Smell perception in normal tension glaucoma patients

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Purpose: The aim of this study was to quantify the ability to identify odors in normal tension glaucoma (NTG) patients and healthy subjects with and without a primary vascular dysregulation (PVD).

Methods: Both self-assessment of smell perception and evaluation of odor identification by means of the 12-item odor identification test (“Sniffin’ Sticks”) were performed in the following groups of subjects: 1) 18 NTG patients with PVD (G+), 2) 18 NTG patients without PVD (G-), 3) 18 healthy subjects with PVD (H+) and 4) 18 healthy subjects without PVD (H-). The subjects self-assessment of smell perception was evaluated before the Sniffin’ Sticks test by asking them to judge their ability to identify odors as either “average,” “better than average,” or “worse than average.”

Results: Subjects with a PVD (G+ and H+) can identify odors significantly better than those without a PVD (G- and H-); in a score scale of 1–12 the score point difference=2.64, 95% CI=1.88–3.40, p<0.001). No significant differences in odor identification was found between NTG (groups G+ and G-) and healthy subjects (groups H+ and H-; score point difference=-0.14, 95% CI=-0.9–0.62, p=0.72).

Conclusions: Subjects with a PVD can identify odors significantly better than those without a PVD.

Smell perception can have a significant impact on our lives [1]. When the sense of smell is lost, it is not just that we cannot differentiate between different smells or enjoy what we eat or drink but we are also not as alert to dangers [2]. Similarly, an enhanced perception of the sense of smell may be just as disturbing [3,4]. The increased sense of smell to different odors can be overwhelming enough to cause nausea, sneezing, headaches or eye pain [5,6].

Disturbances in smell perception are not infrequent [7,8], particularly in patients with neurodegenerative diseases such as Parkinson disease [9], for instance. Olfactory dysfunction among subjects below 65 years of age is more frequent than previously reported [10]. Patients often complain to their physicians about both disturbances of hypoa- and hyperosmia [11]. We have had similar experiences with normal tension glaucoma patients (NTG). Our clinical observations implied that those patients with the better sense of smell had a primary vascular dysregulation (PVD).

PVD is an inborn predisposition to respond different to various stimuli [12,13]. PVD individuals tend to more often have: cold hands or feet even in the summer [14], a reduced feeling of thirst [15], a low blood pressure especially when they are young [16], a longer sleep onset time [17], migraines in comparison to non-PVD subjects [18], and an altered drug sensitivity due to differential expression of ABC transporter proteins [19].

Other leading signs of PVD include increased level of Endothelin-1 [20], blood-pressure dependent Endothelin-

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METHODS

Participants: Patients with normal tension glaucoma (NTG) were recruited from the University Eye Clinic Basel (Basel, Switzerland) between January 2009 and December 2009. Healthy volunteers, age and sex matched to NTG patients, were recruited after a notification in the University Clinic informed potential volunteers of the opportunity to participate in a scientific research project. Ethical approval was obtained.
from the local medical ethics committee, and written informed consent was received from all subjects before entry into the study. The study was designed and conducted in accordance with the tenets of Declaration of Helsinki.

Patients with NTG had to meet the following inclusion criteria: (1) untreated intraocular pressure (IOP) less than 21 mmHg on multiple measurements, (2) progressive changes in either visual fields or optic nerve cupping, and (3) the absence of other known causes of optic neuropathy than glaucoma.

PVD was defined as being present (PVD+) if the subjects answered three of the following seven questions with “Yes,” and it was defined as being absent (PVD-) if the subjects answered less than three questions with “Yes”: 1) Do you suffer from cold hands or feet even in summer [14], 2) Do you have trouble falling asleep, especially when you are cold [17], 3) Are you seldom thirsty and do you have to remind yourself to drink enough [15], 4) Do you suffer from tinnitus [13], 5) Do you suffer from migraine attacks [18], 6) Do you have a rather low blood pressure [16], 7) Do you react sensitively to certain medications [19]. Demographic data of the different groups of participants are given in Table 1.

