PLACEBO EFFECT: A NEW APPROACH TO EXPLANATION OF ITS PSYCHOPHYSIOLOGICAL MECHANISMS

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Abstract

In this theoretical overview will be reconsidered basic mechanisms of placebo effect with a purpose to examine a hypothesis that the generally accepted psycho-physiological mechanisms of the placebo effect that explain many clinical and experimental data are related to search activity. Search related activity in general is a behavioral attitude that is capable to restore mental and physical health in different conditions that may explain basic mechanisms of placebo effect.

Key words: Search activity; Placebo effect; Dopamine; Panic behavior

1. INTRODUCTION

In this article will be reconsidered basic mechanisms of placebo effect and will be suggested that many contradictions in this domain may be solved by using search activity concept presented in previous published studies (for example see Rotenberg, 2009, 2012). By search activity it is understood any behavioral or mental activity designed to change the environment and situation or the subject's attitude to it in the absence of a definite forecast of the results of such activity (i.e. in the case of pragmatic indefiniteness), however with constant monitoring of the results of such activity. According to this definition certain behavioral categories cannot be linked with search activity. For instance, stereotyped behavior is dealing with a definite forecast of results. Panic behavior differs from search activity by the absence of the feedback between the activity and its regulation based on the outcome of activity – during panic behavior when the results of the activity are not considered in order to be used for the correction of behavior. Renunciation of search is opposite to search activity and in animals may assure the form of freezing or learned helplessness and in humans it corresponds to depression and maladaptive anxiety.

Search activity is present in self-stimulation in animals, in creative behavior of humans, as well as in exploratory and active defense (fight/flight) reactions in all species. In research conducted together with V. Arshavsky we found that all forms of behavior which include

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search activity increase body resistance to stress events and prevents different forms of artificial pathology while renunciation of search is leading to the opposite outcome (Rotenberg & Arshavsky, 1979; Rotenberg, 2009). Search activity saves health and determines the development of every representative of the high developed species and of the human society.

The process of search activity by itself does not matter whether it helps to achieve pragmatic goals or not, it determines a positive feedback between behavior and brain monoamines and supports itself causing an excitement and feeling of happiness (in process of creativity, goal achievement and even fight). This happiness caused by the process of search is opposite to happiness of goal achievement and relaxation.

In wakefulness search activity is based on the combination of activating (acetylcholine and dopamine (DA) dependent) and selective inhibitory (norepinephrine and serotonin dependent) influences on cortical neurons. This combination determines the regulation of behavior, its goal direction, its relevance to actual tasks. In addition this predisposition to the goal-oriented selective activity requires discrimination between meaningful and meaningless information elicited by the environment. The pure DA activity determines the predisposition towards chaotic search that can easily change its direction: the process of activity is more important than the concrete goal.

I will try to show that the present data of the scientific investigations of the placebo mechanisms correspond to the above mentioned mechanisms of search activity and that placebo stimulates this activity and exactly for this reason placebo treatment is successful.

2. PLACEBO EFFECT IN ORGANIC BRAIN DISORDERS

Let us start with some neurological disorders. According to De La Fuente-Fernandez et al. (2001), in Parkinson disorders placebo effect is associated with the release of endogenous dopamine (DA) in nigrostriatal and mesoaccumbent projections. Authors emphasized that the factors that control this restorative DA release are not known, nevertheless some years later Lidstone et al. (2010) proposed that it can be an effect of expectation of the positive outcomes of placebo that may induce dopamine release. Expectations were modulated by using verbal manipulations: patients were informed that they will be treated sometimes with active medication and sometimes with placebo, and in every session they got a verbal instruction according the particular probability of getting active medication, from 25% up to 100%. However, actually they got always only placebo. Significant DA release after getting placebo was achieved when the declared probability was 75%.

How is it possible to explain these results in the frame of search activity concept? Placebo is biochemically neutral and cannot stimulate DA release by itself as a substance, without the verbal suggestion. I suppose that the high (although illusive) probability to receive a real treatment changed not only the patient's expectations but also the corresponding behavioral attitudes – increased attention to the outcome and enthusiasm and excitement caused by the expected positive outcome. This psychological effect includes search activity that is a natural part of the orienting behavior, attention and emotional arousal related to the expected outcome.

