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Olfactory potentials in man: clinical results and classification

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Registration of olfactory evoked potentials is described in normal humans in a clinical setting. A new continuous flow olfactory stimulator has been developed by the authors, adapting a similar device described and tested in the laboratory by Kobal and Plattig. The potentials have been registered with the Evoked Potentials Recorder MK15 from Amplaid, Milan, coupled with the stimulator by an interface built for the purpose. Inert gas (N2) was pushed in a continuous flow through the nose at a rate of 8 liters/min. At fixed intervals of 30 sec the flow was substituted by an equal amount of 80% eucalyptol saturated gas 50 times. Each pulse lasted 1 sec. A main time relay triggered both the stimulator and, with a delay corresponding to the time between triggering of the stimulator and exit of the stimulant from the nosepiece, the recorder. Thirty tests were executed in normal males without nasal pathology and with normal sniff-tests. The latencies were (msec): P1: 224.9±15.87; N1: 314.9±18.48; P2: 453.5±17.26; N1: 572.4±17.59; P3: 686.3±25.72. There were no after-stimulation problems and the test was well supported. The authors think that it is now possible to obtain reliable electric olfactory potentials in a clinical setting. Being non-invasive and objective, it may become more useful especially in non-collaborating patients and for those in whom malingering may be suspected.

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OLFACTORY EVOKED POTENTIALS IN MAN

Clinical results with the use of a new continuous flow stimulator device

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Abstract

Registration of olfactory evoked potentials with the use of a continuous flow olfactory stimulator is described in normal humans in a clinical setting. The new stimulating apparatus was built by the authors with the assistance of the technical services of the National Health Services' Local Sanitary Unit N. 51 of Cremona, adapting a similar device described and tested in the laboratory by Kobal and Plattig. The potentials were registered with the Evoked Potential Recorder MK15 from Amplaid, Milan, coupled with the stimulator by an interface built for the purpose. Inert gas (N_2) was pushed in a continuous flow through the nose at a rate of 8 l/min. At fixed intervals of 30 sec the flow was substituted by an equal amount of 80% eucalyptol saturated gas for 50 times. Each pulse lasted 1 sec. A main time relay triggered both the stimulator and the recorder, the latter with a time delay of 300 msec, which we empirically determined to be the compound delay of the electrovalves, the relays and the removal of the residual air in the nose-piece. We did 30 tests in 15 normal males without nasal pathology and with normal sniff-tests. The resulting potentials were classified according to Plattig, and the resulting latencies were: P1: 224.9±15.87; N1: 314.9±18.48; P2: 453.5±17.26; N2: 572.4±17.59; P3: 696.3±25.72. There were no after-stimulation problems and the test was well supported. We think that it is now possible to obtain repeatable electric olfactory potentials in a clinical setting without the use of invasive techniques. As this is the only non-invasive, objective way to test olfactory function independent from the patients' desire to cooperate, it may become of larger use especially when non-collaborating or malingering patients may be involved.

Introduction

Testing of the olfactory capacity can be done by presenting scales of diluted odorous substances and recording the minimum level needed for recognition of the odor by the patient. Most olfactometries are today still based on these so called 'sniff-tests'[1-3], which are perhaps hampered by the necessity of good and motivated patient collaboration and by the difficulty to keep volatile substances at fixed dilutions in many bottles over long periods. The latter problem has been addressed by Doty with his microencapsulated sniff test, which has first been presented to the 12th World Congress in Otolaryngology in 1981[4].

Already in 1895 a Dutch doctor, H. Zwaardemaker[5], described an apparatus that pushed a fixed and known amount of air saturated with an odorous stimulus through the nose of the patient, introducing the air volume as a parameter. The device has been developed further by other researchers, mainly Fortunato and Niccolini[6] and Johnston. In all these methods the test is based on the responses given actively by an awake and collaborating patient. A great qualitative leap forward in olfactory testing would be given by the possibility to register directly the electric activity of the olfactory ways in the brain. Electric potentials have been registered from isolated receptor cells[7] and in animal models[8], but testing on humans requires a non-invasive technique similar to the registration of auditory evoked potentials from scalp electrodes.

The main problem related with registration of event-related electric potentials in man from scalp electrodes is given by their small amplitude in relationship to the basal electric activity

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of the brain. Most of the work in this field has been done in evoked response audiometry. It has been observed that the registration of event-related potentials of the sensory nerves in man requires the use of an averaging device in order to amplify the useful responses. To achieve this, a time-locked, repeatable stimulus must be presented, coupled with the opening and closure of the registering and averaging device. The application of the technique in the area of the chemical senses has been hampered by the difficulty of stimulus presentation. Gaseous (olfaction) or liquid (taste) substances must be brought in contact with the receptor cells in a specific amount, at a specific moment, and must be removed after a fixed time. This presentation cyclus must be repeatable. Furthermore, stimulation of other receptors, specifically tactile and pain receptors, must be minimized or eliminated at all. Taste stimulating devices have been described in the literature[9-11]. In 1972 and 1973 Heberhold[12,13] described an olfactory stimulator and in 1978 Kobal and Plattig[14] presented a device that presented odorous stimuli in a continuous flow fashion and reported results in a laboratory setting.