**DISCUSSION**

In the present study we found that both NTG patients and healthy individuals having a PVD are able to identify various odors better than those without a PVD. As previously mentioned, individuals with a PVD on average tend to respond different to different stimuli [13]. When drugs, for example, are prescribed to PVD subjects they often respond stronger, at times even violently to certain class of drugs. Similarly, they respond less than the average person to a few other classes of drugs. This might be due to a different expression of the ABC transport proteins in these PVD individuals [19].

Proteins also play a role in smell perception. Odorant binding proteins, which are found in the human olfactory mucus [36], bind to different odorants. They are small

| Group | Mean age | N  | Gender   | Male | % | N  | Female | % |
|-------|----------|----|----------|------|---|----|--------|---|
| G+    | 61.6     | 18 | Male     | 9    | 50| 9  | 50     |   |
| G-    | 58.5     | 18 | Male     | 3    | 17| 15 | 83     |   |
| H+    | 56.3     | 18 | Female   | 10   | 56| 8  | 44     |   |
| H-    | 53.4     | 18 | Female   | 9    | 50| 9  | 50     |   |

Demographic data of the different groups of participants showing number (N) of participants in each group, mean age and gender distribution. G+=NTG patients with PVD; G-=NTG patients without PVD; H+=Healthy subjects with PVD; H-=Healthy subjects without PVD; PVD=Primary vascular dysregulation.

**RESULTS**

Results of the subject’s self-assessment of smell perception before Sniffin’ Sticks test are given in Table 2. There was no significant interaction between NTG and PVD (p=0.94), indicating the same score difference in each PVD group. Consequently, the interaction was deleted from the regression model. Subjects with a PVD (G+ and H+) could identify odors significantly better than those without a PVD (G- and H-; p<0.001; Figure 1). No significant differences in odor identification was found between NTG (G+ and G-) and healthy subjects (H+ and H-; p=0.72). No change was observed after correcting for age. Subjects with a better self assessment before Sniffin’ Sticks test had significantly higher score points (p<0.001; Table 3).
abundant extracellular proteins belonging to the lipocalin superfamily [37-39]. These proteins, secreted by the olfactory epithelium in the nasal mucus of vertebrates, are carrier proteins [40]. It is thought that these proteins act as lipophilic ligands which transfer odorants across the mucous layer to the receptors and thereby increase the concentration of the odorants in the layer, relative to air [41-43]. A differential expression of these odorant binding proteins, similar to the differential expression found in ABC transport proteins, may be one explanation for the altered smell perception in PVD subjects.

Olfactory genes form the largest multi-gene family in humans [44,45]. These genes encode olfactory receptors, which interact with odorant molecules in the nose to initiate a neuronal response that triggers the perception of smell. These olfactory receptors are G protein-coupled receptors; upon odorant binding, these receptors couple to G proteins, resulting in an increase in intracellular cAMP levels and subsequent receptor signaling [46]. The altered smell

### Table 2. Self-assessment of Smell Perception Before Sniffin' Sticks Test. Scores are given in %.

| Group | N  | Average % | Better than average % | Worse than average % |
|-------|----|-----------|-----------------------|----------------------|
| G+    | 18 | 39        | 50                    | 11                   |
| G-    | 18 | 56        | 0                     | 44                   |
| H+    | 18 | 33        | 61                    | 6                    |
| H-    | 18 | 11        | 11                    | 78                   |

This table depicts the subject’s self-assessment of their smell perception prior to the Sniffin’ Sticks test. The participants were asked to judge their ability to smell as either “average”, “better than average” or “worse than average”. In the table, G+=NTG patients with PVD; G-=NTG patients without PVD; H+=Healthy subjects with PVD; H-=Healthy subjects without PVD; PVD=Primary vascular dysregulation.