It is interesting that placebo-induced DA release correlated with the DA response to the openly presented administration of the true medication and in order to achieve the positive effect of placebo a patient needs previous positive experiences with real anti-Parkinson drugs. Positive expectations, increased enthusiasm and attention to own feelings cannot arise from nothing. It is similar to what happens with search activity of healthy subjects in every-day life: search activity must be supported at least by episodic achievements in the process of activity while regular and unavoidable failures are often leading to the learned helplessness (see Seligman, 1975).

It is also necessary to take into consideration that the response to the prior organic medication determined DA release in the motor striatum while the expectation of clinical

improvement was additionally required to drive DA release in ventral striatum. It means that positive expectations are activating not exactly the same brain zones that are activated in the process of the previous drug treatment. Probably the activation of motor systems caused by drugs is initially relatively restricted and directed predominantly to the motor system while the positive expectations based on the previous experience of motor improvement incorporates search activity and due to it covers more broad brain areas (Seligman, 1975; Rotenberg & Arshavsky, 1979; Rotenberg, 2009).

The authors emphasized that untreated with real medications Parkinson Disease patients are impaired on tasks of probabilistic learning, do not demonstrate activation of ventral striatum during reward prediction (it means do not display signs of reward prediction) and show reduced capacity to learn on the basis of prediction of positive feedback (Seligman, 1975). These features might be signs of the low search activity.

On the other hand, when a subject is not sure that what he/she got is a real active drug or even is sure that it is not a drug, the negative expectation can decrease the sensitivity of the DA reward mechanisms, and the drug may work as placebo. It means that in this condition search activity drops due to negative expectations and is displaced by the feeling of helplessness (without positive perspectives). At the same time those patients, who were absolutely sure and without any doubts that they always receive levodopa, had negative values for placebo-induced DA release contrary to the expected theoretical effects of medication. This result seems to be in agreement with the role of search activity in placebo effect, because a condition for search activity is the indefinite forecast, i.e. a probability forecast, thus the 100% definite forecast decreases search activity as a process – the subject's personal responsibility, attention to what is going on, a readiness to the new conditions and events is displaced by the lack of responsibility, by the passive relaxed waiting for the positive outcome. In this condition placebo that has no own biological forces does not work.

DA release induced by Levodopa predicted DA release on placebo because subject got an experience that the used drug may have a positive outcome and such experience stimulates search activity when subject receives medication that has a high chance to be levodopa – a high chance but not without any doubts. This outcome is also a sign that DA system is potentially effective and can react on levodopa as well as on search activity provoked by placebo. Placebo effect includes conscious predictions of the positive outcome of the treatment. It is a conditional reaction. Reward probability, prediction of reward depends on expectations, and indefinite expectation is an important part of search activity (Rotenberg & Arshavsky, 1979; Rotenberg, 2009).

Authors emphasized that placebo responses in other disorders may be seen as analogous, may include the expectations of reward, and are also mediated by DA release. It seems reasonable because DA release characterizes the process of activity in general. DA system is involved in positive emotions (Flaten et al., 2011) and induces a negative reward of the previous negative experience, it means reduces the influence of this negative experience on the subject's emotional state and behavior. For this reason the functional deficiency of DA system may play an important role in the pathogenesis of many nervous and psychosomatic diseases. In Parkinson disease search activity stimulated by placebo restores exactly those brain systems that are distorted by the disease.

However, placebo in Parkinson disease induced DA release correlated with DA response to open administration of active medication (Lidstone et al., 2010) not only as a sign of the unspecific restoration of search activity but also because search activity in general, including those stimulated by placebo, restores exactly those body functions that became distorted by the disease (Rotenberg, Arshavsky, 1979; Rotenberg, 2009).

