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The influence of acetylsalicylic acid on cognitive processing: an event-related potentials study

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Abstract The central effects of acetylsalicylic acid (ASA) are discussed controversially. In animal models, it has been shown that ASA can interact with the central serotonergic and catecholaminergic neuronal system. However, the relevance of this interaction for humans is still unknown. We performed a study on the influence of ASA on central cognitive processing. In 25 healthy subjects (age 21–56 years), visually evoked event-related potentials (ERP) and reaction time under IV ASA medication were recorded. ERP were evoked by an oddball paradigm. As compared to placebo, ASA decreased the latency of the P3 component significantly in a time interval of 20–40 min after administration. The latency of the N2 component was significantly decreased about 25 min after administration; the latency of the exogenous P2 component was not influenced by ASA. The mean choice reaction time was significantly decreased by ASA 35 min after administration. At this time point, there was a significant correlation between decrease in reaction time and increase in ASA plasma level. The data show that IV administration of ASA has an accelerating effect on the endogenous components of visual ERP and on reaction time. This finding suggests that ASA can influence central cognitive processing, possibly by ASA induced changes of neurotransmitters. Since serotonin can be released by ASA and serotinin release leads to a decrease of ERP latencies, we assume that ASA most likely influences cognitive processing via the central serotonergic transmitter system.

Key words Acetylsalicylic acid · Event-related potentials · Reaction time · Neurotransmitter

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Introduction

The peripheral antiphlogistic and anti-inflammatory properties of acetylsalicylic acid (ASA) and its inhibitory influence on platelet aggregation are well investigated, but only little is known about the influence of ASA on the central nervous system (CNS).

In analgesic mice, higher cerebral concentrations of ASA were found than in mice without analgesia, although both groups did not differ in ASA plasma levels (Paalzow 1969). Intrathecal installation of substance P and capsacain in mice elicited pain behaviour, which could be reduced by pretreatment with intraperitoneally injected ASA (Hunskaar et al. 1985). In rats, IV injection of lysine-ASA reduced the pain evoked activity of the dorsomedial part of the ventral thalamus without any influence on ascending spinal cords (Carlsson et al. 1988). This reduction could not be antagonized by naloxone. In the same animal model, intrathecally applied ASA also reduced the pain evoked activity of thalamic neurons (Jurna et al. 1992). In humans, amplitudes of the late but not of the early components of pain-related evoked potentials were reduced by ASA (Chen and Chapman 1980); these findings were confirmed by Kobal et al. (1990). The exteroceptive suppression of antinociceptive brain-stem reflex activity was influenced by ASA, which caused an increased duration of ES2 period in migraine and tension-type headache patients (Göbel et al. 1992).

In studies on the influence of ASA and salicylic acid (SA) on neurotransmitter systems, an increased turnover of serotonin (5-HT) in brain tissue and platelets was found (Tagliamonte et al. 1973; Bensemana and Gascon 1978). An influence of ASA and SA on cerebral catecholamines was observed by Paalzow (1973) and by Bensemana et al. (1978). In conscious monkeys, microinjections of ASA in the preoptic anterior hypothalamic area produced a dose-related analgesia. This ASA-induced analgesia could be antagonized by pretreatment with either a serotonergic receptor blocker (cyproheptadine) or two catecholaminergic receptor blockers (haloperidol, yohimbine) (Shyu et al. 1984; Shyu and Lin

1985). Intravenously administered ASA in rats reduced the firing discharge of thalamic neurons evoked by noxious stimuli; concomitantly the concentration of 5-HT increased and the concentration of met-enkephalin decreased in several areas of the brain (Gropetti et al. 1988).

Until now, only a few studies on the unspecific central effects of ASA, especially on cognitive or psychomotor functions in healtyh men, have been performed. In rabbits, ASA caused increased arousal activity and activated the hippocampus and the hippocampo-cortical cords (Monnier et al. 1967). In a study by Luria et al. (1979), EEG and visual evoked potentials in men remained unchanged by ASA. Bromm et al. (1991) did not see any significant effects of ASA on spontaneous EEG, auditory evoked potentials, and reaction time in humans. However, Bradley and Nicholson (1986) observed a decrease of complex reaction time by ASA. In a study on contingent negative variation (CNV) in healthy individuals, an ASA-induced decrease in the early wave and an increase in the late wave amplitudes has been shown (Vein et al. 1995). Nevertheless, an influence of ASA on the psychomotor skills could not be found (Linnoila et al. 1974).

