Antidepressants and Anti-Inflammatory Drugs Differentially Reduce the Release of NGF and BDNF from Rat Platelets

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Abstract

Introduction: Platelets store serotonin and brain-derived neurotrophic factor (BDNF) as well as amyloid precursor protein and nerve growth factor (NGF), thus platelets are of special interest in depression and Alzheimer’s disease, respectively. Both diseases are associated with inflammation and release of NGF or BDNF from platelets may play a potent role.

Methods: Platelets were isolated from adult Sprague–Dawley rats and were incubated with anti-inflammatory drugs (ibuprofen and indomethacin) and antidepressants (citalopram, paroxetine and sertraline) (final concentration: 0.3 μM) with or without 2 mM calcium chloride. The release of NGF and BDNF was analyzed in comparison to serotonin release from rat platelets after 10 or 60 min.

Results: Spontaneous release of serotonin and BDNF was approximately 10–15% of total serotonin or BDNF content in platelets, but nearly all NGF was released within 10 min. All antidepressants increased the serotonin release from rat platelets. NGF release was reduced by sertraline, paroxetine and ibuprofen, but only when calcium was present, except for sertraline after 10 min. BDNF release was only reduced by ibuprofen when calcium was added.

Conclusion: We conclude that antidepressants and anti-inflammatory drugs differentially influence the NGF and BDNF release, in a time-, dose- and calcium-specific pattern.

Introduction

Blood platelets reveal remarkable parallels to the brain. Platelets are the main source of serotonin and a dysfunction of the serotonergic system is implicated in depression [1]. Platelets also express amyloid precursor protein (APP) and contain beta-amyloid (Aβ), which aggregates to amyloid plaques in Alzheimer’s disease (AD). Furthermore, platelets contain growth factors such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) and since both diseases are associated with inflammation, the activation of platelets and the release of NGF or BDNF may play a potent role.

The neurotransmitter serotonin is produced by neurons of the dorsal raphe nucleus and is involved in the regulation of, e.g., mood and cognition [2]. In the blood, platelets are the main source of serotonin and platelets express different serotonin receptors and the serotonin transporter (SERT) [3, 4]. SERT on platelets influences the plasma serotonin levels and the number of SERTs per platelet is sensitive to selective serotonin reuptake inhibitors (SSRIs), which are the most commonly used antidepressants [5]. Serotonin is released from activated platelets and serotonin from platelets may play a role in neuroinflammation [6]. Growth factors are expressed in most tissues and stimulate cellular growth, proliferation and cellular differentiation. NGF and BDNF belong to the neurotrophin family and promote neurogenesis, synaptic plasticity and cell survival in the brain [7]. In the blood NGF and BDNF are stored in platelets and can bind to platelet receptors [8–10]. NGF is implicated in inflammatory and neurodegenerative disorders [11]. It has been reported that NGF can bind to specific platelet receptors and can induce platelet aggregation [8]. So far, it has been shown that peripheral levels of NGF are not increased by antidepressant treatment [12]. However, not much is known on the release of NGF from platelets. BDNF has been implicated in inflammatory and stress-related disorders such as depression, where low BDNF levels have been reported [11, 13]. Antidepressants increase BDNF levels in blood by inducing...
BDNF release from platelets [14, 15]. Also in stressed rodents the administration of BDNF has been shown to evoke an antidepressant-like effect [16]. The secretion of platelet content requires complex processes, including the formation of prostaglandins that can be abolished by anti-inflammatory drugs with cyclooxygenase (COX)-inhibitory properties [17].

So far, the impact of antidepressants and anti-inflammatory drugs on NGF and BDNF release from platelets is unknown and partly not consistent in the literature. Therefore, the present study aims to investigate the effects of anti-inflammatory drugs (ibuprofen and indomethacin) and antidepressants (citalopram, paroxetine and sertraline) on NGF and BDNF release from rat platelets. We will investigate the effects of calcium on the release in a time-dependent manner.