It is interesting that in patients who got antidepressants and at the same time were absolutely sure (on 100%) that they received levodopa, placebo that they received instead of levodopa did not cause DA release (Lidstone, 2010). I suppose that the reason of this effect was that antidepressants stimulate search activity by themselves and in this condition placebo does not cause the additional increase of search behavior. Placebo in general is doing the same

as the antidepressants are doing – stimulate optimistic attitudes, behavioral attitudes towards state improvement, hope, and blocks feelings of helplessness and passivity, and when subjects already received antidepressants placebo has nothing to add.

The excretion of DA caused by levodopa that was presented openly and without doubts is likely an unconditional reflex, while the excretion of DA caused by placebo is a conditional reflex determined by the previous experience of taking levodopa because such positive experience influence the behavioral attitudes and predisposes subject to the positive outcome supporting search activity.

An opportunity to get reward may stimulate active behavior. Authors emphasized that DA release caused by placebo is directly related to positive predictions but is not regularly accompanied by the improvement of Parkinson disease systems. The same happened with psychosomatic disorders – active search predisposes in general to their improvement but it is not an obligate outcome because it depends also on the present clinical state of disease. In addition, the expectation of the reward, of the positive outcome, from my point of view is efficient only if it is not a passive expectation, if it changes the emotional state, increases attention to the environment and creates another view on the reality that stimulates search activity. According to Mosley and Flor (2012) conditional reward is not restricted to selective stimuli – it shows the opportunity of very different interrelationships between numerous factors. Such interrelationships definitely include search activity, at least to check them.

This suggests that even in organic disorders placebo effect can be explained by the alteration of behavioral attitudes, by the increase of search activity.

3. PLACEBO EFFECT IN MENTAL DISORDERS

Now let us discuss the placebo effect in psychiatric disorders where this approach looks even more relevant. For example, in depression antidepressants are more efficacious than placebo (Florian, 2013) however 40% of patients on placebo show a response without remission (de Gray, 2015) and in mild and moderate major depression placebo effect in 67% of cases is as effective as antidepressants (Marchesi et al., 2013). In severe depression it is less effective because depression by itself, and especially severe depression, is opposite to search activity and can block it from the very beginning. Mora et al (2011) suggested that improvement in placebo group may be partly explained through the natural course of moderate depression, its dynamics, but it also reflects investigators' and participants' expectations. I suppose that it would be a mistake to believe that investigators' expectations are tremendously changing their ability to estimate objectively the outcome of placebo treatment. It is more reasonable to believe that in the process of communication between the investigator and patient the expectations of investigators may influence the expectation of patients making them more optimistic and improving their view on their own status.

Mora et al. (2011) have shown that the analysis of "nocebo effect" (adverse effect) confirms impact of expectations: nocebo symptoms reflected the side effect patterns expected by patients in the drug group after they got an experience of such side effect. Probably it means that while presenting placebo it would be reasonable to inform patients that they will get real but even improved drugs without side effect?...

Placebo effect was measured as a difference between placebo response and changes that occur without placebo. Patients with severe depression were characterized by decreased responsiveness to placebo rather than increased responsiveness to medication. Responsiveness to medication was also low, but to placebo it was even lower. As I have already mentioned, it may be caused by the suppression in depressed patients exactly those mechanisms that determine placebo effect (attitudes towards active behavior), as well as by general pessimism, tendency to give up in any challenging and difficult situation etc. Depression by itself decreases the responsiveness to placebo while the natural stimulators of search activity

mechanisms (activation of definite brain zones, stimulation of brain monoamines) that are incorporated in antidepressants are absent in placebo.

Like in the process of the treatment of Parkinson disease, effect size in placebo groups correlated with those in drug groups due to the activation of similar mechanisms. Placebo effect is small when placebo is compared with the absence of treatment. It is understandable because for positive expectations that stimulate all components of active behavior subject needs a previous experience of the state improvement caused by natural (biological) stimulators.

Negative side effect in placebo group is relatively high and it may be a projection of the previous experience of side effects caused by antidepressants (Mora et al., 2011). Another explanation of nocebo effect may be the subject's expectation of his/her state improvement however without any active personal involvement in the process of improvement, passive waiting for positive outcome combined with the disappointment when the expected improvement does not appear. I propose that such disappointment may stimulate the appearance of nocebo effect.

