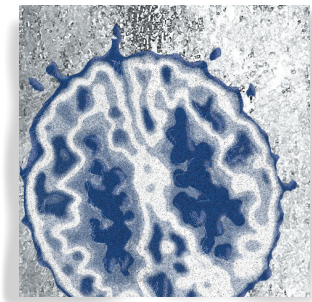# Translational research

Experimental panic provocation in healthy man—a translational role in anti-panic drug development?

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Experimental neurochemical provocation of panic attacks in susceptible human subjects has considerably expanded our knowledge of the pathophysiology and psychopharmacology of panic disorder. Some panicogens also elicit short-lived panic-like states in healthy man. This offers the opportunity to assess the anti-panic action of drugs in proof-of-concept studies. However, from current data it is still unclear whether experimental panic in healthy man is a valid translational model. Most such studies in healthy volunteers have been performed using a cholecystokinin tetrapeptide (CCK-4) challenge. While CCK-4 panic was blocked by alprazolam pretreatment, escitalopram showed negative results in healthy man. Preliminary findings on novel investigational drugs and a few problematic results will be reviewed. Small sample sizes in many panic provocation studies, lack of dose-response aspects, and still-insufficient knowledge about the biological underpinning of experimental and spontaneous panic limit the interpretation of existing findings and should inspire further research.

Experimental provocation of panic attacks in panic disorder patients

Panic attacks are defined as sudden and short-lived anxiety spells with various somatic and cognitive symptoms. According to *DSM-IV*, these discrete periods of intense fear or discomfort develop abruptly and reach a peak within 10 minutes. Furthermore, at least four of the following thirteen symptoms evolve: palpitations or accelerated heart rate; sweating, trembling, or shaking; sensations of shortness of breath or smothering; feeling of choking, chest pain, or discomfort; nausea or abdominal distress; feeling dizzy, unsteady, lightheaded, or faint; derealization or depersonalization; fear of losing control or going crazy; fear of dying; paresthesias; chills or hot flashes. Panic attacks can occur sporadically in healthy man, but also in the context of anxiety disorders (if the panic attacks are not due to the direct physiological effect of a substance or a general medical condition). Diagnostically, recurrent panic attacks are the hallmark of panic disorder, which is a disabling anxiety disorder that has a lifetime prevalence of about 5%.[1]

The interest in the neurobiology of panic attacks has considerably been stimulated by the discovery that these spontaneous anxiety paroxysms can be provoked exper-

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imentally in susceptible subjects in the laboratory under controlled conditions. The seminal report about neurochemical provocation of panic attacks in man was published by Pitts and McClure in 1967.[2] Based on the observation that patients with "anxiety neurosis" were exercise-intolerant and developed high blood levels of lactic acid during standardized workload, these researchers developed the idea that the lactate molecule might be the elicitor of anxiety attacks in vulnerable individuals. In a double-blind study with intravenous infusion of 10 mL/kg body weight of 0.5 molar sodium lactate over a maximum of 20 minutes, 13 out of 14 patients with anxiety neurosis (all of them with a history of spontaneous anxiety spells), but only 2 out of 10 healthy controls, developed typical anxiety attacks. This observation laid the foundation for extensive research efforts on the experimental psychopathology of panic, which offers a unique opportunity in the field of psychiatry.

The scientific and clinical promises of such symptom provocation studies for the pathophysiology and psychopharmacology of psychiatric disorders have been drafted as follows[3]:

> In this paradigm investigators administer a psychopharmacologic agent or psychological challenge procedure to patients under controlled conditions to probe psychiatric symptoms and other neurobiological responses. The principle scientific rationale behind this approach is to learn more about the underlying pathophysiological mechanisms responsible for the symptomatic expression of psychiatric illnesses. In addition, the knowledge gained from this type of study might lead to better predictors of treatment response or identification of novel therapeutic interventions.