Figure 1. Sniffin’ Sticks score results in healthy and normal tension glaucoma (NTG) subjects. Healthy subjects with a PVD as well as glaucoma patients with a PVD could identify odors better than those without a PVD.
perception in PVD subjects could potentially also be due to an altered expression of these receptors.

As with the TAS2R50 bitter receptor gene, a single nucleotide polymorphism in the OR13G1 (olfactory receptor, family 13, subfamily G, member 1) gene has been linked with an increased risk of myocardial infarction [47]. This olfactory receptor gene may play an indirect role in increasing the risk of myocard infarction by affecting food preferences that are determined by the sense of smell. Similarly, we could argue an olfactory receptor gene may play an indirect role in increasing the risk for a PVD syndrome.

In conclusion, subjects with a PVD can identify odors significantly better than those without a PVD. We do not know the cause of this different smell perception and can only speculate on it. Further research on the role of odorant-binding proteins and the genetics of olfactory receptors is warranted.

REFERENCES

1. Smeets MA, Veldhuizen MG, Galle S, Gouweloos J, de Haan AM, Vernooi J, Visscher F, Kroeze JH. Sense of smell disorder and health-related quality of life. Rehabil Psychol 2009; 54:404-12. [PMID: 19929122]
2. Frasnelli J, Hummel T. Olfactory dysfunction and daily life. Eur Arch Otorhinolaryngol 2005; 262:231-5. [PMID: 15133691]
3. Henkin RI. Hyperosmia and depression following exposure to toxic vapors. JAMA 1990; 264:2803. [PMID: 2232068]
4. van TC. Kiesswetter E, Schaper M, Juran SA, Blaszkewicz M, Kleinbeck S. Odor annoyance of environmental chemicals: sensory and cognitive influences. J Toxicol Environ Health A 2008; 71:776-85. [PMID: 18569576]
5. Heinrichs L. Linking olfaction with nausea and vomiting of pregnancy, recurrent abortion, hyperemesis gravidarium, and migraine headache. Am J Obstet Gynecol 2002; 186:S215-9. [PMID: 12011889]
6. Hummel T. von MR, Huch R, Kolble N. Olfactory modulation of nausea during early pregnancy? BJOG 2002; 109:1394-7. [PMID: 12504977]
7. Smith W, Murphy C. Epidemiological studies of smell: discussion and perspectives. Ann N Y Acad Sci 2009; 1170:569-73. [PMID: 19686194]
8. Hoffman HJ, Cruickshanks KJ, Davis B. Perspectives on population-based epidemiological studies of olfactory and taste impairment. Ann N Y Acad Sci 2009; 1170:514-30. [PMID: 19686188]
9. Kranick SM, Duda JE. Olfactory dysfunction in Parkinson's disease. Neurosignals 2008; 16:35-40. [PMID: 18097158]
10. Landis BN, Konnerth CG, Hummel T. A study on the frequency of olfactory dysfunction. Laryngoscope 2004; 114:1764-9. [PMID: 15454769]
11. Bromley SM. Smell and taste disorders: a primary care approach. Am Fam Physician 2000; 61:427-36. [PMID: 10670508]
12. Flammer J, Pache M, Resink T. Vasospasm, its role in the pathogenesis of diseases with particular reference to the eye. Prog Retin Eye Res 2001; 20:319-49. [PMID: 11286986]
13. Flammer J. Glaucoma a guide for patients an introduction for care-providers a reference for quick information. Bern: Hans Huber; 2001.
14. Guthauser U, Flammer J, Mahler F. The relationship between digital and ocular vasospasm. Graefes Arch Clin Exp Ophthalmol 1988; 226:224-6. [PMID: 3402743]
15. Teuchner B, Orgul S, Ulmer H, Haufschild T, Flammer J. Reduced thirst in patients with a vasospastic syndrome. Acta Ophthalmol Scand 2004; 82:738-40. [PMID: 15606473]
16. Orgul S, Kaiser HJ, Flammer J, Gasser P. Systemic blood pressure and capillary blood-cell velocity in glaucoma patients: a preliminary study. Eur J Ophthalmol 1995; 5:88-91. [PMID: 7549448]
17. Pache M, Krauchi K, Cajoche C, Wirz-Justice A, Dubler B, Flammer J, Kaiser HJ. Cold feet and prolonged sleep-onset latency in vasospastic syndrome. Lancet 2001; 358:125-6. [PMID: 11463418]
18. Gasser P, Meienberg O. Finger microcirculation in classical migraine. A video-microscopic study of nailfold capillaries. Eur Neurol 1991; 31:168-71. [PMID: 2044632]
19. Wunderlich K, Zimmerman C, Gutmann H, Teuchner B, Flammer J, Drewe J. Vasospastic persons exhibit differential expression of ABC-transport proteins. Mol Vis 2003; 9:756-61. [PMID: 14735061]
20. Pache M, Schwarz HA, Kaiser HJ, Wuest P, Kloti M, Dubler B, Flammer J. Elevated plasma endothelin-1 levels and vascular dysregulation in patients with rheumatoid arthritis. Med Sci Monit 2002; 8:CR616-9. [PMID: 12218941]
21. Gass A, Flammer J, Linder L, Romero SC, Gasser P, Haefeli WE. Inverse correlation between endothelin-1-induced peripheral microvascular vasoconstriction and blood pressure

