

Pharmacological Support of Neurorehabilitation

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Abstract: The administration of numerous facilitatory drugs in combination with appropriate physiotherapeutic approaches is reported to facilitate neurorehabilitation. First evidence of the possible beneficial influence of facilitatory drugs in neurorehabilitation arose from studies investigating the pharmacology of learning in healthy humans. Amphetamine, for example, has shown to improve performance of different somatosensory and motor skills. Paired with physical therapy in stroke patients, it also increases the rate and extent of motor recovery and supports treatment of aphasia. Amphetamine is however known as a “dirty drug”, because it acts non-specifically by increasing centrally the levels of dopamine, serotonin, and noradrenaline. Thus, first approaches intend to scrutinize the role of more specifically acting pharmacological agents on learning and neurorehabilitation.

In this review, focus is placed on two main topics: (i) studies that aimed to investigate the pharmacological basis of motor and sensory skills in healthy humans and (ii) studies investigating whether the same drugs may also support neurorehabilitation. First, different sensorimotor paradigms are discussed, which were introduced to investigate basic influences of facilitatory pharmaceuticals on cortical plasticity. Then, emphasis is placed on the role of these drugs acting to gate synaptic plasticity in neurorehabilitation. It is concluded that further studies in large populations should focus on more specifically acting pharmaceuticals, their side effects and their capacity in supporting different patterns of physical therapy.

Key Words: Cortical reorganization, behavior, dopamine, serotonin, noradrenaline, neurorehabilitation.

INTRODUCTION

Despite much progress in prevention and acute treatment of different neurological disorders, recovery and rehabilitation have traditionally received relatively little scientific attention [1]. Increasing interest, however, arises from a growing number of studies that impressively document beneficial effects of different “recovery drugs” alone, or in combination with innovative rehabilitation techniques. First evidences of a possible beneficial influence of particular drugs on neurorehabilitation came from studies investigating the pharmacology of learning in animals and healthy humans. These studies suggest that there might be only few, but very basic mechanisms that control regulation of synaptic transmission and thus synaptic plasticity [2].

While there are many approaches to block plastic processes pharmacologically, less is known about drugs, which enhance learning and cortical plasticity. Amphetamine, for example, when administered peripherally, increases centrally the level of dopamine, serotonin and noradrenalin. These monoamines in turn modify long-term changes in synaptic function [3, 4] with serotonin being more potent than noradrenalin [5]. Many studies provided evidence for the facilitatory role of amphetamine on learning processes [2, 6] that might relate to the induction of long-term potentiation (LTP) [3], a basic mechanism of learning. Paired with

physical therapy in stroke patients, it also increases the rate and extent of motor recovery [1, 7, 8] and supports treatment of aphasia [9-11]. However, amphetamine is known as a “dirty drug” because of its non-specific mode of action. Thus, first approaches intend to scrutinize the role of more specifically acting pharmacological agents, like those modulating serotonergic and dopaminergic neurotransmission on learning and neurorehabilitation.

In this review, focus is placed on two main topics: (i) studies that investigated whether particular pharmaceuticals can be used to improve motor and sensory skills in healthy humans and (ii) studies investigating whether the same facilitatory drugs may also support neurorehabilitation. First, different motor and sensory paradigms are discussed, which were introduced to investigate basic influences of facilitatory pharmaceuticals on cortical plasticity. Then, emphasis is placed on different approaches, which aimed to extend these basic experiences to the investigation whether these drugs can also act to gate synaptic plasticity in neurorehabilitation. Generally, it should be underlined that although most of these clinical trials presented convincing results, they also have major shortcomings. To test for specific pharmacological effects, most of them use very simple behavioral paradigms with low clinical relevance. More importantly, most results are based on short observation periods and small numbers of patients with heterogeneous clinical pictures.

ADRENERGIC NEUROTRANSMISSION

In the beginning of the 1980s, a growing number of cellular and animal studies provided first evidence that amphetamine might enhance the induction of LTP as a basic

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mechanism of learning processes [3, 12]. This effect can be assigned to its capacity to increase synaptic dopamine primarily by stimulating presynaptic release and its role as an indirect catecholaminergic agonist combining known influences on the GABAergic and glutamatergic system.