A quintessential ethical framework of challenge studies includes preserved decision-making capacity, informed consent, potential scientific and future clinical benefits, consent of an ethical committee, a favorable or acceptable risk:benefit ratio, absence of severe or long-lasting effects of the challenge agent, and follow-up studies on the effects of participation in symptom-provoking studies.

In addition to lactate infusion, several further methods to provoke experimental panic attacks in patients with panic disorder by pharmacological means have been developed during the past decades (overview in ref 4). These display many different modes of action and have different targets. They include other agents that influence respiration, such as carbon dioxide inhalation or doxapram infusion.

Further established panicogens act specifically on neurotransmission, such as the noradrenergic substances yohimbine and isoprenaline, the serotonergic agents metachlorophenylpiperazine (mCPP) and fenfluramine, benzodiazepine-receptor agents, such as the inverse agonist FG 7142 and the antagonist flumazenil, agonists at the CCK-2 (formerly type B) receptor, such as cholecystokinin tetrapeptide (CKK-4) and pentagastrin, and the adenosine receptor antagonist caffeine.

The following criteria for an ideal panicogen for human use have been proposed (compiled according to Gutmacher et al[5] and Gorman et al[6]):

- It should be safe
- It should mimic naturally occurring panic attacks
- It should foster both central and peripheral manifestations of panic
- It should be replicable
- The phenomena should be either short-lived or readily reversible
- It should differentiate between healthy subjects and those with pathology
- It should reflect the potential for a state response; those who have been successfully treated clinically should not respond or respond far less than those who have had no treatment
- The effects should not be blocked by drugs, which do not work against spontaneous panic.

Concerning the claimed "potential for a state response" in patients after successful anti-panic treatment, the further discourse of this paper will be restricted to drug treatment (and will not address findings after psychotherapeutic treatment or spontaneous remission).

Pharmacological modulation of experimental panic in panic disorder patients

The use of experimental panic provocation by panicogens after psychopharmacological anti-panic treatment may be a more advantageous means to assess drug effects than just waiting for days and weeks for spontaneous panic attacks to occur, and having the patients keep panic diaries to characterize panic frequency and severity. In some regard, this procedure resembles the role of the well-known exercise stress test in diagnosis and treatment of angina pectoris in internal medicine. Several studies, mostly with lactate, carbon dioxide, or CCK-4, have demonstrated that the established anti-panic drug treatments with nonselective serotonin reup-

take inhibitors (the tricylic antidepressants imipramine and clomipramine), various selective serotonin reuptake inhibitors (SSRIs) and benzodiazepines (particularly alprazolam) indeed diminish experimentally induced panic in patients with panic disorder.

In detail, in studies with sodium lactate infusions prior medication with the benzodiazepines diazepam[7,8] and alprazolam[9-11] as well as with the tricyclic antidepressant imipramine[8,12,13] significantly decreased induction of panic anxiety in panic patients and thus appeared to increase the threshold for lactate-induced panic attacks. Carbon dioxide (35%)-induced panic was attenuated in panic disorder patients after treatment with the benzodiazepines clonazepam[14,15] and alprazolam,[16] with imipramine or clomipramine,[17-19] paroxetine, sertraline, or fluvoxamine.[18-20] CCK-4-elicited panic was decreased in panic patients after imipramine treatment[21] and after citalopram or fluvoxamine.[22,23] The response to the further panicogens after treatment with standard anti-panic drugs are less intensively studied in patients—alprazolam blocked the panic symptoms provoked by mCPP (piperazine)[24] and yohimbine,[25] long-term imipramine did not alter yohimbine-induced increases in ratings of anxiety-nervousness,[26] but fluvoxamine reduced yohimbine-induced anxiety.[27]

For some investigational drugs experimental panic provocation has been used in patients with panic disorder (without prior testing in panic models in healthy man, as described in the following paragraphs). The emerging data might give valuable information for decision making as to whether further study on their action on spontaneous attacks is worthwhile. However, a definite evaluation of the informative value of this approach at this stage is not yet possible due to the paucity of studies.