Materials and Methods

Blood collection and platelet isolation and treatment

Platelets were isolated as reported previously [18]. In total 24 adult Sprague-Dawley rats were used. They were anaesthetized with a high dose of thiopental (Sandoz, Kundl, Austria) and blood was drawn directly from the heart by using a butterfly blood collection system (Becton Dickinson, Schwechat, Austria). The blood was collected in EDTA tubes (Sarstedt, Wr. Neudorf, Austria) and centrifuged at 250 g for 15 min to obtain platelet-rich plasma (PRP). 500 nM prostaglandin-I2 sodium salt (PGI2, prostacynl-sodium salt, Sigma, Vienna, Austria) was added to prevent platelet activation during processing. Platelets were separated from PRP by centrifugation at 2300 g for 10 min and were washed in calcium-free Tyrode buffered (pH 7.4). All centrifugation steps were performed at room temperature. Freshly isolated platelets (1 × 10⁸) were incubated for 10 min and were finally resuspended in 1 mL Tyrode buffer (adjusted to pH 7.4). All centrifugation steps were performed at room temperature. Freshly isolated platelets (1 × 10⁸) were incubated with 0.3 μM citalopram (Sigma) or 0.3 μM ibuprofen (Sigma) or 0.3 μM indomethacin (Sigma) or 0.3 μM paroxetine (Smith Kline, Vienna, Austria) or 0.3 μM sertraline (Pfizer, Vienna, Austria) (final concentration) at 37 °C for 10 min or 60 min in Tyrode buffer (pH 7.4). In addition, platelets were incubated with or without 2 mM calcium chloride (Ca²⁺). To stop the release 1.7 mM EDTA (final concentration) were added and samples were centrifuged at 2300 g for 10 min. The supernatant was collected and frozen at −80 °C until analysis.

Serotonin analysis by HPLC

Serotonin was measured by high-performance liquid chromatography (HPLC) and electrochemical detection as reported previously [19]. Samples were thawed and 20 μL supernatant were injected into the HPLC. The samples were separated on a reversed-phase C18 Nucleosil column (Bartelt, Graz, Austria) at a flow rate of 1 mL/min using the following mobile phase: 0.05 M trichloric acid (Merck, Darmstadt, Germany), 0.26 mM EDTA (Merck), 1.36 mM NaCl (Roth, Karlsruhe, Germany), 1.81 mM heptanesulfonic acid (Sigma) and 15 % acetonitrile (BDH Prolabo, Vienna, Austria) in HPLC water. Detection was performed with an electrochemical detector (Antec IL Leyden, Netherlands) at +0.55 V and 30 °C. All unknown samples were correlated to external standards of serotonin (Sigma). Analysis was performed by measuring peak heights at the respective retention times of the substances (serotonin 7.8 min).

NGF and BDNF immunoassays

BDNF and NGF levels were measured using commercial enzyme-linked immuno-sorbent assay (ELISA) kits (Promega, Mannheim, Germany). Detection of BDNF and NGF was performed as described by the manufacturer. Briefly, 100 μL standards or samples were added to coated wells and incubated for 6 h at room temperature. After washing, the detection antibodies were added and samples were incubated over night at 4 °C. Wells were washed again and incubated with horseradish peroxidase conjugate for 2.5 h. After washing, TMB one solution was added. After 10 min the reaction was stopped and the absorbance was measured at 450 nm in a Zenyth 3100 ELISA reader.

Data and statistical analysis

All data obtained from NGF, BDNF and serotonin release were analyzed with a one-way ANOVA and a subsequent Fisher LSD posthoc test, where p < 0.05 was considered statistically significant. Quantitative data are presented as mean values ± SEM in % of totals. Due to variabilities in isolation and analysis, the number (n) of treatments was not always identical.

Results

Control conditions

The total content of 1 × 10⁸ platelets was 747 ± 215 ng serotonin (n = 17), 255 ± 49 pg NGF (n = 9) and 418 ± 100 pg BDNF (n = 15) (Table 1). Under calcium-free conditions only a low amount of serotonin and BDNF (approximately 10–16%) of total content was released after 10 and 60 min, however, almost all NGF was released (Table 1). Calcium did not significantly influence the release of serotonin, although there was a tendency for an increase (Table 1). Calcium significantly reduced the NGF release after 60 min, but not after 10 min (Table 1). Calcium significantly increased the release of BDNF after both 10 and 60 min (Table 1).