To assess behavioral consequences of these facilitatory effects in rats, Mayfield *et al.* tested amphetamines influences on reaction time responses. Animals were shaped to release a lever in response to an auditory/visual stimulus to avoid mild foot shock. The characteristics of the reaction time response of primary interest were percent successful avoidance and response latency. Successful avoidance was not affected by amphetamine treatment. However, response latencies were dose-dependently decreased in response to amphetamine [13].

In humans, Bütetfisch *et al.* investigated whether the administration of d-amphetamine facilitates use-dependent plasticity within the motor cortex. Healthy volunteers underwent a training period of voluntary thumb movements under the effects of placebo or d-amphetamine in different sessions in a randomized double-blind, counterbalanced design. The endpoint measure of the study was the magnitude of training-induced changes in transcranial magnetic stimulation (TMS)-evoked kinematic and electromyographic responses in the d-amphetamine and in the placebo conditions. Motor training resulted in increased magnitude, faster development and longer lasting duration of use-dependent plasticity under d-amphetamine compared to the placebo session. In fact, these results document a facilitatory effect of d-amphetamine on use-dependent plasticity and associated plastic changes in the human motor cortex [14]. In another study that aimed to investigate the influence of amphetamine on human motor cortex plasticity, Tegenthoff *et al.* used a so-called co-contraction task [6]. Repetitive synchronized movements of the deltoid and one hand muscle [15, 16] were followed by shifts in the representations within the primary motor cortex, which can be assessed by transcranial magnetic stimulation (TMS) [17, 18]. Cortical plastic changes observed 1 h after training were more pronounced with amphetamine, whereas motor performance did not differ between training sessions with and without amphetamine. These findings support the conclusion of Bütetfisch *et al.* [14], who emphasized that amphetamine seems to be able to enhance training-induced motor cortex plasticity [6]. In line with these findings, Sawaki *et al.* investigated six subjects in whom training alone failed to elicit behavioral effects and found that a single dose of 10 mg of d-amphetamine was enough to enhance motor learning substantially [19].

Recently, our study-group showed that not only the motor but also the somatosensory cortex is subject to amplification by amphetamine. We induced perceptual learning by Hebbian-like coactivation of the skin of the tip of the right index finger in humans. Under placebo, tactile two-point discrimination was improved on the coactivated but not on the left index finger. The application of a single dose of amphetamine boosted perceptual and neurophysiological changes in the somatosensory system in comparison to a placebo-controlled subgroup. No drug effects were found on

the left, non-coactivated index finger. Within the primary somatosensory cortex, individual lateral shifts in cortical representation of the index finger, as assessed by mapping of somatosensory evoked potentials (SEP), were linearly correlated with the pharmacological modulation of discrimination thresholds, implying that perceptual learning and associated cortical changes are controlled by basic mechanisms known to mediate and modulate synaptic plasticity [2].

Based on these recent studies, analyzing basic principles to enhance the effects of sensorimotor training by amphetamine suggest its beneficial role in rehabilitative efforts in patients. In fact, several animal and human studies provide evidence that amphetamine combined with motor neurorehabilitative therapy promotes recovery of motor function after brain injury or stroke [20-23].