A single oral dose of 50 mg of L-365,260, a central CCK receptor antagonist, had shown a differential action on CCK-4- and lactate-induced panic attacks in patients with panic disorder. In a double-blind, placebo-controlled, crossover study in 29 patients, CCK-4 90 minutes after L-365,260 significantly reduced the number and sum intensity of provoked panic symptoms.[28] In contrast, a double-blind, placebo-controlled parallel-group study in 24 patients with sodium lactate infusion given after the same dosage of the compound and in the identical time frame failed to reveal statistical differences on these panic attack parameters.[29] In a multicenter, placebo-controlled, double-blind trial with L-365,260 30 mg qid for 6 weeks no clinically significant treatment

effects in panic attack frequency or intensity were found and testing higher doses was suggested,[30] but has not been performed so far.

In a double-blind, placebo-controlled, crossover design, nine panic patients were given an intravenous infusion of 150 μg of atrial natriuretic peptide (ANP) followed by experimental panic induction using CCK-4.[31] The rationale was derived from observations that ANP is released during panic attacks in humans and has anxiolytic-like effects in preclinical studies.[32] The CCK-4 response as per Acute Panic Inventory (API) ratings was significantly reduced after ANP versus placebo pretreatment. These findings of anti-panic activity of ANP were replicated in another study in ten panic patients under comparable experimental conditions with a lower dose of CCK-4.[33] Unfortunately, until now no study about the action of ANP (or another agonist at the type A natriuretic peptide receptor) on spontaneous panic attacks in patients with panic disorder has been reported.

An early study in outpatients suffering from panic disorder using the panic response to CCK-4 challenge as the primary outcome parameter was conducted with the novel neurokinin-3 (NK-3) receptor antagonist SR142801 (osanetant).[34] Fifty-two patients who had developed a panic attack with CCK-4 were randomized to 4 weeks of treatment (200 mg/d orally) in a double-blind, placebo-controlled design and then a second CCK-4 challenge was performed. However, with regard to the primary efficacy end point, ie, the increase of API total score, osanetant was not significantly different from placebo. On the Panic and Agoraphobia Scale no significant treatment effects of this compound were detected during these 4 weeks.

Experimental provocation of panic attacks in healthy volunteers

For many panic patients it is quite aversive and frightening to undergo an experimental panic challenge and to be treated with an investigational product due to catastrophizing disorder-immanent cognitions, fears of side effects, and the possibility of being randomized to placebo treatment. To bridge the gap between preclinical panic models[35] and studies in patients, experimental panic provocation in healthy human subjects might serve as a valuable tool for assessment of novel anti-panic compounds during the early phase of drug development in proof-of-concept studies. Healthy volunteer transla-

tional studies might deliver valuable information on whether it is worthwhile to consider further, more thorough studies in patients.

However, standard sodium lactate panic is not an apt panic model in healthy subjects, because, as already mentioned, in contrast to patients with panic disorder, only a small percentage of healthy humans develop panic symptoms to it. Interestingly, Sinha et al[36] investigated, in a single-blind pilot study, whether additional pretreatment with naloxone, an opioid receptor antagonist, could render healthy controls who are nonresponsive to panic induction by lactate infusion sensitive to the latter panicogen. Indeed, substantial increases in the API scores were displayed by 8 out of 12 subjects during such treatment; naloxone alone did not result in panic symptoms. In a following more sophisticated investigation in 25 volunteers (using a crossover, randomized design) further evidence was shown that impairment of the endogenous opioid system by naloxone accentuates symptomatic response to lactate, but no significant differences in API ratings were detected.[37] Notwithstanding, the authors suggest testing the specificity of the naloxone-lactate model in healthy man comparing specific anti-panic medications with ineffective anti-panic agents, and furthermore screening for putative anti-panic agents with this method. Further studies will demonstrate whether this complex model is applicable for translational panic research in healthy humans.