| Table 3. Sniffin' Sticks Score results in the four different groups of participants. |
|--------------------------------|------------------|------------------|------------------|------------------|
| Group            | Mean | Median | Minimum | Maximum |
| G+              | 9.7  | 9.5    | 8        | 12       |
| G-              | 7.0  | 7.0    | 4.0      | 9.0      |
| H+              | 9.8  | 10.0   | 8.0      | 12.0     |
| H-              | 7.2  | 7.5    | 1.0      | 12.0     |

G+=NTG patients with PVD; G-=NTG patients without PVD; H+=Healthy subjects with PVD; H-=Healthy subjects without PVD; PVD=Primary vascular dysregulation.
in glaucoma patients. Graefes Arch Clin Exp Ophthalmol 1997; 235:634-8. [PMID: 9349947]

22. Waldmann E, Gasser P, Dubler B, Huber C, Flammer J. Silent myocardial ischemia in glaucoma and cataract patients. Graefes Arch Clin Exp Ophthalmol 1996; 234:595-8. [PMID: 8897049]

23. Kaiser HJ, Flammer J. Vision disorders and their causes. Ther Umsch 1996; 53:6. [PMID: 8650625]

24. Messerli J, Flammer J. Central vein thrombosis in younger patients. Klin Monatsbl Augenheilkd 1996; 208:303-5. [PMID: 8766034]

25. Flammer J, Kaiser H, Haufschild T. Susac syndrome: a vasospastic disorder? Eur J Ophthalmol 2001; 11:175-9. [PMID: 11456021]

26. Prunte C, Flammer J. Choroidal capillary and venous congestion in central serous chorioretinopathy. Am J Ophthalmol 1996; 121:26-34. [PMID: 8554078]

27. Gasser P, Flammer J. Blood-cell velocity in the nailfold capillaries of patients with normal-tension and high-tension glaucoma. Am J Ophthalmol 1991; 111:585-8. [PMID: 2021167]

28. Flammer J, Prunte C. Ocular vasospasm. 1: Functional circulatory disorders in the visual system, a working hypothesis. Klin Monatsbl Augenheilkd 1991; 198:411-2. [PMID: 1886371]

29. Gugleta K, Zawinka C, Kochkorov A, Katamay R, Flammer J, Orgul S. Analysis of retinal vasodilation after flicker light stimulation in relation to vasospastic propensity. Invest Ophthalmol Vis Sci 2006; 47:4034-41. [PMID: 16936120]

30. Kochkorov A, Gugleta K, Zawinka C, Katamay R, Flammer J, Orgul S. Short-term retinal vessel diameter variability in relation to the history of cold extremities. Invest Ophthalmol Vis Sci 2006; 47:4026-33. [PMID: 16936119]