For example, in rats with thrombotic infarction of the vibrissal cortical barrel-field within the primary somatosensory cortex, it was investigated whether the administration of d-amphetamine sulfate affects the rate and completeness of behavioral recovery [24]. In a learning task requiring sensory-motor integration, rats were trained to perform a motor response in a T-maze consequent to the detection of a vibrissal deflection cue. Once training was complete, unilateral or sham infarction was produced by a non-invasive photochemical technique. After infarction, T-maze performance was assessed repeatedly in rats receiving 2 or 4 mg/kg d-amphetamine sulfate or saline 24 hours prior to testing on several days. The sham-operated control rats received d-amphetamine sulfate or no injections. All three infarcted groups displayed a reliable and sustained behavioral deficit in performance that was not present in the sham-operated control animals. Although the performance of each infarcted group improved over the testing sessions after the first injection, the amphetamine-treated groups improved at a faster rate than the saline-injected group. The results further demonstrated a dose-response effect, with the 4 mg/kg amphetamine group recovering within preinfarction levels of 6-8 days earlier than the 2 mg/kg amphetamine and saline-injected groups. Moreover, both amphetamine-treated groups recovered more completely than the saline-injected group. This may indicate enduring vulnerability to transient reinstatement of focal neurological deficits as previously shown for an adrenergic antagonist like prazosin after traumatic brain injury [25]. Quantification of the chronic infarct area revealed no differences among the amphetamine-treated and saline-injected groups. These animal data provide evidence of the facilitatory effect of d-amphetamine sulfate on recovery from brain injury, and extend this effect to the enhancement of recovery subsequent to thrombotic infarction of the primary somatosensory cortex [24].

In humans, Crisostomo *et al.* conducted a double-blind study of 8 patients with established cerebral infarction to evaluate the effect of a single dose of amphetamine on recovery of motor function. Four patients received amphetamine; the rest were given placebo. All underwent a session of physical therapy. Patients treated with amphetamine obtained greater increments in motor scores than the controls. Along with the aforementioned animal study, these

findings may allow the development of a pharmacological approach to stroke rehabilitation [26].

In 1995, Walker-Batson *et al.* administered d-amphetamine, paired with physical therapy, to hemiplegic stroke patients. Ten patients who suffered an acute ischemic infarction were entered between days 16 and 30 after stroke and randomly assigned to receive either 10 mg of d-amphetamine or placebo every 4th day for 10 sessions paired with physical therapy. The Fugl-Meyer Motor Scale, indicating the degree of motor impairment, was used at baseline, within each session, and for 12 months after onset as the dependent measure. Confounding medications such as alpha-adrenergic antagonists or agonists were excluded in all subjects. Although there were no differences between the groups at baseline, there was a significant difference between the groups when the drug had been discontinued for 1 week and at the 12-month follow-up visit. Thus, administration of d-amphetamine paired with physical therapy increased the rate and extent of motor recovery in this group of hemiplegic stroke patients. These data support and extend previous findings of the facilitatory aspects of certain types of drugs on recovery from brain injury [7].

In 2001, the same study-group investigated whether d-amphetamine might support recovery from communication deficits subsequent to stroke. In a prospective, double-blind study, 21 aphasic patients with an acute non-hemorrhagic infarction were randomly assigned to receive either 10 mg d-amphetamine or placebo. Patients were entered between days 16 and 45 after onset and were treated on a 3-day/4-day schedule for 10 sessions. Thirty minutes after drug/placebo administration, subjects received a 1-hour session of speech/language therapy. Communicative ability was assessed at baseline, at 1 week the drug, and at 6 months after onset as the dependent language measure. Although there were no differences between the drug and placebo groups before treatment, by 1 week after the 10 drug treatments ended, there was a significant difference in gain scores between the groups, with the greater gain in the d-amphetamine group. The difference was still significant when corrected for initial aphasia severity and age. At the 6-month follow-up, the difference in gain scores between the groups had increased. These findings suggest that the administration of d-amphetamine paired with speech/language therapy facilitated recovery from aphasia in a group of patients in the subacute period after stroke. Neuromodulation with d-amphetamine, and perhaps other drugs that increase central nervous system noradrenaline levels, may therefore facilitate recovery when paired with focused behavioral treatment [11]. The use of such neuromodulation may moreover allow the nervous system to adapt previously unused or alternative pathways to relevant external input [7].