Even a treatment with antidepressants requires for its success the active participation of patients in their life events. My own clinical experience is that when patients being on the treatment are passively waiting for the improvement it takes more time than when they are involved in some goal directed activity even if they have strong doubts that they are able to perform such activity.

According to Schedlowski et al. (2015) only placebo responders demonstrate the increase of the pre-frontal activity of brain cortex, and such activity was not observed neither in non-responders nor in patients on medication. Such increase of pre-frontal activity associated with the metabolic increase in the prefrontal anterior cingulate cortex, premotor, parietal and posterior cingulate cortex may be a sign of the subject's readiness to perform a goal-directed behavior. This hypothesis corresponds to data of the antidepressive effect of psychotherapy oriented on the stimulation of the subject's active behavior.

In patients with schizophrenia placebo responses in clinical trials according to Schedlowski et al. (2015) are similar in magnitude quality and impact to those observed in depression trials. It was shown that difference in the number of responders between antipsychotics and placebo in patients with psychosis was low – around 18%, and both positive and negative symptoms including apathy and social withdrawal as well as cognitive symptoms (poor executive functions and working memory) are sensitive to placebo treatment. However, authors emphasized that the neuropsychological mechanism of this positive outcome is not known. The decrease of positive psychotic symptoms on placebo is especially strange if these symptoms are determined by themselves as rewarding (Dunn et al., 2006) what corresponds to my explanation of positive symptoms as a very particular and socially maladaptive search activity (see Rotenberg, 2012).

My hypothesis is that the rewarding and stimulating function of placebo effect may be incorporated in delusions and became a dominating part of delusion, changing its direction; many initial delusions as symptoms of the disease may be displaced by the delusive idea of the very effective and supporting role of placebo and as a result such suggested illusion may improve some clinical symptoms and turn some thoughts and behavior in a "positive" direction.

In anxiety placebo effect is between 10% and 60% (Schedlowski et al, 2015). What is interesting and important for the explanation of the placebo effect, those patients who got only anti-anxious pills (alprazolam) suffered relapses to baseline level after its discontinuation while improvement in placebo (in patients who got pills together with placebo) remained stable after pills discontinuation. I suppose that it was the effect of the improvement of behavioral attitudes that at least partly depends on the psychological features. Placebo reminded subject the previous positive experience and fixed this experience predisposing patient to the free and active behavior - that's why placebo responses in anxiety disorders can be long lasting.

Placebo responses in social anxiety disorders were accompanied by attenuated amygdala activity but only in subjects that are homozygous for long allele (L) of the serotonin transporter gene (that determines search activity, Rotenberg, 2013). Anxiety-relieving placebo response in healthy subjects decrease the activity in amygdala, insula, dorsal ACC (emotionally responding brain areas) and increase activity in subgenual anterior cingulate cortex and ventral striatum (Schedlowski et al, 2015). It corresponds to the reward related response induced by cognitive factors such as volunteers expectations. These expectations reflect the orientation of healthy subjects on active behavior with positive outcome. Actually placebo includes the same brain and psychological mechanisms that anxiolytics do (amygdala, cognitive mechanisms, mechanisms of expectations). However, it is necessary once more to emphasize that it is not a passive expectation – it is a readiness to participate in the active change of the own emotional state in positive direction, and the reward that regularly mentioned authors of these investigations is the reward of this active change – the reward of search activity, in my terms.

Placebo is used sometimes in the process of treatment of psychosomatic disorders. Meissner (2001) investigated the specificity of the placebo effect on autonomic nervous system. Placebo used for the improvement of stomach functions affected only gastric motility but does not affect cardio-vascular functions. It means that placebo improves only the disturbed functions that have to be improved. It corresponds to the outcome of search activity. According to the investigations on animals performed by Arshavsky (see Rotenberg, Arshavsky, 1979) behavior that includes search activity restores exactly those somatic functions that were previously artificially destroyed but does not influence other somatic systems. Of course in animals it happens without any direct suggestions.