Effects of drugs on serotonin release from rat platelets

All 3 antidepressants (citalopram, sertraline or paroxetine) increased the serotonin release under calcium-free conditions after 10 and 60 min (Table 2A). The anti-inflammatory drug indomethacin increased the serotonin release under calcium-free conditions only after 60 min. Ibuprofen did not alter the serotonin release under calcium-free conditions (Table 2A). Under calcium conditions ibuprofen and paroxetine significantly released more serotonin after 10 min, while all other treatments with calcium did not increase the serotonin release from platelets either after 10 or 60 min (Table 2B).

Effects of drugs on NGF release from rat platelets

Under calcium-free conditions only sertraline reduced the NGF release from platelets after 10 min (Table 3A). NGF release was reduced under calcium conditions by ibuprofen, paroxetine and sertraline after 10 min, but not after 60 min (Table 3B). Citalopram and indomethacin did not affect NGF release (Table 3A, B).

Effects of drugs on BDNF release from rat platelets

No effect on BDNF release was seen under calcium-free conditions with all tested drugs (Table 4). Treatment of rat platelets with citalopram, paroxetine, sertraline and indomethacin did not influence the release of BDNF under calcium conditions after 10 and 60 min (Table 4A, B). BDNF release was significantly...
Platelets and storage of molecules
Platelets have 3 types of secretory granules: dense bodies, alpha granules and lysosomes. Dense bodies contain ATP, ADP, serotonin and calcium. Alpha granules contain different growth factors, such as platelet-derived growth factor (PDGF), transforming growth factor-beta 1 (TGF-β1), platelet factor 4 as well as other proteins necessary for functional activity (e.g., fibrinogen, von Willebrand factor, factors V and VIII). Lysosomes contain acid hydrolases [17]. The granules content is secreted following activation by a wide variety of stimuli, such as ADP and thrombin. Thrombin is a very strong stimulus that has been widely used to study platelet secretion. Thrombin causes exocytosis of dense bodies and degranulation of alpha granules, while thrombin induces alpha granule secretion at a lower concentration than the secretion of dense bodies. Furthermore, it was shown that the secretion induced by different stimuli requires the formation of arachidonic acid metabolites or depends on temperature or calcium concentration [17]. Also, it has been shown that NGF is stored in dense bodies, while BDNF is stored in alpha granules [17,20].

Role of calcium on platelet release
Calcium regulates various cellular processes, including cellular activation and degranulation in platelets [21]. Elevation in calcium concentrations derive from either the release of intragranular stores or extracellular calcium, which plays an important role in platelet activation and secretion. The calcium ionophore A23187 causes platelet secretion in a similar manner as thrombin and high concentrations of calcium and thrombin lead to an immediate release of diverse growth factors including PDGF and TGF-β1 [22,23]. In human and rat platelets a weak inhibiting effect of calcium on serotonin reuptake has been shown [24]. In our study we used 2 mM calcium, which is a well established extracellular concentration. We show that calcium had slight but not significant effects on serotonin release and a pronounced strong effect on BDNF release from platelets after 10 and 60 min.

Serotonin release from platelets as a positive control
Already in the 1960s Bartholini and Pletscher [25] had shown that platelets incubated in physiological medium (e.g., Tyrode buffer) release only a small amount of serotonin, which is induced by thrombin within a few minutes. The vesicular monoamine transporter inhibitor reserpine induces the release of serotonin from platelets and inhibits the reuptake of serotonin in dense granules [26]. Several antidepressants directly increase the release of serotonin and inhibit the reuptake of serotonin into dense granules [27,28]. In addition, SSRIs induce depletion of platelet serotonin levels and reduce platelet activation [29,30]. Our data are in full agreement, showing low secretion of serotonin and that SSRIs inhibit the reuptake of serotonin from platelets.

NSAIDs are COX inhibitors, which suppress prostaglandin synthesis from arachidonic acid and suppress platelet aggregation reduced by the anti-inflammatory drug ibuprofen after 10 and 60 min (Table 4B).