Although amphetamine was shown to have no severe side effects when given as an adjunct to stroke rehabilitation [27], it acts non-specifically by increasing centrally the levels of different neurotransmitters, namely dopamine, serotonin, and noradrenalin. Thus, first approaches that intend to scrutinize the apparently ubiquitous role of only one of these neurotransmitter systems used more specifically acting pharmacological agents. For example, it has been proposed that norepinephrine plays a critical role in the

modulation of cortical excitability, which in turn is thought to influence functional recovery from brain lesions. Plewnia *et al.* investigated if it is possible to modulate cortical excitability with the selective norepinephrine reuptake inhibitor reboxetine in intact humans. Recruitment curve and intracortical facilitation, assessed by transcranial magnetic stimulation were increased after oral intake of 8 and 4 mg reboxetine, suggesting an enhanced cortical excitability. This, in turn, may rise the possibility that reboxetine could act as a plasticity enhancing substance potentially useful in combination with neurorehabilitative strategies geared to enhance neurorehabilitation [28, 29].

In a clinical study, Miyai *et al.* investigated whether L-threodops (L-DOPS), a norepinephrine precursor, improves rehabilitation outcome in patients with initial hemiparetic supratentorial ischemic stroke. Five patients who agreed to be treated with L-DOPS received 45-minute physical therapy (PT) and occupational therapy (OT) for 2 months, 3 days a week, with an oral dose of 200 mg L-DOPS 2 hours before each session, followed by PT and OT without L-DOPS for 2 months (DOPS group). Eight patients who disagreed received PT and OT for 4 months and served as control. Each group demonstrated comparable age, sex, complications, Mini-Mental State Examination, and the baseline Functional Independence Measure (FIM), Fugl-Meyer motor scale (F-M), and ambulation endurance. DOPS group had significantly greater gain than control in FIM score at 4 and 6 months, ambulation at 4 and 6 months, and F-M score at 4 months. There were no side effects that required discontinuation of the drug. These results suggest that despite amphetamine, more specifically acting modulators of adrenergic neurotransmission like L-DOPS may also be effective in improving functional outcome in stroke when paired with neurorehabilitation [30].

SEROTONERGIC NEUROTRANSMISSION

In cell cultures, serotonin causes long-term facilitation of sensorimotor synapses. Beside its known effect as a monoamine modifying changes in synaptic function, serotonin might also drive the growth of new presynaptic varicosities [31]. Regarding the modulatory influences of serotonin on behavior, several animal experiments showed the capacity to modulate motor responses purposefully [32-36]. In rats, for example, serotonergic neurons were activated in association with increased muscle motor activity, especially if the motor activity was in the repetitive or central pattern generator mode [37].

In humans, the selective serotonin reuptake inhibitor (SSRI) fluoxetine, accumulates in the brain relative to the plasma and promotes an amplified serotonin concentration [38, 39]. Recently, we investigated the effect of a single dose of fluoxetine on the co-contraction task as described in the previous paragraph [6] and associated cortical changes in healthy right-handed subjects [40]. Subjects performed repetitive synchronized movements of the abductor pollicis brevis (APB) and the deltoid muscle with and without fluoxetine in a placebo-controlled double-blinded crossover study design. Immediately before and after motor learning, motor output maps of the APB muscle were assessed in order to get insight into plastic changes of the muscle representation. We found a significantly improved motor

performance under both conditions without having substantial differences between placebo and fluoxetine. After the completion of the motor task, there was a medial shift of the APB muscle motor output map. Only after the administration of fluoxetine, the sum of MEP amplitudes (SOA) increased and the motor output map enlarged. These findings suggest that a single dose of fluoxetine facilitates use-dependent cortical excitability but not motor performance [40]. In another study, Ilic *et al.* investigated whether the selective serotonin reuptake inhibitor sertraline, modulates human motor cortex excitability in healthy subjects [41]. Using the method of TMS, they found that sertraline increases the steepness of the intensity curve suggesting an increased excitability of the cortico-spinal neuron. In our study, under the influence of fluoxetine, repetitive co-contraction of the APB and the deltoid muscle resulted in an increase of the SOA and an enlargement of the APB representation. Selective serotonin reuptake inhibitors like sertraline and fluoxetine seem therefore to have complex influences on different parameters of cortical excitability [40, 41].