In conclusion, there is a central effect of ASA which is involved in the serotonergic and catecholaminergic neuronal systems and is independent from the opiate mechanisms. These transmitter systems are not only parts of the nociceptive system, but are also involved in general information processing. This is the theoretical background to study the influence of ASA on cognitive functions.

Event-related potentials (ERP) have been shown to be a useful tool to examine such cerebral functions as information processing and short time memory. The P3 component of ERP is related to target evaluation and decision making (McCarthy and Donchin 1983; Kügler et al. 1993). Latency of P3 component, unlike reaction time, can hardly be manipulated by the subject. Several parts of the brain contribute to the generating of ERP, for instance the association cortex in the frontal and parietal lobes and the hippocampus (Kügler et al. 1993). The neurotransmitter systems involved in this process are cholinergic (Harrison et al. 1988), dopaminergic (Glover et al. 1988), noradrenergic (Pineda et al. 1987) and serotonergic (Ito et al. 1989; Meador et al. 1993; Evers et al. 1994).

Measuring ERP is a reliable method which has been assessed in several studies on the effects of drugs on cognitive processing (Münte et al. 1986; Meador et al. 1993; Evers et al. 1994). To study the influence of ASA on these cerebral functions, we measured latencies of visually evoked ERP (P2, N2, and P3 component) and mean choice reaction time in young healthy subjects after IV administration of ASA in a randomized, placebo-controlled, cross-over design.

Materials and methods

Subjects

We enrolled 31 voluntary unpaid subjects (13 female, 18 male) with a mean age of 24.4 years (range 21–56 years). All subjects had given written informed consent. The study was approved by the local ethic committee. All subjects were in a healthy state, free of medication for at least 14 days and free of alcohol, coffeine, and nicotine for at least 24 h.

Procedure

ERP measurements for every subject were performed on 2 different days with an interval of at least 10 days and at the same time of day in a dark (2.5 candela/m^2) and air-conditioned room. Subjects received 200 ml water with 800 mg ASA (with ascorbic acid) on one day and placebo (ascorbin acid only) on the other day. The order of the days was randomized. ERP were measured 10 and 5 min before drug administration, immediately and 5, 10, 15, 20, 25, 30, 35, 40, 50, and 60 min after drug administration (altogether 13 measurements).

ERP and reaction time measurement

ERP were elicited by an oddball paradigma using red (frequency of 15%; 5 cd/m^2) and white (frequency of 85%; 16 cd/m^2) flashes of light. The flashes illuminated a 25×36 cm screen which was placed in front of the subject at a distance of 200 cm. The light flashes had a single duration of 100 ms and were produced in a random sequence with an interval of 1300 ms. At every measurement, 100 flashes of light were presented (15 red and 85 white); the whole duration of one measurement was 2 min and 10 s. Subjects were asked to respond only to the red flashes by pressing a button with the dominant hand. EEG following the flashes was recorded by an EEG amplifier and averaged by a computer system for a period of 100 ms prestimulus and 900 ms poststimulus interval. EEG was averaged separately for the red and white flashes of light (at least 50% artifact-free EEG curves). Ag-AgCl surface electrodes were