No olfactory stimulating apparatus useful for our purpose is at the moment commercially available. So we decided to construct our own device, following in part that described by Kobal and Plattig with our own changes as exposed in other sites previously[15].

Materials and methods

A new continuous flow olfactory stimulating apparatus has been built by the authors with the assistance of the technical services of the National Health Services' Local Sanitary Unit N. 51 of Cremona. In this device a continuous flow of inert purified gas (N_2) is divided into two branches of equal flow volume, one to provide neutral air and one to obtain air charged with an olfactory stimulus. The gas is passed through $CaCO_3$, activated charcoal and then humidified in distilled water. The stimulation channel is furthermore divided into two branches, one carrying plain air, the other charged with one of four olfactory stimulants. The first branch is used to obtain dilution of the second. Both airflows, neutral and charged with olfactory stimulants, converge on a two-channel electrovalve in such a way that one is always directed towards the nose and one discharged to an exhaustor. On stimulus the plain air is discharged and the charged air directed towards the nose, otherwise the plain air flows through the nose and the stimulant is discharged. All time intervals of the stimulus sequence can be individually selected and are given by electric timers. Once the stimulus sequence is started, it runs automatically until the full test is over. The stimulator can be connected to an external registration device through a specific exit relay.

In our test series the flow was fixed at 8 l/min. A main time relay triggered the stimulation sequence every 30 seconds. The neutral air flow was substituted by an equal amount of 80% eucalyptol saturated gas. Each pulse lasted 1 sec. A full test consisted of 50 stimulations. The potentials were registered with the Evoked Potential Recorder MK15 from Amplaid, Milan, coupled with the stimulator by an interface built for the purpose. The registration was done from the vertex with the electrodes put at the positions Cz and A_1. The main time relay triggered both the stimulator and the recorder, the latter with a time delay of 300 msec, which we empirically determined to be the compound delay of the electrovalves and the relays. The time needed by the air to flow through the nose piece and the nose is contained in the latencies. The registration window of the recorder was fixed at 2 sec. A white masking noise of 50 dB through headphones was used to cover the clicking noise of the electrovalves and the sound of the airflow through the tubing. We performed a total of 30 stimulations in 15 voluntary subjects. All patients reported normal olfaction and underwent an ENT examination, rhinomanometry and standard olfactometry by sniff tests to exclude local pathology, such as inflammation or mechanical obstruction, or hyposmia. Seven subjects were taken from the medical and paramedical staff and eight were patients present in the hospital for unrelated pathology and who volunteered to participate. All subjects were tested in the right and left nostril, in two subsequent sessions separated by not less than two days.

Results

The tests were generally well supported. In one subject the test had to be suspended in a first session, since the stimulus was felt too strong, but could be correctly repeated in a second session. In two cases the tests were repeated because of unclear responses, in the second session the results were comparable with the other test in our trial. Only the latencies of the resulting potentials were taken into account and they were classified, according to Plattig[16], as P1, N1, P2, N2, P3. The values of these latencies were:

- P1: 224.9±15.87
- N1: 314.9±18.48
- P2: 453.5±17.26
- N2: 572.4±17.59
- P3: 696.3±25.72

No after-stimulation problems were reported by the subjects, the overall test time was with explanations about 45 minutes. No significant left to right differences were observed. We did not analyze the traces for offset potentials at this point. The olfactory potentials started to stabilize after 30-35 stimulations and could seen to be satisfactory at the end of the test.

Discussion

Olfaction and taste are the so-called 'chemical senses', part of the lower senses according to Von Skramlik[17]. While the higher senses have always been in the focus of attention of many researchers, the lower ones have been less considered, only recently there has been a rise in interest in both basic science researchers and otolaryngologists. The role of the chemical senses should not be underestimated, being quite important in food intake and in sexual as well as social behavior in general[9,18]. The general wellbeing of a person depends also on an acceptable level of olfactory capacity. Development and cell dynamics in the olfactory epithelium are actively studied in animal models[19,20]. The exact molecular mechanism of olfaction remains still to be defined. The molecular receptor thesis[21] seems to be most probable. In cell and animal models action potentials can be registered after depolarization of the receptor cells by odor molecules[7,8] and antibodies against mucosal surface proteins that may act as receptors, can block responses[22]. Interest in olfaction has also risen by learning that this sense is specifically compromised in certain endocrine disorders. However, especially medical-legal problems, like detection of real olfactory levels in persons suspected of malingering, have underlined the usefulness of objective olfactometry. Several researchers have tried their fortune in the field of electro-olfactometry, many abandoning it after some more or less unsatisfactory results. Skepticism regarding its useful application in patients is still high among physicians and the active research in the field is mostly confined to animal models with direct nerve derivations, not usable in humans. The development of electro-olfactometers able to give repeatable results could be considered as a useful step forward. Our test results, together with those reported in the literature, have been able to underline a few points. First, it is now possible to obtain repeatable electric responses from the central nervous system after olfactory stimulation in the normal person through a non-invasive, non-dangerous technique. Second, the tests are well supported and fairly inexpensive, since besides the olfactory stimulator, specific for the test, no new equipment is required. Auditory evoked potential recorders, already present in most settings, can be easily adapted. Third, the test is still fairly time consuming. We used a quite long interval between subsequent stimuli, considering the easy adaptation of the olfactory system. It may be that shorter time constants could be used. With the refinement of the technique, the number of necessary stimuli may also be reducible.