The prediction of the positive outcome of placebo treatment reduces systolic but not diastolic arterial blood pressure in healthy subjects and in patients with hypertension (Schedlowski et al, 2015). The reason of it may be that the systolic blood pressure is related to the increased heart rate that is often caused by the maladaptive emotional tension (anxiety) that is opposite to the mobilizing activity for search.

4. PLACEBO EFFECT IN ANALGESIA

Placebo is also often used in pain treatment (see Schedlowski et al., 2015). Usually analgesia that is achieved by opioids is accompanied by the decreased heart rate and its variability. Placebo analgesia is also related to the decrease of stress experience and heart rate as a result of positive anticipations. These anticipations are absent in the Alzheimer disease where the prefrontal cortex loses its relationships with other brain zones.

Benedetti et al. (2006) have shown that placebo related mechanism of positive expectation can explain the lack of pain treatment (analgesia) in Alzheimer disease. Patients with Alzheimer disease showed reduced placebo effect due to a reduced connectivity of the prefrontal lobe with the rest of the brain. The crucial role of cognition and prefrontal lobe in the therapeutic outcome of placebo related analgesia confirms the important role of behavioral attitudes toward the positive outcome and goal-directed search based on the prefrontal cognitive activity in placebo effect.

Now let us discuss the some mechanisms of placebo effect in a more general way. Schedlowski et al. (2015) presented a list of different psychological mechanisms that are considered to be responsible for placebo effect that might be considered in the frame of Search Activity Concept (SA).

5. POSITIVE EXPECTATIONS

It is without doubts that expectations can mediate psychological variables, however it is not clear how they can mediate physiological outcomes that characterize placebo effect in psychosomatic disorders. From my point of view, it is available only if they are changing behavioral attitudes in the objective state and condition, and it means that these expectations is not a passive waiting for the positive outcome.

Pecina et al. (2014) have shown that brain regions – anterior cingulate cortex, orbito-frontal cortex, nucleus accumbens – responsible for the prediction error processing (the comparison of expectations with the real outcome) overlap with brain regions involved in placebo effect. It corresponds to my explanation of placebo effect because prediction error processing is an active mental activity. The comparison of expected outcome with a real outcome determines the flexibility of SA, the opportunity to change its direction.

When we are speaking about positive expectations that have a healing effect when patient uses placebo it is reasonable to take into consideration data published by Pacheco-Lopez et al. (2006) indicating that expectations activate neurobiological mechanisms capable to release endogenous neurotransmitters and/or neurohormones that mimic expected pharmacological effect. It seems that the brain is capable to modulate peripheral immune reactivity.

Positive expectations and associations may heal in the process of placebo treatment because they overcome helplessness and increase reward neural process that can affect peripheral immunoresponse via direct sympathetic innervations of immune system. Pure positive expectations by themselves during analgesia were associated with opioid system activation in dorsolateral prefrontal cortex but not with greater behavioral placebo responses because expectation without its comparison with the real outcome does not represent search activity. In order to achieve a stable positive outcome it is necessary to displace the passive expectation by the active search behavior (Pacheco-Lopez et al., 2006; Benedetti et al. 2006).

However, it is necessary to take into consideration that in contrast to behavior, placebo treatment does not change the environment by itself but only the subject's inner state and attitudes due to the readiness to accept new pleasant feelings and to estimate them. Anticipated placebo effects and mismatch between anticipated and perceived outcomes are related to activation of nucleus accumbens dopamine neurotransmission during placebo administration and the positive associations created by the environmental context may improve mood and increase placebo effect (Sutterlin et al., 2015) by orienting subject on the search of the new associations.

The estimation of the distinction between the anticipated and real anaesthesia is by itself a sign of active mental behavior (SA). When subject beliefs in the positive outcome of the treatment without any doubts, it excludes search activity. Very high positive expectations are accompanied by the lower placebo response; also because such 100% positive expectations are usually not realized they may cause a distress that subject is unable to overcome because such expectations without doubts and without attempts to control the outcome can block search activity. Opioids are involved in analgesia provoked by the positive expectations according to pain relief, but subject is oriented exactly on this positive outcome due to the increase of search activity related not to the opioid but to the DA excretion. For this reason increased DA activity participates in analgesia caused by placebo (Sutterlin et al., 2015).