Discussion
Our present study shows that anti-inflammatory drugs and antidepressants influence release of NGF and BDNF from rat platelets in a calcium-sensitive way. Serotonin was used as a positive control.

Table 2: Serotonin release by anti-inflammatory drugs and antidepressants.

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<thead>
<tr>
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<th>10min</th>
<th>60min</th>
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<tr>
<td></td>
<td>P&lt;sub&gt;1&lt;/sub&gt;</td>
<td>P&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>control</td>
<td>10.1 ± 2.4 (14)</td>
<td>5.1 ± 1.2 (12)</td>
</tr>
<tr>
<td>ibuprofen</td>
<td>22.2 ± 3.7 (9)</td>
<td>10.4 ± 1.9 (9)</td>
</tr>
<tr>
<td>indomethacin</td>
<td>34.3 ± 7.0 (9)</td>
<td>25.7 ± 6.7 (9)*</td>
</tr>
<tr>
<td>paroxetine</td>
<td>45.9 ± 9.2 (10)**</td>
<td>50.5 ± 9.5 (7)**</td>
</tr>
<tr>
<td>sertraline</td>
<td>38.1 ± 6.0 (7)**</td>
<td>30.1 ± 8.6 (10)**</td>
</tr>
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</table>

Rat platelets were isolated from whole blood. Anti-inflammatory drugs or antidepressants without (A) or with (B) Ca<sup>2+</sup> were added and platelets were incubated at 37°C for 10 or 60 min. Supernatants were collected and serotonin was analyzed by HPLC-EC and ELISA, respectively. Values are given as mean ± SEM ng/ml/10<sup>8</sup> platelets or pg/ml/10<sup>8</sup> platelets (NGF, BDNF). Values in brackets give the mean ± SEM % of total control. The number of analyzed samples is given in parenthesis. Statistical analysis was performed by one-way ANOVA with a Fisher LSD posthoc test. *p < 0.05; **p < 0.01; ***p < 0.001; ns, not significant.
very low agonist concentrations [17]. Tryptophan-kynurenine pathway and triggers the synthesis of 2,3-dioxygenase (IDO). IDO is the rate-limiting enzyme in the
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restrain the stimulation by cytokines. Inhibition of pro-inflammatory agents and antidepressants [A] or with [B] Ca²⁺. Platelets were incubated at 37 °C for 10 or 60 min. Supernatants were collected and NGF was analyzed by ELISA. Values are given as mean ± SEM % of total. The number of analyzed samples is given in parenthesis. Statistical analysis was performed by one-way ANOVA with a Fisher LSD post-hoc test. *p<0.05; **p<0.01; ns, not significant

NGF release from platelets and effects of drugs
The function of NGF in blood is unclear and little is known about NGF in platelets. A recent study has shown that NGF serum concentrations were not altered by antidepressant treatment and that serum concentrations were not related to the antidepressant type [12]. Our data show, for the first time, that NGF is markedly released from rat platelets. This was an interesting novel observation showing that almost all (90%) of NGF is spontaneously released from platelets. In the brain, release of NGF is highly regulated and influenced by neuronal activity [33]. NGF is generated from a precursor molecule (proNGF), which undergoes processing to generate mature NGF [33]. The NGF precursor and proteases are stored in neuronal compartments from which they are simultaneously released after neuronal stimulation [34]. In neurons, a basal constitutive secretion of NGF can be partially blocked by, e.g., lowering the incubation temperature [33]. In platelets, NGF is contained in dense bodies and mainly the whole granular content is spontaneously released within minutes. However, serotonin release accounts only for about 10–15% and thus it seems likely that NGF and serotonin release are differentially regulated, because markedly more NGF is released than serotonin. This finding points to uptake mechanisms, degradation or binding to extracellular molecules or to platelet membranes. Our data show for the first time that sertraline partially blocked serotonin release of NGF, but only after 10 min under calcium-free or calcium-containing conditions. It is fully unclear why the release was not altered after 60 min. This may indeed indicate that the effect of sertraline is only a fast and transient one and that NGF is further released with time. Similarly, ibuprofen and paroxetine also reduced NGF release but only when calcium was present. Thus, we conclude that the release of NGF from platelets is uncontrolled and can only be partly and transiently inhibited by some specific drugs. The mechanism of such a fast release needs to be further explored in detail.