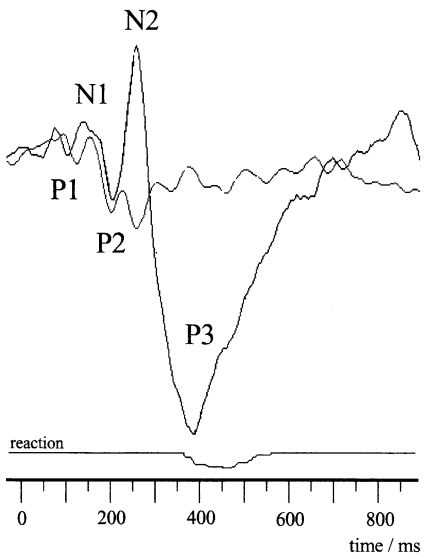

Fig. 1 Typical computer print-out of an averaged event-related potential curve (centroparietal) of one subject. *Black line*: ERP following the red light; *grey line*: ERP following the white light. ERP components P1, N1, P2, N2, and P3. Reaction: graphically averaged presses of the button

placed according to the international 10–20 system at centrofrontal, centrocentral, and centroparietal (different electrode) linked to mastoid (indifferent electrode). Eye movement was controlled by electrooculography (EOG). The high frequency filter was set at 100 Hz, low frequency filter at 0.1 Hz, sensitivity was set at 20 μV. A typical computer print-out of one measurement at centroparietal is shown in Fig. 1. The latencies of P2, N2, and P3 components were evaluated according to the recommendations of Goodin et al. (1994). The reaction time was evaluated as mean choice reaction time in pressing the button after occurring of the red light. The duration of pressing the button was also measured. All evaluations were done separately for all 13 measurements of 1 day.

Blood samples

Blood samples were taken from the left cubital vein before drug administration and 7.5, 12.5, 17.5, 32.5, and 52.5 min after drug administration. A 10-ml aliquot of blood was mixed with heparin and ice-cooled until centrifugation, which was done within 1 h after measurement. Plasma was prepared according to the procedure described by Scheidel and Blume (1989). Plasma levels of ASA and SA were measured in the Zentrallaboratorium Deutscher Apotheker in Frankfurt, Germany.

Statistics

Comparison between ERP latencies and reaction time during ASA medication and during placebo medication was performed by Wilcoxon rank test for paired samples. A possible systematic difference between measurement on day 1 and day 2 was examined by Mann-Whitney *U*-test. The correlation between ERP latencies and reaction time and the plasma levels of ASA and SA was analysed by Spearman rank correlation.

Results

In 25 of the 31 enrolled subjects, artifact-free ERP could be elicited. Only ERP which could be identified at all three scalp places of recording (centrofrontal, centrocentral, centroparietal) were included in analysis. Latencies of ERP were evaluated at centroparietal. Thirteen subjects received placebo and 12 subjects received ASA on day 1 of measurement. There were no differences between the ERP data of placebo and the data of ASA, which could be related to the order of administration (day 1 or day 2).

ERP latencies

There was a significant decrease in the latency of P3 component 10, 20, 25, 30, and 40 min after oral administration of 800 mg ASA as compared to placebo (Fig. 2, Table 1). The most significant decrease was 20 min after intake of ASA ($P<0.002$; $t=3.13$). There were no significant differences in ERP data after ASA and after placebo application at the other time points of measurement. The latency of the N2 component was decreased significantly by ASA only at 25 min after intake. The latency of P2 component showed no significant difference between measurement after ASA and after placebo administration.

Reaction time

The reaction time was significantly decreased 35 min after ASA administration as compared to the reaction time 35 min after placebo administration (Table 2). At the other time points of measurement, no significant differences between ASA and placebo could be observed. It was interesting that the duration of pressing the button decreased during the procedure for both ASA and placebo medication. This effect was significantly better 35, 40, and 60 min after intake of ASA, with a difference of 135±19 ms (ASA) versus 143±12 ms (placebo) after 60 min ($P<0.05$).

Plasma levels of ASA and SA

The plasma levels of ASA and SA at the different time points of the procedure are shown in Fig. 3. There were no significant correlations between the latencies of the ERP components and the plasma levels of ASA or SA for all subjects. However, 35 min after ASA intake, there was a significant correlation between the decrease in reaction time and the plasma level of ASA (Spearman rank correlation: $r=0.69$; $P<0.001$).