Panic provocation in healthy volunteers is more feasible using CCK-4 or carbon dioxide. The further discourse will be restricted to these two panicogens, because we are not aware of any published studies testing anti-panic drugs in normal volunteer challenge studies using other substances. Although patients with panic disorder show an enhanced sensitivity to intravenous bolus injection of CCK-4, increasing its dose brings about a substantial panic-like reaction also in normal controls. While the panic rate after injection of 25 µg was 91% for patients and only 17% for controls, 50 µg of CCK-4 induced a full-blown panic attack in 100% of patients and in a sizable 47% of controls.[38] Among healthy volunteers significant dose-related differences were also found for the number of panic symptoms and their sum intensity,[39] which makes CCK-4 a useful research model for dimensional aspects of panic also in the nonclinical subjects who do not develop a full-blown panic attack.[40] Also, with a single breath of 35% carbon dioxide inhalation panic patients show significantly stronger symptoms of panic anxiety

than normal controls.[41,42] The induced cluster of symptoms in healthy volunteers is, however, similar to those elicited in panic attacks naturally occurring in patients affected by panic disorder.[43] But the panic signal obtained with one breath of 35% carbon dioxide seems to be weaker than with injection of 50 µg of CCK-4 in healthy subjects: Direct comparison of only 25 µg of CCK-4 and 35% carbon dioxide revealed significantly more intense symptoms with CCK-4, but not a significantly greater number of symptoms; the incidence of panic attacks was similar: 21% for CO2 and 17% for 25 mg of CCK-4.[44]

A methodological problem is that psychometric assessment of induced panic does not follow consistent rules – different panic rating scales, such as the API and the DSM-derived Panic Symptom Scale (PSS) are used and different criteria to divide panickers from non-panickers. To provide a basis for the use of the CCK-4 model in proof of concept studies in healthy volunteers, the psychometric, cardiovascular, and neuroendocrine responses to 50 µg of CCK-4 were studied in 85 healthy men.[45] The API-derived panic rate was 78.8% and thus 10.6% higher than that derived from the PSS ratings (68.2%). This should be taken into account when comparing studies and when choosing a categorical instead of a dimensional outcome parameter of panic provocation. Another result of this study was that cardiovascular and hormonal alterations to CCK-4 challenge are not valuable as an objective readout of panic. We must bear in mind to depend on relatively "weak" data from self-report when assessing panic anxiety.

Pharmacological modulation of experimental panic in healthy volunteers

Because the vast majority of studies on pharmacological modulation of experimental panic in healthy volunteers was performed using CCK-4, the focus here will be on this panicogen (for synopsis of results, please see *Table I*). In the 35% carbon dioxide model of panic in healthy volunteers an acute dose of 1 mg alprazolam 2 hours before inhalation resulted in significant anti-panic effects in a double-blind, placebo-controlled, three-way crossover study in 12 healthy subjects.[46] With an SSRI, only one study in healthy man using the 35% CO_2 challenge has been published.[47] In this 2-week double-blind, placebo-controlled trial in 24 subjects, who were at high risk for panic disorder because of a personal history of panic attacks or a family history of treated panic disor-

der, and who had reacted with a panic attack to prior carbon dioxide testing, 10 mg/d of escitalopram failed to affect experimental panic. However, the caveat must be applied that time of treatment with an SSRI of only 14 days might not be long enough to manifest anti-panic action, because clinical benefits for SSRI in panic disorder typically take longer. Further studies must clarify, whether the 35% carbon dioxide panic model is sensitive to modulation with serotonergic antidepressants and other anti-panic drugs in healthy man.