BDNF release from platelets and effects of drugs
Stress activates several neurotransmitters and the endocrine system including the hypothalamic-pituitary-adrenal (HPA) axis as a key hormonal component [35]. BDNF signaling plays a critical role in the regulation of the HPA axis suggesting an endocrine role for BDNF [36, 37]. In depression the HPA axis is disturbed and BDNF serum levels are decreased. However, the function of BDNF in the blood is still poorly understood and conflicting results about BDNF serum, plasma and platelet BDNF levels have emerged. In serum of antidepressant-naïve or -free depressed patients decreased BDNF concentrations have been observed. The serum BDNF levels increased after antidepressant treatment [14, 38, 39]. It has been suggested that BDNF released from platelets directly correlate to serum BDNF levels. Indeed, platelet BDNF is reduced in depressed patients and serum BDNF levels are enhanced after stimulation on platelets by antidepressant treatment [10, 15]. Furthermore, Serra-Millas et al. [40] reported high platelet BDNF and low plasma BDNF levels in healthy controls. Recently it has been reported that antidepressants induce a marked BDNF release from rat platelets in a time- and dose-dependent manner [15]. Contrary, it has been shown that collagen induces platelet activation and aggregation is inhibited by antidepressants by inhibiting granule secretion from platelets [28]. Another study showed that aspirin (a non-specific COX-inhibitor) reduces the release of BDNF from platelets [41], while a recent study reported that aspirin did not affect BDNF release

Table 3 NGF release by anti-inflammatory agents and antidepressants.

<table>
<thead>
<tr>
<th>A</th>
<th>10 min</th>
<th>60 min</th>
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<tbody>
<tr>
<td>control</td>
<td>90.4 ± 20.7 (9)</td>
<td>89.3 ± 12.6 (9)</td>
</tr>
<tr>
<td>citalopram</td>
<td>91.6 ± 8.3 (4) ns</td>
<td>85.6 ± 5.1 (6) ns</td>
</tr>
<tr>
<td>ibuprofen</td>
<td>86.8 ± 8.9 (4) ns</td>
<td>73.6 ± 8.4 (5) ns</td>
</tr>
<tr>
<td>indomethacin</td>
<td>112.0 ± 5.5 (6) ns</td>
<td>69.6 ± 15.2 (6) ns</td>
</tr>
<tr>
<td>paroxetine</td>
<td>87.0 ± 15.1 (6) ns</td>
<td>64.1 ± 18.9 (5) ns</td>
</tr>
<tr>
<td>sertraline</td>
<td>41.0 ± 15.1 (5) * **</td>
<td>60.3 ± 15.9 (5) ns</td>
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B

<table>
<thead>
<tr>
<th>10 min</th>
<th>60 min</th>
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<tbody>
<tr>
<td>control + Ca²⁺</td>
<td>97.6 ± 12.8 (9)</td>
</tr>
<tr>
<td>citalopram + Ca²⁺</td>
<td>63.8 ± 7.4 (6) ns</td>
</tr>
<tr>
<td>ibuprofen + Ca²⁺</td>
<td>53.3 ± 5.0 (5) *</td>
</tr>
<tr>
<td>indomethacin + Ca²⁺</td>
<td>63.3 ± 6.2 (6) ns</td>
</tr>
<tr>
<td>paroxetine + Ca²⁺</td>
<td>55.7 ± 8.2 (6) *</td>
</tr>
<tr>
<td>sertraline + Ca²⁺</td>
<td>56.8 ± 13.6 (5) *</td>
</tr>
</tbody>
</table>

Platelets were isolated and incubated with or without anti-inflammatory drugs or antidepressants without (A) or with (B) Ca²⁺. Platelets were incubated at 37 °C for 10 or 60 min. Supernatants were collected and NGF was analyzed by ELISA. Values are given as mean ± SEM % of total. The number of analyzed samples is given in parenthesis. Statistical analysis was performed by one-way ANOVA with a Fisher LSD post-hoc test. *p<0.05; **p<0.01; ns, not significant

Table 4 BDNF release by anti-inflammatory agents and antidepressants.