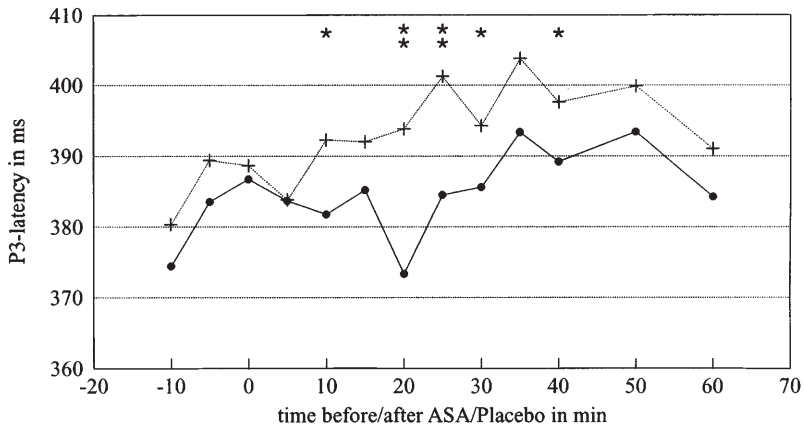

Fig. 2 Mean P3 latency before and after oral administration of 800 mg ASA (–•–) and placebo (---+---); level of significance (Wilcoxon test for paired samples): **P*<0.05; ***P*<0.01

Table 1 Mean latency of the P3 component of ERP (ms)±SD before and after oral administration of 800 mg ASA and placebo; comparison by Wilcoxon test for paired samples (n=25)

Time before/ after administration of ASA/placebo	ASA	Placebo	Level of significance (Wilcoxon test for paired samples)
10 min before	374.4±25.5	380.3±32.7	NS
5 min before	383.6±25.8	389.4±32.3	NS
0 min after	386.8±29.2	388.7±28.8	NS
5 min after	383.7±31.2	383.8±35.2	NS
10 min after	381.7±30.1	382.2±32.4	P<0.05
15 min after	385.2±30.8	392.2±35.3	NS
20 min after	373.3±35.5	393.8±29.7	P<0.002
25 min after	384.5±35.6	401.2±38.9	P<0.007
30 min after	385.6±32.3	394.2±36.8	P<0.05
35 min after	393.3±35.8	403.8±36.8	NS
40 min after	389.2±32.8	397.6±28.7	P<0.05
50 min after	393.4±36.5	399.9±41.5	NS
60 min after	384.3±34.0	391.0±29.3	NS

Table 2 Mean reaction time (ms)±SD before and after oral administration of 800 mg ASA and placebo; comparison by Wilcoxon test for paired samples (n=25)

Time before/ after administration of ASA/placebo	ASA	Placebo	Level of significance (Wilcoxon test for paired samples)
10 min before	381.8±46.1	382.0±42.0	NS
5 min before	381.3±37.6	377.2±42.4	NS
0 min after	387.8±41.3	382.8±35.7	NS
5 min after	380.7±36.6	379.0±46.5	NS
10 min after	381.8±39.8	389.7±47.8	NS
15 min after	379.4±40.1	383.0±44.4	NS
20 min after	386.2±45.1	384.3±43.2	NS
25 min after	381.9±45.1	393.4±47.5	NS
30 min after	379.6±47.7	390.9±49.8	NS
35 min after	380.2±38.2	390.4±50.7	P<0.05
40 min after	379.2±43.6	378.8±43.6	NS
50 min after	378.8±45.2	389.8±46.6	NS
60 min after	379.1±38.8	379.8±46.2	NS

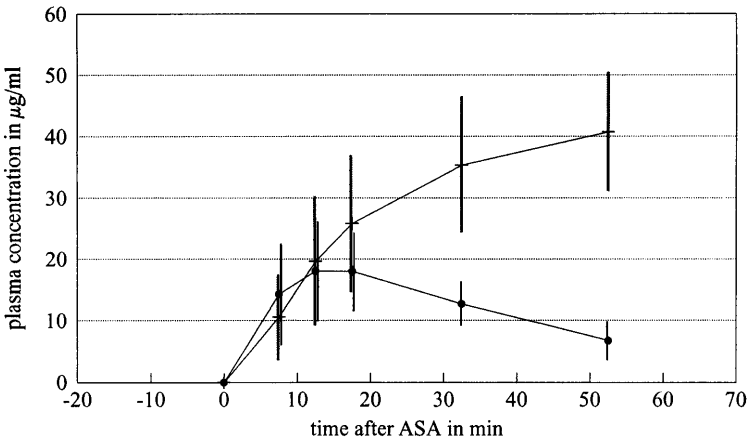

Fig. 3 Mean plasma concentration and standard deviation (*vertical lines*) of ASA (–•–) and SA (---+---) after oral administration of 800 mg ASA