6. CONDITIONING THEORY

According to this theory, placebo effect is based on the associations of the unconditional stimuli elicited by the real drug that was used before placebo and conditioning stimuli. This association is related to the superficial similarity between this drug and placebo (they both are pills) and the similarity of conditions in which they both are used. This similarity is supported by the direct suggestion of the clinician that placebo is a real drug with the strong positive

effect. However, this mechanism requires the mental (conscious or unconscious) comparison between the unconditional and conditional stimuli with all their features and such comparison by itself is an active mental behavior that includes search. Conditioning determined by placebo is a provocation of this search activity.

According to Mora et al. (2011) in depression placebo effect as a conditional reaction depends on the prior experiences of combining drug features (pill) with antidepressant effect thus helping subject to prescribe this effect to the similar pills of placebo. However, not all participants are exposed to conditioning processes. This suggests that the positive expectancy based on relevant suggestions from doctors is more important.

Environmental conditions while using real drugs may create new context and associations for the further placebo treatment. These associations may stimulate the same mechanisms that were previously activated by real drugs but they may cause also a broader outcome. They may help to change the general view on the environment as well as self-feeling, stimulate search activity. Probably sometimes it can be even enough to inform patient that after using a new drug (actually placebo) the subject's state will become similar to the state before the disease, and the all experiences of previous healthy behavior including search activity may come back.

It is interesting that placebo may have a more convincing effect if its use is accompanied by the suggestion that it has the side effect profile similar to the side effect of the real drug the patient is familiar with. Paradoxically (on the first glance) it increases the positive orientation on placebo and is strengthening the belief that it is a real drug (Mora et al. 2011). The previous experience of positive drug effect is more important than the side effect and increases the enthusiasm of patients according to the treatment. Enthusiasm by itself stimulates search activity, makes subject ready to it. But in this case placebo effect may be accompanied by the imagined side effects.

7. PERSONALITY FACTORS

Personality factors are also very important in placebo effect. Reward responsiveness (traits related to reward) characterizes 25%-30% of the variance in placebo analgesia responses. Reward is associated with DA activation, and I have already mentioned that DA characterizes the active although chaotic search without feedback (without checking the relationships between initial goal and the outcome of goal-oriented behavior, Rotenberg, 2011). However for the restoration of body functions and health this feedback is less important than for the adaptation to the real environment. The most important for health is the process of search by itself. Reward supports active behavior because it suppresses helplessness and increases positive expectations.

Novelty seeking as a personality factor also supports placebo effect and its relation to search activity that does not need additional explanation (Rotenberg, 2011). Altruism and empathy are also important both for the placebo effect and for active behavior without which these personal features can't be realized.

According to Flaten et al. (2011) pain relief on placebo is achieved due to the reduction of stress and anxiety. On the other hand, during war were collected many data indicating that strong fight and anger can decrease pain feelings. According to the search activity concept, it means necessary to discriminate eustress (that provokes adaptive behavior in stressful conditions and is accompanied by search activity) and distress with maladaptive anxiety that causes renunciation of search. I suppose that only the reduction of distress and maladaptive anxiety correlates with placebo pain relief, and only in such cases relaxation can stimulate opioid activity and reduce pain.

High level goals like related to positive emotional relationships with physician also determine long term placebo response by enlarging positive experiences (reward) that comes from the social environment and supports search activity. High level goals may be more

general and more stable than the restricted low level goals (being spiritual and including implicit or explicit orientation towards searching for and expressing personal needs to transcend the reality). The search for the realization of such needs and for achievement of existential goals may predispose subject also to the successful placebo effect due to the orientation on the health restoration just for such achievements that may be for the subject more important than health by itself.