Furthermore, Loubinoux *et al.* emphasized a putative role of monoamines and, more specifically, of serotonin in the regulation of cerebral motor activity in healthy subjects. In their study, the effects on cerebral motor activity of a single dose of fluoxetine and fenozolone, an amphetamine-like drug, were assessed by functional magnetic resonance imaging (fMRI). Subjects performed sensorimotor tasks with the right hand. Functional magnetic resonance imaging studies were performed in two sessions on two different days. The first session, with two scan experiments separated by 5 hours without any drug administration, served as time-effect control. Drug effects were assessed in a second, similar session, with the drug being administered after the first scan. A large increase in evoked signal intensity occurred in the ipsilateral cerebellum, and a parallel, large reduction occurred in primary and secondary motor cortices. Both drugs elicited comparable effects, that is, a more focused activation in the contralateral sensorimotor area, a greater involvement of posterior supplementary motor area, and a widespread decrease of bilateral cerebellar activation. These findings provide further evidence for a direct or an indirect involvement of monoamines and serotonin in the facilitation of cerebral motor activity [42]. Based on these studies describing the capacity of fluoxetine in facilitating motor cortex activity, it is conceivable that it may influence outcome after ischemic brain injury in humans [43]. In order to determine the influence of a single dose of fluoxetine on cerebral motor activation of lacunar stroke patients in the early phase of recovery, Pariente *et al.* conducted a prospective, double-blind, crossover, placebo-controlled study on 8 patients with pure motor hemiparesia. Each patient underwent two fMRI examinations: one under fluoxetine and one under placebo. The first was performed 2 weeks after stroke onset and the second, a week later. During the two fMRI examinations, patients performed an active controlled motor task with the affected hand and a passive one conducted by the examiner with the same hand. Motor performance was evaluated by motor tests under placebo and under fluoxetine immediately before the examinations to investigate the effect of fluoxetine on motor function. Under fluoxetine, during the active motor task, hyperactivation in

the ipsilesional primary motor cortex was found. Moreover, fluoxetine significantly improved motor skills of the affected side. Taking together, these findings suggest that a single dose of fluoxetine was enough to modulate cerebral sensory-motor activation in patients. This redistribution of activation toward the motor cortex output activation was associated with an enhancement of motor performance [44].

Regarding the capacity of SSRIs in changing human brain function and motor performance, it should be mentioned that this was found to be dose dependant [45, 46]. Moreover, their efficiency, for example, in the treatment of depression, mainly increases with time because long-term application leads to upregulation of serotonergic [47-49] and also β -adrenergic receptors [50]. Future studies investigating the influence of long-term treatment with SSRIs as an adjunct to physical therapy may therefore extend our knowledge of their beneficial influences on neurorehabilitation.

DOPAMINERGIC NEUROTRANSMISSION

Despite encouraging studies impressively documenting how adrenergic and serotonergic pharmaceuticals enhance sensorimotor capacities in healthy humans and patients, less is known about how the dopaminergic neurotransmission can be modulated pharmacologically in order to drive cortical excitability changes and associated changes in behavior. For example, Ziemann *et al.* used TMS to test the acute effect of a single oral dose of different dopaminergic (levodopa, selegiline, bromocriptine) and antidopaminergic pharmaceuticals (sulpiride, haloperidol) on motor cortex excitability in healthy volunteers. Motor thresholds, intracortical inhibition and intracortical facilitation were tested in the abductor digiti minimi muscle. The latter two parameters were studied in a conditioning-test paired stimulus paradigm. The principal findings were an increase in intracortical inhibition by bromocriptine, and, conversely, a decrease in intracortical inhibition and an increase in intracortical facilitation by haloperidol. Effects peaked at delays consistent with the pharmacokinetics of the two drugs and were fully reversible. The authors concluded that dopamine receptor agonists and antagonists can be considered inverse modulators of motor cortex excitability: the former enhance inhibition while the latter reduce it [51].

To evaluate the efficacy of carbidopa L-dopa in reducing left spatial neglect after stroke, Mukand *et al.* enrolled a sample of 4 women with right brain strokes and left neglect. Three of 4 subjects had significant improvements in their modified Behavioral Inattention Test scores and their functional status. In this case series, carbidopa L-dopa has thus shown to reduce unilateral spatial neglect and thereby improve rehabilitation outcomes [52].