Discussion

Our data suggest that oral administration of ASA decreases the P3 latencies of visually evoked ERP for 10–40 min after intake, with a maximum at 20–25 min. A similar but less impressive effect could be found for the N2 latencies. P2 latencies were not influenced by ASA, suggesting that the endogenous components of ERP in particular are influenced by ASA.

Our data support the hypothesis that there is an improving effect of ASA on cognitive processing independent from the analgesic effect of ASA. It has previously been shown in EEG studies that ASA has an influence on the arousal activity of rabbits (Monnier et al. 1967)

and on spontaneous EEG activity (Pfeiffer et al. 1967; Horne et al. 1980; Fink and Irwin 1982). Even the amplitude of CNV can be influenced by ASA (Vein et al. 1995). However, measurements of visual evoked potentials (Luria et al. 1979) and auditory evoked potentials (Bromm et al. 1991) failed to prove a central effect of ASA. In pain-related potentials, Kobal et al. (1990) found a decreasing effect of ASA on the latency of P2 and N2. The influence of ASA on the late ERP components has not been studied so far.

We found a significantly decreasing effect of ASA on reaction time about 35 min after intake. A similar effect has been shown by Bradley and Nicholson (1986) in a psychophysiological experiment for complex reaction time. Bromm et al. (1991) did not see any effect of ASA on reaction time, but they only measured the simple and not, as in our study, the choice reaction time. In the study of Luria et al. (1979), ASA did not influence the choice reaction time, but they measured reaction time after ASA administration within a time interval longer than in our study. However, we found only a weak effect of ASA on reaction time, and therefore no definite conclusions can be drawn.

The time curves of the ASA and SA plasma levels of our subjects (Fig. 3) are consistent with results of other pharmacokinetic studies (Petersen et al. 1982; Blume et al. 1993). There was a high interindividual variability in absolute plasma level. The changes of ASA plasma levels are very similar to the changes in P3 latencies and the mean reaction time, i.e. at the time of high ASA plasma levels, very short P3 latencies and short mean reaction times were measured. At 35 min after ASA administration, there was a significant correlation between decrease of reaction time and ASA plasma level (r=0.69; P<0.001). The lack of more significant correlations may result from the fact that we measured ASA concentration in plasma and not in cerebral spinal fluid. It has been shown that ASA penetrates the blood-brain barrier (Gonzalez et al. 1975; Lin and Hoo 1979). The shortest P3 latency was about 10 min after the highest plasma level of ASA. This time interval may reflect the time taken by ASA to pass the blood-brain barrier.

There is no definite explanation for the influence of ASA on ERP. Probably, ASA induces changes in concentrations of neurotransmitters involved in generating ERP. The serotonergic system plays a very important role in this context. ASA can lead to a central release of 5-HT (Tagliamonte et al. 1973; Gropetti et al. 1988). Serotonergic influence on CNS induces a decrease in P3 latencies, and anti-serotonergic influence on CNS induces an increase (Meador et al. 1993; Evers et al. 1994). Thus, ASA probably decreases ERP latencies by releasing 5-HT.

In conclusion, oral administration of ASA has a mild but significant influence on cognitive functions as measured by ERP. In previous studies, a central effect of ASA on cognitive functions was shown only indirectly by measurement of psychomotor and arousal activity. In this study, a central effect of ASA on cognitive functions can be observed directly by measurement of ERP. The underlying mechanisms of this effect are not yet clarified. It seems likely that ASA modulates neurotransmitter systems, probably the serotonergic system, which are involved in generating ERP.

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