We think that for the moment the test may be used for all-or-nothing kind of responses. Before specific quantitative evaluations can be related to pathology, more research has to be done in a larger amount of collaborating laboratories. We suggest the creation of a specific study group connecting interested researchers in both laboratories and hospitals.

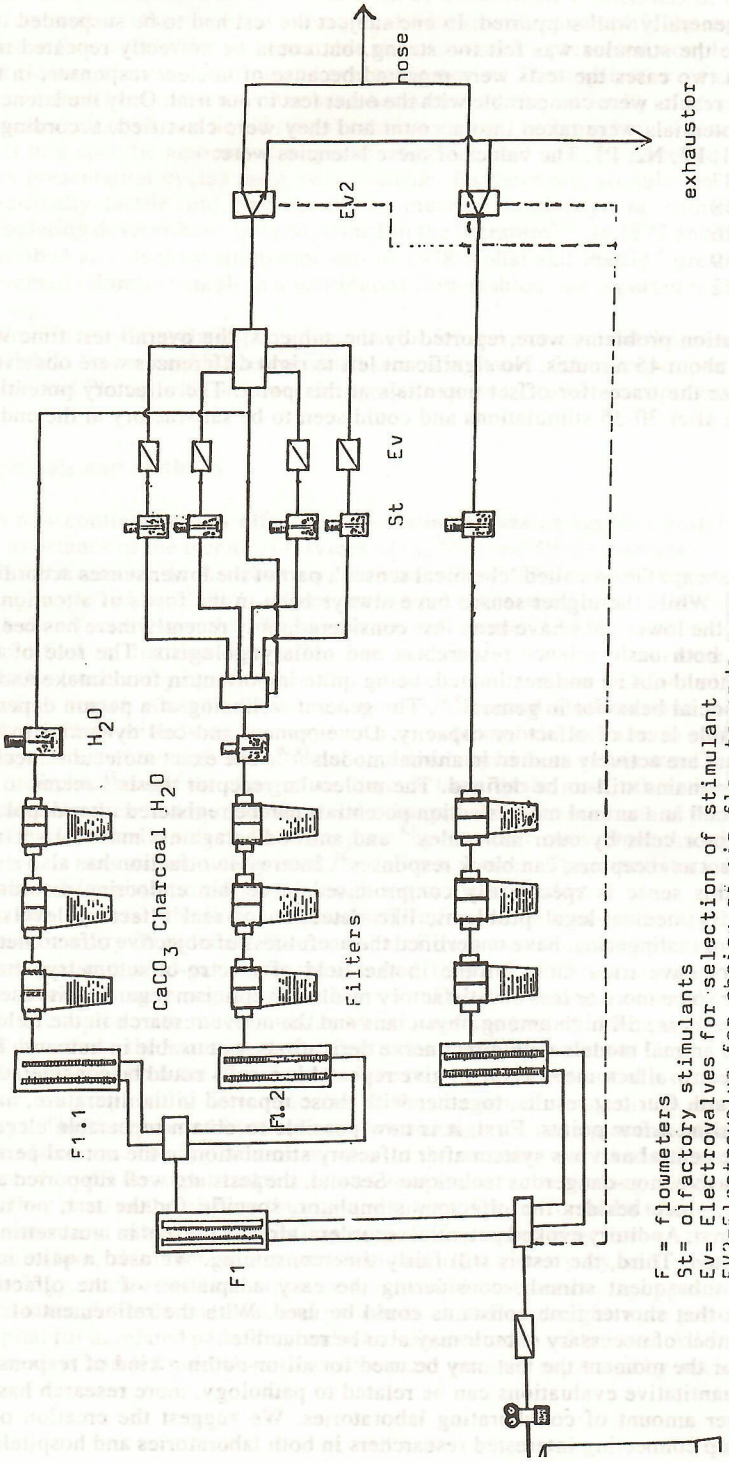

Fig. 1. Continuous flow olfactory stimulator - air flow schema.

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