31. Gugleta K, Kochkorov A, Katamay R, Zawinka C, Flammer J, Orgul S. On pulse-wave propagation in the ocular circulation. Invest Ophthalmol Vis Sci 2006; 47:4019-25. [PMID: 16936118]

32. Grieshaber MC, Terhorst T, Flammer J. The pathogenesis of optic disc splinter haemorrhages: a new hypothesis. Acta Ophthalmol Scand 2006; 84:62-8. [PMID: 16445441]

33. Gasser P, Orgul S, Dubler B, Bucheli B, Flammer J. Relation between blood flow velocities in the ophthalmic artery and in nailfold capillaries. Br J Ophthalmol 1999; 83:505. [PMID: 10434882]

34. Girardin F, Orgul S, Erb C, Flammer J. Relationship between corneal temperature and finger temperature. Arch Ophthalmol 1999; 117:166-9. [PMID: 10037559]

35. Haehner A, Mayer AM, Landis BN, Pournaras I, Lill K, Gunduzil V, Hummel T. High test-retest reliability of the extended version of the “Sniffin’ Sticks” test. Chem Senses 2009; 34:705-11. [PMID: 19759361]

36. Briand L, Eloit C, Nespoluous C, Bezirard V, Huet JC, Henry C, Blon F, Trotier D, Pernollet JC. Evidence of an odorant-binding protein in the human olfactory mucus: location, structural characterization, and odorant-binding properties. Biochemistry 2002; 41:7241-52. [PMID: 12044155]

37. Hajjar E, Perahia D, Debat H, Nespoluous C, Robert CH. Odorant binding and conformational dynamics in the odorant-binding protein. J Biol Chem 2006; 281:29929-37. [PMID: 16849331]

38. Flower DR. Beyond the superfamily: the lipocalin receptors. Biochim Biophys Acta 2000; 1482:327-36. [PMID: 11058773]

39. Lobel D, Marchese S, Krieger J, Pelosi P, Breer H. Subtypes of odorant-binding proteins—heterologous expression and ligand binding. Eur J Biochem 1998; 254:318-24. [PMID: 9660186]

40. Pevsner J, Reed RR, Feinstein PG, Snyder SH. Molecular cloning of odorant-binding protein: member of a ligand carrier family. Science 1988; 241:336-9. [PMID: 3388043]

41. Matsunami H, Mainland JD, Dey S. Trafficking of mammalian chemosensory receptors by receptor-transporting proteins. Ann N Y Acad Sci 2009; 1170:153-6. [PMID: 19686127]

42. Lescop E, Briand L, Pernollet JC, Guittet E. Structural basis of the broad specificity of a General Odorant-Binding Protein from honeybee. Biochemistry 2009; 48:2431-41. [PMID: 19624863]

43. Gong DP, Zhang HJ, Zhao P, Xia QY, Xiang ZH. The odorant binding protein gene family from the genome of silkworm, Bombyx mori. BMC Genomics 2009; 10:332. [PMID: 19624863]

44. Malnic B, Godfrey PA, Buck LB. The human olfactory receptor gene family. Proc Natl Acad Sci USA 2004; 101:2584-9. [PMID: 14983052]

45. Niimura Y, Nei M. Extensive gains and losses of olfactory receptor genes in mammalian evolution. PLoS One 2007; 2:e708. [PMID: 17684554]

46. Kato A, Touhara K. Mammalian olfactory receptors: pharmacology, G protein coupling and desensitization. Cell Mol Life Sci 2009; 66:3743-53. [PMID: 19652915]

47. Timpson NJ, Christensen M, Lawlor DA, Gaunt TR, Day IN, Ebrahim S, Davey SG. TAS2R38 (phenylthiocarbamide) haplotypes, coronary heart disease traits, and eating behavior in the British Women's Heart and Health Study. Am J Clin Nutr 2005; 81:1005-11. [PMID: 15883422]