Regarding the possibility to enhance the efficacy of physiotherapy by interfering dopaminergic neurotransmission, Scheidtmann *et al.* performed a prospective, randomized, placebo-controlled, double-blind study in which they applied levodopa to 53 primary stroke patients in early poststroke period. For the first 3 weeks, patients received single doses of levodopa 100 mg or placebo daily in combination with physiotherapy. For the second 3 weeks, patients had only physiotherapy. Motor recovery was significantly improved after 3 weeks of drug intervention in those on levodopa

compared with placebo, and the result was independent of initial degree of impairment. The advantage of the levodopa group was maintained at study endpoint 3 weeks after levodopa was stopped. A single dose of levodopa is well tolerated and, when given in combination with physiotherapy, enhances motor recovery in patients with hemiplegia. In view of its minimal side effects, levodopa will be a possible add-on during stroke rehabilitation [53, 54].

SUMMARY AND CONCLUSION

Although neurorehabilitation has received relatively little scientific attention during the last decade [1], a growing number of studies provide evidence that different approaches for neurorehabilitation can be enhanced by facilitatory pharmaceuticals. The underlying knowledge of how those pharmaceuticals modulate synaptic plasticity mainly arises from studies investigating the pharmacology of learning in animals and healthy humans. In a first step of this review, we focused on studies that aimed to investigate the pharmacology of motor and sensory skills in healthy humans. Secondly, we reviewed studies investigating whether the same drugs may also support neurorehabilitation.

Growing evidence from human studies support the suggestion that learning and training is subject to amplification by amphetamine [2, 6, 14, 19]. Its capacities to enhance the effects of motor training were then used to enhance rehabilitative efforts in patients in whom training alone failed [7, 11, 20-24, 26]. Amphetamine however, acts non-specifically by increasing centrally the levels of dopamine, serotonin, and noradrenaline. Thus, first approaches that intend to scrutinize the apparently ubiquitous role of only one of these neurotransmitter systems used more specifically acting pharmacological agents. Serotonin, for example, has the capacity to modulate purposeful motor responses in animals [32-36]. Selective serotonin-reuptake inhibitors (SSRI), like fluoxetine, that enhance serotonin concentration in the human brain can be used to facilitate use-dependent cortical excitability [40] and motor skills, not only in healthy subjects [42] but also in stroke patients [44].

Despite these encouraging studies impressively documenting how adrenergic and serotonergic pharmaceuticals enhance motorsensory capacities in healthy humans and patients, less is known about how the dopaminergic neurotransmission can be modulated pharmacologically in order to drive cortical excitability and associated behavior. However, it has been shown that a single dose of levodopa, when given in combination with physiotherapy, enhances motor recovery in patients with hemiplegia. In view of its minimal side effects, levodopa may become a possible add-on during stroke rehabilitation [53].

In summary, it was shown to which extent different pharmaceuticals with a known mode of action are able to facilitate behavior in healthy humans. In fact, the possibility to control neuroreceptor activity substantially may be instrumented to alter plasticity purposefully; for instance, to enhance plastic changes and recovery of function in neurological disorders [55, 56]. However, we just started to understand basic mechanisms of synaptic plasticity and how these can be controlled pharmacologically. Most of the

clinical trials mentioned here used very simple behavioral paradigms with low clinical relevance. Moreover, we need to emphasize on the fact that those results are mainly based on short observation periods and small populations of patients with heterogeneous clinical pictures. Therefore, the question whether neurorehabilitation should be supported pharmacologically or not remains unanswered. Moreover, we must keep in mind that many patients are able to live lives despite their residual deficits. Each of the aforementioned drugs has a number of side effects. Amphetamine, for example, is popular for its potential to cause addiction, but usually, only when given in much higher doses than in any of the mentioned studies. Although none of those clinical trials revealed any side effects under the administered drugs, benefits and risks of therapy should be taken into careful consideration.

Thus, before we can revise established clinical standards, further studies in large populations are necessary that focus on more specifically acting pharmaceuticals, their side effects and their capacity in supporting different patterns of neurorehabilitative therapy.

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