Established anti-panic drugs and CCK-4 panic in healthy volunteers

The acute inhibitory effect of benzodiazepines on CCK-4 panic in normal man has been demonstrated in two studies. In an early, small exploratory open-label study De Montigny[48] showed that pretreatment with lorazepam (1 mg at 4 PM and 2 mg at bedtime on the preceeding day, 1 mg at 8 AM 1 hour before CCK-4 challenge) prevented the psychic effects of CCK-4 (doses between 75 and 150 µg) in four subjects who had experienced a panic-like attack with the same dose of this peptide before. In a double-blind, placebo-controlled, parallel-group study in 30 healthy volunteers treated with 1 mg alprazolam 1 hour prior to a 50-µg CCK-4 challenge, a significant reduction of API and PSS scores and of the number of reported symptoms compared to placebo pretreatment were found.[49] A recent

study (following an unbalanced, three-arm, two-period, crossover, double-blind, placebo-controlled design) in 21 male volunteers who received 1 mg of lorazepam 2 hours before CCK-4 did not show an attenuated panic signal in any PSS parameter.[50] However, this dose of lorazepam was considerably lower than in the two previous studies reported above.

Concerning anti-panic non-selective serotonin reuptake inhibitors (imipramine or clomipramine) no study on CCK-4 panic in healthy volunteers has been published. With an SSRI, Kellner et al[51] could not demonstrate an inhibitory effect of escitalopram (6 weeks of 10 mg/d) on a 50-µg CCK-4 challenge in a double-blind, placebo-controlled, randomized, within-subject crossover design in 30 healthy young men. Induced panic under escitalopram was even significantly more pronounced in the subgroup of subjects with the short/short genotype for the serotonin transporter linked polymorphic region in this study. Another investigation with an identical dose and duration of escitalopram pretreatment also failed to show a significant inhibitory effect on CCK-4 panic in healthy man (I. Tõru, personal communication).

Investigational anti-panic drugs and CCK-4 panic in healthy volunteers

To test the effectiveness of a single oral 100 mg dose of the cholecystokinin B antagonist CI-988 in attenuating panic symptoms induced by CCK-4 a randomized,

	Healthy man: CCK-4	Panic disorder patient: CCK-4	Panic disorder patient: diary
Established antipanic drugs			
Imipramine	?	(+)	+
Selective serotonin reuptake inhibitors	0	+	+
Alprazolam	+	?	+
Investigational antipanic drugs			
CCK-B antagonist CI-988	+	0	0
CCK-B antagonist L-365,260	?	+	0
mGlu 2/3 agonist LY544344	(+)	?	?
Atrial natriuretic peptide	0	+	?
NK-3 antagonist SR142801	?	0	0
β–blocker propranolol	(+)	?	0
GABA reuptake inhibitor tiagabine	(+)	(+)	0
GABA transaminase inhibitor vigabatrine	(+)	?	?
Translocator protein (18 kD) ligand XBD173	+	?	?

Table I. Cholecystokinin-tetrapeptide (CCK-4)-induced panic in humans – inhibition of panic symptoms by drug pretreatment? +, evidence for inhibition of panic as per a double-blind, placebo-controlled study, (+), limited evidence for inhibition of panic; 0, no inhibition of panic observed; ?, no study published; mGlu, metabotropic glutamate; NK-3, neurokinin 3; GABA, γ-aminobutyric acid

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placebo-controlled, double-blind, three-way crossover design was used in 30 healthy men.[52] A small (14%), but significant decrease of sum intensity scores of panic symptoms was observed under CI-988. However, there was no marked difference in the number of panic symptoms. In contrast, a subsequent study in 14 patients with panic disorder who were given 50 or 100 mg of CI-988 in a double-blind, two-period incomplete block design 2 hours before injection of CCK-4 failed to show a statistically significant treatment effect on the total intensity score on the PSS (the primary efficacy parameter), as well as on the number of panic symptoms, time to and occurrence of the first panic symptoms, duration of symptoms, intensity of apprehension, and the percentage of patients who did not have a panic attack.[53] In a randomized, double-blind, placebo-controlled trial with 100 mg tid of CI-988 in panic patients no superiority to placebo in reducing panic attacks could be shown.[54]