According to the role of positive expectations in placebo effect it is relevant to discuss the role of optimism as a personal trait. Geers et al. (2010) have shown that subjects with the dispositional optimism display, in comparison to subjects without such optimism, lower pain ratings in placebo conditions but not in control conditions. It means that to have optimistic attitudes is not enough for resistance to negative emotions, it must be a definite object to prescribe to it something that may determine a positive outcome (a drug or placebo that displaces drug). When faced with adversity, optimism is associated with active behavior and mental coping. The belief in positive future – dispositional optimism – represents also the belief in the subject's own abilities to cope with problems. Optimists often shift their focus of attention away from adversity to positive features – especially while dealing with adversity that is out of their control – and this shift of attention in the helpless situation is an active behavior. Optimists are actively searching for some features that confirm optimistic attitudes and they are actively selecting positive experiences even those that are not directly related to the actual stressful conditions. In this context it is understandable that placebo expectation stimulates the orientation on the positive information and feedback (Geers et al., 2010).

In placebo conditions participant is often informed that clinicians and researchers are searching for a new drug for instance for the local anesthetics. Thus participant became involved in the investigation and is not passively waiting for the positive outcome. He is oriented on the active estimation of the outcome. It is especially effective when participant was told that the new drug he/she receives now was already successfully used previously, but this effect must be confirmed (Geers et al., 2010).

Without the inclusion of the optimism variable it was no difference in pain reports between placebo condition and control condition. Optimism stimulates active reconsideration of the situation and it prevents helplessness due to the orientation on the possible positive outcome. If subject is oriented on negative outcome, and even if he/she is actively searching for negative features, he/she is searching for them not in order to overcome these features but to confirm that it is impossible. In pessimism a search for signs of the negative outcome is working with a negative feedback – this “search” blocks search activity, let us say, blocks itself because it is leading to helplessness and hopelessness (Geers et al., 2010).

What is especially interesting, that according to the results of the investigations optimists are initially no more persuaded by positive placebo expectations than are pessimists; but expectation of optimist is not a passive expectation that the effect will come by itself from something the subject is separated from – it is an active inclusion in the process of expectations, it is like an absorption by expectations, with the imagination of the possible positive outcome. It is an emotional relationship with the possible positive outcome combined with an unconscious and involuntary search for any weak positive sign.

For this reason optimist is a moderator, not a mediator of placebo responding and changes the reaction on placebo. According to the results of investigations, dispositional optimism correlates with neuroticism (I suppose, it is a wrong term that actually means a high emotional sensitivity), trait anxiety, locus of control, self mastery. To moderate reaction on placebo, means to include search activity into behavioral attitudes (Geers et al., 2010. In this context, Flaten et al. (2011) suggest that analgetic action of placebo acquires its positive effect through the verbal information that pain will be reduced or through the conditional associations between the placebo and effective drugs. The effective treatment that was used before placebo treatment is effective also because it causes positive attitudes to the treatment and reduces feelings of helplessness.

It is likely that unpleasantness will decrease after placebo presentation due to the activation of the DA system that is involved in positive emotions. However, it needs to consider that this statement does not correspond to the idea that placebo decreases negative emotions and pain through relaxation. Of course, relaxation may decrease maladaptive emotional tension, but DA system does not cause relaxation and stimulates activity in different directions, although often chaotic activity. DA system displays a positive reinforcement of chaotic search (see Rotenberg, 2011), and positive expectations help to reduce pain not only via a reduction of destructive negative emotions but also via stimulation of the active behavior and excitement related to this behavior. Placebo response is a reaction to signals that an unpleasant state is enabled by the belief and constructive feelings of the ability to cope with problems and to control the situation (Rotenberg, 2013).

Of course, it does not mean that relaxation does not help to decrease pain. Probably analgesia achieved through positive emotions of relaxation is really based on opioid activity while analgesia achieved through emotional excitement is based on DA activity. Placebo analgesia may use both mechanisms (in different conditions). This proposition could be useful to consider in further investigations.