<table>
<thead>
<tr>
<th>A</th>
<th>10 min</th>
<th>60 min</th>
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<tbody>
<tr>
<td>control</td>
<td>13.2 ± 3.1 (12) –</td>
<td>15.9 ± 3.0 (12) –</td>
</tr>
<tr>
<td>citalopram</td>
<td>10.9 ± 4.0 (8) ns</td>
<td>18.4 ± 1.9 (6) ns</td>
</tr>
<tr>
<td>ibuprofen</td>
<td>16.0 ± 5.4 (6) ns</td>
<td>18.7 ± 6.3 (7) ns</td>
</tr>
<tr>
<td>indomethacin</td>
<td>18.9 ± 3.9 (8) ns</td>
<td>21.6 ± 6.8 (9) ns</td>
</tr>
<tr>
<td>paroxetine</td>
<td>17.1 ± 4.3 (9) ns</td>
<td>20.2 ± 2.9 (7) ns</td>
</tr>
<tr>
<td>sertraline</td>
<td>13.4 ± 2.8 (8) ns</td>
<td>25.4 ± 5.8 (7) ns</td>
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B

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>control + Ca²⁺</td>
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<td>citalopram + Ca²⁺</td>
<td>67.3 ± 7.7 (6) ns</td>
</tr>
<tr>
<td>ibuprofen + Ca²⁺</td>
<td>43.8 ± 16.3 (5) *</td>
</tr>
<tr>
<td>indomethacin + Ca²⁺</td>
<td>76.6 ± 13.7 (6) *</td>
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<tr>
<td>paroxetine + Ca²⁺</td>
<td>58.9 ± 20.2 (6) ns</td>
</tr>
<tr>
<td>sertraline + Ca²⁺</td>
<td>77.8 ± 16.4 (6) ns</td>
</tr>
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</table>

Platelets were isolated from rat blood. Anti-inflammatory drugs or antidepressants without (A) or with (B) Ca²⁺ were added and platelets were incubated at 37 °C for 10 or 60 min. Supernatants were collected and BDNF was analyzed by ELISA. Values are given as mean ± SEM % of total. The number of analyzed slices is given in parenthesis. Statistical analysis was performed by one-way ANOVA with a Fisher LSD post-hoc test. *p<0.05; **p<0.01; ns, not significant
Taken together, there is a strong controversy on showing release of BDNF from platelets. It seems likely that the type of isolation of platelets may markedly affect the results, such as, e.g., using EDTA/citrate tubes, puffers with or without calcium, pH during isolation and use of diverse inhibitors. Our data are in clear contrast to those of Watanabe et al. [15] showing that all antidepressants did not affect the release of BDNF under calcium-free conditions. Unfortunately, Watanabe et al. [15] did not provide detailed information on platelet isolation, thus differences in platelet preparation may account for the differences in our study. Furthermore, they did not provide raw values, making it difficult to directly compare our data. Our data also show that only ibuprofen affected BDNF release but only when calcium was present. This goes in line with the work of Fujimura et al. [43], who observed a rapid release of BDNF from human platelets with the calcium ionophore A23187. We suggest that ibuprofen reduced BDNF release possibly involving COX inhibition and calcium-mediated release from alpha granules.

Conclusion

In our present study we use platelets from rats, which allows us to study cellular mechanisms in a simple homogenous and reproducible cell type. Our study is the first to investigate the influence of 3 antidepressants (citalopram, sertraline, paroxetine) and 2 non-steroidal anti-inflammatory drugs (ibuprofen, indomethacin) with or without calcium on NGF and BDNF release and serotonin as a control from rat platelets. The influence of antidepressants and anti-inflammatory drugs on NGF and BDNF release differs depending on the drug type, dose and maybe on the incubation period. It is concluded that the release of the 2 growth factors NGF and BDNF contributes to blood levels, which may indicate a role in platelet-derived function, including vascular mechanisms. Further studies should clarify the mechanisms of NGF and BDNF release also in human platelets.

Acknowledgements

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Conflict of Interest

The authors declare no conflicts of interest.

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