After the metabotropic glutamate 2/3 receptor agonist LY544344/LY354740 had shown acute anxiolytic-like action in preclinical studies, a pilot study on panic anxiety induced by CCK-4 was performed in healthy humans.[55] Twelve male volunteers were treated with 80 mg bid LY544344 orally for 1 week in a randomized placebo-controlled double-blind crossover design. While no significant treatment effect for the number of CCK-4-induced panic symptoms and subjective anxiety ratings emerged in the entire sample, the ten subjects who showed an endocrine response to the test substance displayed a significant reduction on these two measures. Unfortunately, due to emerging problems in long-term preclinical safety, no subsequent clinical studies were performed with this compound.

The finding of a significant anti-panic effect of atrial natriuretic peptide (ANP) in patients with panic disorder has already been mentioned above.[31] In this double-blind, placebo-controlled, crossover study also nine healthy control subjects matched for sex and age were included and they were given an intravenous infusion of 150 µg of ANP followed by CCK-4 panic induction. However, no significant treatment effect of ANP on API ratings was observed in healthy man.

The β-blocker propranolol (0.2 mg/kg given intravenously over 20 minutes) has been observed to significantly decrease the CCK-4 response (sum intensity and number of panic symptoms) in a study in 30 healthy male volunteers who were randomly assigned to propranolol or placebo.[56] In panic patients no study with a β-blocker has been reported using the CCK-4 model and in a 5-week double-blind placebo-controlled study, no efficacy of propranolol on spontaneous attacks was detected.[57] Interestingly, using the CCK-B receptor agonist pentagastrin for panic provocation in a double-blind, randomized, placebo-controlled study with identical dose and application of propranolol as above in a predominantly female group of 16 healthy adult subjects, no significant effect on total symptom intensity as per the API was observed.[58]

Regarding GABA (γ-aminobutyric)-ergic drugs other than benzodiazepines both the GABA reuptake inhibitor tiagabine and the GABA transaminase inhibitor vigabatrin have been studied in this experimental panic paradigm. Fifteen healthy volunteers received 15 mg tiagabine daily for 1 week in an open study. Both API- and PSS-scores showed a significant reduction to a CCK-4 stimulus that was performed before and after treatment.[59] In a following double-blind placebo-controlled pilot study with 4 weeks of tiagabine in 19 patients with panic disorder a subset of seven patients (three treated with tiagabine, four treated with placebo) was challenged with 25 µg of CCK-4 at baseline and after 14 and 28 days.[60] Patients of the tiagabine vs the placebo group showed considerably decreased sensitivity to CCK-4 (as per API ratings). However, clinical benefits of tiagabine on the Panic and Agoraphobia Scale were not detected. Also a 10-week open study suggested that tiagabine may be of little benefit on this measure.[61]

Vigabatrine (2 mg/d) was given for 7 days to ten healthy volunteers in an open-label study after placebo-controlled administration of CCK-4 and a second CCK-4 challenge followed after the treatment period.[62] A marked and significant attenuation of CCK-4 induced panic symptoms (as per API and PSS scores) and of anxiety was observed with vigabatrine. However, no placebo-controlled and double-blind study has followed so far and the effect of vigabatrine has not been investigated in the CCK-4 paradigm in panic patients. Current data on the clinical efficacy of vigabatrine in panic patients are still casuistic.[63]

Recently, the translocator protein (18 kD) ligand XBD173, which enhances GABAergic neurotransmission via induction of neurosteroidogenesis, was tested in 71 healthy male volunteers who had shown a clear panic response to an initial CCK-4 challenge.[64] In this double-blind study the subjects were randomized to 7 days of treatment with placebo, 10, 30, or 90 mg/day of XBD173

or 2 mg/d alprazolam as active control condition. A significant difference from placebo in the difference of the API ratings between the first and the second challenge (on day 7) with CCK-4 was found for alprazolam and the highest dose of XBD173. Studies in panic patients with this compound are being awaited.