Behavior that has pleasant consequences has a chance to occur more frequently in the future due to positive reinforcement. Negative reinforcement stimulates behavior that removes unpleasant stimuli. In both cases behavior includes search activity. Reduction of pain is not always an outcome of the negative reinforcement, it can be caused by the positive reinforcement of exaltation (in fight, in positive expectations of placebo effect etc.). In any case, pain increases the probability of the occurrence of behavior that reduced pain in the past if subject had such experience (Rotenberg, 2011). On the other hand, search activity even in negative stressful conditions contains elements of a self-reinforcing behavior because search by itself as a process contains positive emotions. Behavior that helps to achieve goals and increases health resistance is self-reinforcing behavior that increases positive emotions (Rotenberg, 2011).

Placebo taken during stress caused by pain reduces this stress, and stress reduction predicted placebo analgesic response. It means that the reduction of stress is the main and initial factor in placebo anesthesia (Aslasker & Flaten, 2008). It is reasonable to suggest that this reduction of stress even before pain reduction is determined by the alteration of general attitudes caused by placebo. How else can placebo reduce negative emotions (distress) before pain reduction? It is possible that the relationships between pain reduction and stress reduction are bidirectional – the reduction or alteration of stress decreases pain feeling and the decrease of pain reduces stress.

Placebo analgesia was observed also in the absence of stress reduction (stress was assessed by cortisol activity). As I have already emphasized, it can be explained by taking into consideration that stress by itself is different: destructive stress combined with the renunciation of search increases pain feeling, while constructive stress combined with search activity, stress in the process of goal achievement reduces pain feeling (Aslasker & Flaten, 2008). In addition, Schedlowski et al. (2015) mentioned the decreased activity in pain processing areas (thalamus, insula, somatosensory cortex) related to placebo, while nocebo (a sign that pain will appear) increases activity in these areas. Placebo engages descending pain modulating networks in which prefrontal cortex plays a crucial role. However, this cortex plays also an important role in goal-oriented behavior. Temporary functional lesions in prefrontal cortex by transcranial magnetic stimulation, as well as degeneration and disconnection of frontal lobe in Alzheimer disease are associated with the loss of the verbally induced placebo analgesia. It may be an outcome of the disturbance of verbal contact but it may be also an outcome of the lost search activity.

Individual placebo analgesia correlates with the increased DA neurotransmission in nucleus accumbens, putamen, caudate nucleus (Aslasker & Flaten, 2008; Schedlowski et al., 2015). DA related personality traits like novelty, fun and sensation seeking (they all represent search activity) are related to gray matter density in ventral striatum and to magnitude of

placebo analgesia. However, the authors emphasized that it is not clear whether striatal DA activity is causally involved in the generating analgesia or only reflects reward processes associated with pain relief (Schedlowski et al., 2015). From my point of view, reward process by itself is causally involved in pain relief due to emotional exaltation and search activity. Also Scott et al. (2007) confirmed experimentally that reward responsiveness is linked to placebo analgesia and the expectation of DA release enhanced reward learning.

On the other hand, haloperidol (DA antagonist) may block placebo-related activity in striatum but have not an effect on analgesia. It may be a sign that DA activity is not obligate for analgesia. However, most versions of placebo analgesia are explained by activity changes in intracortical emotion oriented circuitry rather than by changes in sensory brain areas, and analgesia can occur without changes in cortical response to afferent spinothalamic input. It means that analgesia is emotionally determined and may depend on emotional exaltation. In addition, according to Luby et al. (2011) increased fear of pain as a trait measure abolished the placebo analgetic response. Fear of pain is an anticipatory stress prior to administration of painful stimulation and this stress of negative emotions (distress) reduces placebo analgesic response – probably by causing a state of giving up. On the other hand, placebo reduced the processing of negative emotions in the brain if subject belief that it is an anxiolytic.

8. CONCLUSION

An attempt to explain the placebo effect with all its contradictions by using the “Search Activity Concept” might indicate that the positive outcome of placebo in different mental and psychosomatic disorders may be at least partly explained by the change of behavioral attitudes in the constructive direction caused by placebo. This explanation is still speculative and requires experimental confirmations but it helps to concentrate attention on some important aspects that were not discussed previously.

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