coventry, CV2 2DX, UK

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Raised blood pressure (or hypertension) is the commonest underlying cause of cardiovascular disease, responsible for the most deaths, morbidity and disability in the world [1]. The natural development of hypertension is determined by a complex interaction between a polygenic background of risk which is modulated by epigenetic interactions with a number of clearly identified environmental and behavioural – yet modifiable – factors. The latter include metabolic and nutritional influences like positive energy balance and obesity, and excessive salt consumption. In the last few decades, high as well as middle and low-income countries have recorded an epidemic of obesity, diabetes and hypertension, attributable in great part to a shift in behavioural aspects of daily living like overeating, increased portion sizes, reduced energy expenditure due to physical inactivity, increase in consumption of low quality food rich in sugar, fat and salt. The need for a more comprehensive understanding of the factors that drive food choices has led biomedical research to studying the relationships between specific food preferences and their consumption. Neuro- and chemo-sensory pathways, like those regulating odours and flavours, are well known to determine human behaviour towards food and drink consumption. These pathways may lead to the perception of perfect happiness – or *bliss* – and, for food, the *bliss point* is defined as the "quantity of consumption where any further increase would make the consumer less satisfied" [2].

One well studied food component with its neuro- and chemo-sensory pathways is sodium. High sodium consumption leads to a rise in blood pressure and, eventually, to hypertension and cardiovascular complications like strokes, heart attacks and kidney and heart failures [3]. A major factor underlying excess sodium intake is human preference for salted foods. Although this preference may well be shaped by innate (genetic perhaps) components, dietary experience contributes significantly to the liking of salt and its consumption, with important effect of dietary experiences in shaping salt taste responses being detectable very early in life [4]. All known human societies, even the most primitive, consume per capita more salt than they physiologically require. Salt has been referred to as the "primordial addiction" [5]. The consumption of salt began to rise between 5000 and 10,000 years ago [6]. The Neolithic revolution saw a move away from traditional hunter-gatherer practices and the introduction of human settlement, agriculture, and animal husbandry [7]. These practices marked profound changes to the composition of the human diet and to the availability of various foods, finally culminating in today's modern diet [8]. Salt became a necessity of life and the first international commodity of trade [6]. It became a way to affirm "social distance" [9] because of its unique properties of enhancing flavours and fulfilling hedonic rewards [10]. This mechanism was later understood to be an acquired characteristic of salt taste bud regulation [11]. Probably the most important factor leading to an increase in human salt consumption was its power to preserve food against decay [6]. With the advent of electricity and refrigeration the need for salt as a preservative rapidly diminished. However, the human consumption of salt has not declined and has increased in

* University of Warwick, Warwick Medical School, Gibbet Hill Road, Coventry, CV4 7AL, UK.
E-mail address: f.p.cappuccio@warwick.ac.uk.

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some instances [12], contributing to the development of chronic diseases. Landmark studies in the field have established that relatively short periods of increased sodium intake result in an increase in sodium preference in the absence of changes in salivary electrolytes or recognition threshold [13]. These findings suggest that high sodium intake drives salt preference and that the more salt we eat, the more salt we demand. This concept is at the basis of the food and drink manufacturing strategy to maintain salt content of food high to sustain consumer demand and profit [14]. This contributes to high salt intake, high burden of hypertension and cardiovascular disease [15]. However, these neuro- and chemo-sensory pathways often follow a bidirectional route. For example, studies have shown that a reduction in the sodium content of white bread by a quarter can be delivered over a short time period, while maintaining consumer acceptance [16], due to up-regulation of taste buds. A strategy of gradual reduction in the salt content of bread and other food items has been implemented with success in many countries [17], backing up the current World Health Organization policy strategy of population salt reduction by gradual reformulation of the salt content of processed food without consumer detection [18].

In the abovementioned context, the study by Liu et al. in the present issue of the Journal [19] is a valuable stimulus to further discussion. The authors report the relationships between self-reported taste and smell perception assessed by questionnaire at baseline (in 2012) and the change in blood pressure that occurred in the subsequent two years, in a population of 5190 Chinese adults (men-to-women ratio 4:1) from the Kailuan community of the city of Tangshan in northern China. The exposure (taste and smell perception) was measured by using a limited version of the National Health Interview Survey (NHIS-D) [20]; one of four questions were used for smell perception and one of three for taste perception. The results were grouped in four categories: self-reported problems with both smell and taste perceptions, problems with only one of the senses, neither. The majority (n = 5051 or 97.3%) did not report any problem with either senses whilst only 30 (0.6%) reported problems in both senses. This prevalence is comparable to that seen in a US population screened with a similar tool in 1994–5 [20]. Blood pressure was measured twice at baseline with a mercury sphygmomanometer and twice at follow-up with an electronic blood pressure device (Omron HEM-8102A). After adjustments for multiple confounders the only group that showed a rise in blood pressure over the two years was the small group of 30 individuals reporting both smell and taste problems. The authors cautiously conclude that the results suggest an association between chemosensory functions and blood pressure. The study is an example of the nascent field of olfactory and taste epidemiology [20]. What do the results mean? How are they directing to a better understanding of the pathophysiology of hypertension? Are there limitations we need to consider?

The first step to follow before we accept epidemiological observational evidence is to establish the validity of the findings by ruling out three important alternative explanations to the findings: (a) are the results likely to be due to chance? This question is answered by statistical inference. In the present study the change in blood pressure in the group combining altered smell and taste perception is higher only for systolic blood pressure and mean arterial pressure; (b) are the results due to bias? One aspect that might introduce an important bias is the use of different methods of measuring blood pressure between the two periods, the first clearly open to biased readings more than the second [21]. Furthermore, there is no mention of whether blood pressure observers were masked to the sensory group of the participants; salt intake was inferred by a simple question which is unable to identify individual levels of salt consumption [22,23], so that the results could be biased and open to residual confounding; finally, the assessment of exposure by questionnaire may suffer from lack of validation in populations other than US, as clearly indicated in the wide global variations in sensory sensitivity worldwide [20]; (c) are the results due to confounding? The combined altered sensory group was significantly older, it had disproportionately more men, it was heavier with fewer physically inactive participants. However, the final model managed to take these differences into account.

The application of some of the Bradford–Hill criteria for causality [24] to this study may help address the question of causality. The reported *effect size*, although limited to systolic blood pressure in the combined altered sensory group only, is large enough to represent an important health effect. There is lack of similar studies to assess the *consistency* of results across different persons and places and their *specificity*. The prospective design provides evidence of *temporality* between the exposure (sensory alteration) and the effect (change in blood pressure). There does not seem to be a *biological gradient*, since the effect is only detected when both smell and taste modalities are altered in the same person. The authors provide some suggestions of *plausible mechanisms* to explain the results; they postulate either an effect mediated by epithelial sodium-channels present not only in the kidneys but also in olfactory receptors involved in the regulation of renin secretion, hence blood pressure [25], or the induction of olfactory receptors by gut microbiota [26] that may somehow lead to a rise in blood pressure.

In conclusion, this study provides an interesting approach to a totally new area of research by the application of epidemiology. However, the field is still in its infancy. Measures of exposure are primordial and, as yet, not properly validated. Control for important confounders will require greater attention to more accurate measurements, as for salt intake as a possible important mediator or confounder.

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