Conclusions

Despite ample exciting research efforts, we are still far from having reliable information on model validity of experimental panic provocation paradigms in healthy man as tools to test novel anti-panic drugs. A few false-negative or false-positive findings question the usefulness of this approach. Existing preliminary data need replication using exclusively double-blind, placebo-controlled designs. Comparability of results is hampered by

different psychometric methods applied. Especially for multicenter trials, standardization of the test environment and subjects' instruction need careful attention. Many findings were obtained with relatively small samples and few studies had included women. Rarely have dose-response aspects been investigated. Challenge studies with genetically precharacterized and homogenized samples are worth considering and may achieve clearer results.[65] Another problem is that our growing understanding of the complex pathophysiology of panic suggests that there may be no unitary model but possibly different phenocopies, leading to a similar pathophysiological phenomenon. Hopefully, further research will eventually lead us to more definite knowledge on which panicogens in healthy man are capable of predicting the usefulness of various anti-panic drugs for treatment in panic disorder. ❏

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La provocación experimental de pánico en hombres sanos: ¿un procedimiento traslacional para el desarrollo de fármacos antipánico?

La provocación neuroquímica experimental de ataques de pánico en seres humanos susceptibles ha ampliado considerablemente nuestro conocimiento acerca de la fisiopatología y psicofarmacología del trastorno de pánico. Algunos agentes panicogénicos también provocan estados tipo pánico de corta duración en hombres sanos. Esto ofrece la oportunidad de evaluar la acción antipático de fármacos en estudios de prueba de concepto. Sin embargo, a partir de la información actual aun no está claro si el pánico experimental en hombres sanos es un modelo traslacional válido. La mayoría de los estudios en voluntarios sanos se han efectuado empleando la provocación con el tetrapéptido colecistoquinina (CCK-4). En hombres sanos el pánico con CCK-4 fue bloqueado al pretratar con alprazolam, efecto que no se consiguió con escitalopram. Se revisan los hallazgos preliminares de nuevos fármacos de investigación y algunos resultados controvertidos. La interpretación de los hallazgos existentes está limitada por el pequeño tamaño de las muestras en muchos estudios de provocación, la falta de investigación en los aspectos dosis-respuesta y el conocimiento aun insuficiente sobre los fundamentos biológicos del pánico experimental y espontáneo, por lo que es necesario promover futuros estudios.

Provocation expérimentale de la panique chez l'homme sain, un rôle translationnel dans le développement de médicaments antipanique ?

La provocation neurochimique expérimentale d'attaques de panique chez les sujets humains sensibles a considérablement enrichi notre connaissance de la physiopathologie et de la psychopharmacologie des troubles paniques. Certains produits induisant la panique provoquent des états de panique de courte durée chez des hommes sains, ce qui offre l'opportunité d'évaluer le pouvoir antipanique des médicaments dans des études de faisabilité. Cependant, les données actuelles ne permettent pas de savoir si la panique expérimentale chez l'homme sain est un modèle translationnel valable. La plupart de ces études chez des volontaires sains ont été réalisées grâce à l'aide d'un tétrapeptide de cholécystokinine (CCK-4). Alors que la panique provoquée par le CCK-4 a été bloquée par un prétraitement par l'alprazolam, l'escitalopram a donné des résultats négatifs chez l'homme sain. Des résultats préliminaires concernant des nouveaux produits en développement seront discutés ainsi que quelques résultats problématiques. Les petits échantillons de nombreuses études de provocation de la panique, le manque de visibilité sur la réponse selon la dose et la connaissance encore insuffisante des bases biologiques de la panique expérimentale et spontanée limitent l'interprétation des résultats existants, et devraient conduire à la réalisation de nouvelles recherches.

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